A COMPARISON OF THE EFFECTS OF PARACETAMOL
AND A CORTICOSTEROID AGAINST A NON-STEROIDAL
ANTI-INFLAMMATORY DRUG ON THE SEQUELAE FOLLOWING
THE SURGICAL REMOVAL OF MANDIBULAR THIRD MOLARS

A thesis submitted to the
Faculty of Medicine and Surgery,
University of Malta,
for the
Degree of Master of Science (Pharmacology/Clinical Pharmacology).

ADAM BARTOLO
To my wife, Adriana and our newborn son, Abel
TO WHOM IT MAY CONCERN:

I hereby declare that the thesis entitled:

A COMPARISON OF THE EFFECTS OF PARACETAMOL AND A CORTICOSTEROID AGAINST A NON-STEROIDAL ANTI-INFLAMMATORY DRUG ON THE SEQUELAE FOLLOWING THE SURGICAL REMOVAL OF MANDIBULAR THIRD MOLARS;

which I am submitting for my Degree of Master of Science, is:

(1) not one for which another degree has been or will be conferred by this or any other University.

I also confirm that:

(2) the work of the thesis and its composition are my own.

Finally, I certify that:

(3) the work of the thesis has not been presented to any other institution.

ADAM BARTOLO.
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ABBREVIATIONS

\( \mu g \) microgram(s)
\( \chi^2 \) Chi-Squared
5-HT 5-hydroxytryptamine
ACTH adrenocorticotrophic hormone
AGEPC acetyl-glyceryl-ether-phosphorylcholine
ANOVA analysis of variance
ATP adenosine triphosphate
Ca calcium
cAMP cyclic adenosine monophosphate
CBG corticosteroid-binding globulin
CNS central nervous system
COX cyclo-oxygenase
CRF corticotrophin-releasing factor
CT computerised tomography
CV coefficient of variation
DNA deoxyribonucleic acid
DPF Dental Practitioners’ Formulary
fig. figure
g gram(s)
GABA \( \gamma \)-aminobutyric acid
GM-CSF granulocyte-macrophage-colony stimulating factor
HETE hydroxyeicosatetraenoic acid
HPA hypothalamus-pituitary-adrenal
HPETE hydroperoxyeicosatetraenoic acid
ID inferior dental
Ig immunoglobulin
IL interleukin
leu leucine
LT leukotriene
LTA lipoteichoic acid
ITT intention-to-treat
met methionine
mg milligram(s)
mL millilitre(s)
mm millimetre(s)
Na sodium
NGF nerve growth factor
NMDA N-methyl-D-aspartate
NSAID non-steroidal anti-inflammatory drug
OPT orthopantomograph
PAF platelet-aggregation factor
PG prostaglandin
PMNs polymorphonuclear leucocytes
pmol picomoles
q.d.s. quater die sumendus (four times daily)
RCT randomised controlled trial
RNA ribonucleic acid
SEM standard error of the mean
t.d.s. ter die sumendus (three times daily)
t½ half-life
TX thromboxane
UK United Kingdom
VAS visual analogue scale
ABSTRACT

The reduction of postoperative discomfort from oral surgical procedures is an area of great concern to all practicing dental surgeons, as well as their patients. Pain, swelling and trismus (limitation of opening) are the common sequelae after surgical removal of impacted mandibular third molars, and a wide variety of therapeutic measures have been used to reduce the incidence of these sequelae.

The factors contributing to the postoperative pain, oedema, and trismus (a form of loss of function) are complex, but many of the contributing factors are related to the inflammation following tissue trauma. These may, therefore, be reduced in intensity or severity by pharmacologically controlling the extent of the inflammatory process. In most cases, unless contraindicated, non-steroidal anti-inflammatory drugs (NSAIDs) have been used to prevent postoperative pain, while corticosteroids appear to have maximal effect in controlling oedema, but have minimal analgesic effects.

In this double-blind randomised controlled clinical trial, a combination of oral paracetamol 1g and oral dexamethasone 1mg four times daily, was evaluated against oral diclofenac sodium 50mg three times daily, for the control of postoperative pain, swelling and trismus following the surgical removal of mandibular third molars under local anaesthesia. The purpose for such a study was to find an alternative drug regimen for the control of the common postoperative sequelae of oral surgery, especially for those patients in whom the usual drug regimens (e.g. NSAIDs) are contraindicated.

Postoperative pain was recorded 8-hourly by the patients using a visual analogue scale pain chart for 7 days, while facial swelling and trismus were assessed by the investigator on the second, fourth and seventh postoperative days. Facial
swelling was determined using a measuring tape, while trismus was evaluated by measuring maximal interincisal opening.

ANOVA for repeated measures analysis indicated that the patients in the paracetamol and dexamethasone group experienced an overall mean reduction of 36% in pain \((p<0.05)\), of 76% in facial swelling \((p>0.001)\) and of 56% in trismus \((p>0.001)\) as compared to the patients in the diclofenac sodium control group. Levene's test for equality of variances showed that the inter-patient variation with respect to pain, swelling and trismus in the paracetamol and dexamethasone group, was also significantly less than that in the diclofenac sodium group \((p<0.05)\). Pearson bivariate correlation tests show that the reduction in swelling and trismus \((p<0.05)\) are significantly correlated in both groups. None of the patients reported any adverse drug reactions.

It could therefore be concluded that in the absence of contraindications, a combination of oral paracetamol 1g and oral dexamethasone 1mg four times daily, was significantly superior to oral diclofenac sodium 50mg three times daily, in safely reducing the postoperative pain, swelling and trismus following the surgical removal of mandibular third molars under local anaesthesia in otherwise healthy patients. Also, a more predictable and consistent patient response could be expected with paracetamol and dexamethasone combination therapy than with the diclofenac sodium.

This may be especially beneficial for those patients in whom the usual drug regimens (e.g. NSAIDs) are contraindicated. The use of paracetamol and dexamethasone combination therapy following this kind of oral surgical procedure, may also obviate the need for the common hospital practice to admit patients overnight in order to allow parenteral administration of opioid analgesia if necessary, thus reducing healthcare costs and avoiding opioid-associated adverse effects.
1. GENERAL INTRODUCTION

1.1. INTRODUCTION

The reduction of postoperative discomfort from oral surgical procedures is an area of great concern to all practicing dental surgeons, as well as their patients (Neupert et al., 1992). Pain, swelling and trismus are the common sequelae after surgical removal of impacted mandibular third molars (Baxendale et al., 1993; Hyrkas et al., 1993; Milles & Desjardins, 1993; Troullos et al., 1990; Beirne & Hollander, 1986; Sisk & Bonnington, 1985; Van Gool et al., 1977), and a wide variety of therapeutic measures have been used to reduce the incidence of these sequelae (Esen et al., 1999; ElHag et al., 1985; Van Gool et al., 1977). The factors contributing to the postoperative pain, oedema, and trismus are complex, but many of the contributing factors are related to the inflammatory process following tissue trauma (Esen et al., 1999; Schultze-Mosgau et al., 1995; Hyrkas et al., 1993; Troullos et al., 1990; Sisk & Bonnington, 1985). Postoperative sequelae such as pain, swelling, and trismus, may be reduced in intensity or severity by pharmacologically controlling the extent of the inflammatory process (Hyrkas et al., 1993; Troullos et al., 1990; Sisk & Bonnington, 1985; von Graffenried et al., 1980).

The ideal agent for use after third molar surgery should alleviate pain, reduce swelling and trismus to a minimum, promote healing and have no unwanted effects (Sisk & Bonnington, 1985; Seymour & Walton, 1984). Unfortunately, such an agent does not exist. Analgesics are the obvious choice for the relief of pain. Where possible, an analgesic with additional anti-inflammatory properties should be used (Seymour & Walton, 1984).
In most cases, non-steroidal anti-inflammatory drugs (NSAIDs) have been used to prevent postoperative pain (Hyrkas et al., 1993; Hyrkas et al., 1992), and corticosteroids have been used to control swelling and trismus (Gersema & Baker, 1992; Olstad & Skjelbred, 1986a). However, no clear consensus of opinion or practice has emerged, because published studies lack comparability with regards to patient selection, surgical procedure, drug dosage, timing, and route of administration (Baxendale et al., 1993; Neupert et al., 1992).

Corticosteroids appear to have maximal effect in controlling oedema but have minimal analgesic effects (Campbell & Kendrick, 1991; Troullos et al., 1990; Olstad & Skjelbred, 1986a; Sisk & Bonnington, 1985). A combination of NSAIDs and corticosteroids may be necessary to control the sequelae of oral surgical procedures most effectively (Sisk & Bonnington, 1985). However this carries an increased risk of gastrointestinal bleeding and ulceration (British Dental Association, 2002d; Hargreaves, 1995).

Also, in patients allergic to aspirin (acetylsalicylic acid) and aspirin-like compounds, NSAIDs are contraindicated (British Dental Association, 2002c). In such cases paracetamol (acetaminophen), opioid analgesics or a combination of both are often used instead. However, the efficacy of these drugs in postoperative third molar sequelae is poor (Ong & Tan, 2004; Seymour et al., 2003; Ahmad et al., 2000; Mehlisch et al., 1995; Forbes et al., 1990a; Forbes et al., 1990b; Forbes et al., 1989; Frame et al., 1989; Giles et al., 1986; Sunshine et al., 1986; Kantor, 1986; Olstad & Skjelbred, 1986b; Henrikson et al., 1985; Seymour & Walton, 1984; Seymour et al., 1983b; Skjelbred & Lokken, 1982a), and the use of opioid analgesics is often associated with an increased degree of adverse effects (Chang et al., 2004; Breivik et
In this double-blind randomised controlled clinical trial, a combination of paracetamol with a corticosteroid is compared with an NSAID in controlling the postoperative sequelae following the surgical removal of mandibular third molars under local anaesthesia.

1.2. CHOICE OF THE MANDIBULAR THIRD MOLAR SURGERY MODEL

Patients undergoing the surgical removal of impacted mandibular molar teeth usually experience significant postoperative pain and swelling (Esen et al., 1999; Milles & Desjardins, 1993; Meechan & Seymour, 1993). These patients, therefore, present an ideal clinical experimental model to study the sequelae and compare the potential therapeutic effects of analgesics and anti-inflammatory drugs (Esen et al., 1999; Milles & Desjardins, 1993; Meechan & Seymour, 1993; Cooper & Beaver, 1976).

Further practical advantages of the mandibular third molar surgery model are that it is a relatively common procedure, of short duration, that is performed consistently on a regular basis in an outpatients setting. The procedure can be standardised without difficulty, and any variations between cases can be easily categorised and classified as shall be discussed in Chapter 4. Also the changes in the postoperative sequelae are relatively simple to determine and quantify (see Section 4.4). Very few procedures afford all these advantages, which further add to the value of this model in clinical pharmacology studies (Jackson, 1999; Meechan & Seymour, 1993).
1.3. CHOICE OF PARACETAMOL AND ITS DOSAGE REGIMEN

1.3.1. Choice of paracetamol as an analgesic

Paracetamol is a non-opioid analgesic similar in efficacy to aspirin, but has no or only minimal anti-inflammatory activity; it is indicated for mild to moderate pain and pyrexia, but it is less irritant to the stomach and for that reason is now generally preferred to aspirin (British Dental Association, 2002b). Paracetamol is very safe if used in therapeutic doses. Its favourable risk/benefit balance makes it a good analgesic for acute postoperative pain in dental patients. Paracetamol is devoid of the side effects that accompany NSAIDs. It is therefore also the analgesic of choice if there is a contraindication to an NSAID (Haas, 2002; Seymour & Walton, 1984).

Paracetamol has been used to reduce postoperative pain significantly in a number of studies using the mandibular third molar surgery model (Skjelbred, 1984; Forbes et al., 1984b; Seymour & Rawlins, 1981; Lokken & Skjelbred, 1980; Skjelbred & Lokken, 1979). In a more recent study paracetamol adequately relieved intense postoperative pain and a multiple dose regimen maintained adequate pain relief thereafter (Kubitzek et al., 2003).

Paracetamol has also proved capable of reducing postoperative swelling by about 30% when compared to aspirin in common analgesic doses (Skjelbred & Lokken, 1993). Lokken and Skjelbred measured significantly less swelling after mandibular third molar surgery when paracetamol was given; on the third day it averaged 71% of that with placebo. This reduction in postoperative swelling was
greater than the reduction previously obtained with ibuprofen using the same clinical model (Lokken & Skjelbred, 1980; Skjelbred & Lokken, 1979).

Other advantages of paracetamol are that it has no effect on bleeding time or platelet aggregation (Seymour et al., 1984) and that it has a tendency to reduce local inflammatory temperature increase and cause less postoperative bleeding (Lokken & Skjelbred, 1980). Paracetamol is, therefore, a recommendable option for reducing acute postoperative pain and swelling (Skjelbred & Lokken, 1993).

For this study, it was decided to use a paracetamol only preparation, as this is the most commonly used and widely available type, and because compound preparations contain other active ingredients, such as codeine that may induce more adverse effects but do not increase postoperative dental analgesia (Breivik et al., 1999; Campbell & Kendrick, 1991; Skjelbred & Lokken, 1982a).

1.3.2. **Choice of the paracetamol dosage regimen**

In adults, the optimum unit dose of paracetamol is 1g. The maximum daily dosage is 4g and this is consistent with the decline in analgesic activity, which is usually over 6 hours (Bannwarth & Pehourcq, 2003). Adequate postoperative pain relief with paracetamol may require doses as high as 1g four times daily (Lokken & Skjelbred, 1980). Seymour showed that a 1g dose is more effective than a 500mg dose for controlling postoperative pain immediately after surgery (Seymour, 1983).

In a study comparing a double dose 2g twice a day to a standard dose 1g four times a day, pain intensity scores indicated that the double dose regimen gave less analgesia toward the end of the dosing interval than the standard regimen.
For this study, it was therefore decided to use the standard maximum daily dosage regimen as in fact recommended in the provided package insert (GlaxoSmithKline Consumer Healthcare, 2000) and in the latest edition of the Dental Practitioners’ Formulary (British Dental Association, 2002b), that is, two 500mg tablets four times daily/every six hours (1g q.d.s).

1.4. CHOICE OF THE CORTICOSTEROID AND ITS DOSAGE REGIMEN

1.4.1 Choice of a corticosteroid

Although paracetamol was recommended as a good option for reducing acute postoperative pain and swelling (Skjelbred & Lokken, 1993), a number of other studies have shown that when administered alone, it is generally considered to be a weak analgesic and a poor anti-inflammatory agent following oral surgery (Seymour et al., 2003; Mehlisch et al., 1995; Forbes et al., 1990b; Forbes et al., 1989; Liashek, Jr. et al., 1987; Sunshine et al., 1986; Seymour & Walton, 1984; Seymour et al., 1983b), and may not be effective enough in sufficiently reducing third molar post-extraction pain in a number of patients (Jackson, 1999). Possibly, the main reason for the relatively poor efficacy of paracetamol in adequately controlling the pain, swelling and trismus experienced by patients following the surgical removal of mandibular third molars, is that local inflammation due to surgical tissue trauma lies at the origin of these common postoperative sequelae, and paracetamol lacks any significant anti-inflammatory effects (British Dental Association, 2002b; Rang et al., 1999a; Seymour et al., 1999d).
Theoretically, a reduction in the inflammatory sequelae of swelling and trismus should result in a reduction in pain and hence analgesic requirements (Baxendale et al., 1993). It was therefore decided to combine paracetamol with another drug with high anti-inflammatory and, possibly, also analgesic activity. Opioid analgesics and NSAIDs were excluded for reasons already mentioned (see sections 1.1 and 1.3.1) and because this study ultimately aims to find a better alternative to these drugs for use in oral surgery.

Corticosteroids have been particularly well studied because they are potent anti-inflammatory agents (Beirne & Hollander, 1986), and in fact they have also been extensively evaluated in the management of postoperative sequelae after third molar surgery (ElHag et al., 1985; von Graffenried et al., 1980).

The preoperative intravenous administration of 125mg methylprednisolone resulted in a significant decrease in oedema, trismus and pain on the second postoperative day, compared to placebo (Esen et al., 1999).

The administration of 32mg methylprednisolone twelve hours preoperatively and postoperatively, combined with the postoperative administration of 400mg ibuprofen on the day of the operation and on the first two postoperative days produced a clear reduction in postoperative pain and cheek swelling after impacted third molar removal (Schultze-Mosgau et al., 1995).

In a comparison of diclofenac with and without single-dose intravenous steroid to prevent postoperative pain after third molar removal, the administration of 40mg methylprednisolone and diclofenac resulted in greater pain relief than did administration of diclofenac alone (Hyrkas et al., 1993).

A 16mg dose of methylprednisolone the night before surgery, followed by a single intravenous dose of 20mg immediately preoperatively reduced facial swelling.
after the surgical removal of impacted third molars by 42% when compared with placebo. However, this dosing regimen did not sustain a meaningful reduction in facial swelling past the third postoperative day, nor did it significantly affect trismus or the need for postoperative pain analgesic medication during the week following surgery. According to the authors, the dose of corticosteroids used in this study to achieve a 42% reduction in postoperative swelling on the second day was considerably less than that used in previous studies, however they still suggest that that a sustained release formulation or a multi-day course may be preferable to sustain the effect on oedema formation (Milles & Desjardins, 1993).

In a study to evaluate the prevention of postoperative swelling and pain by dexamethasone after operative removal of impacted third molar teeth, the difference in the increase in cheek swelling on the first day after surgery was 54.3% as measured with a tape, 46% as measured with a gauge in the first molar area and 29% by sonographic measurement of the cheek diameter in the molar area. The limitation in the jaw opening was reduced by 17.7% after dexamethasone. Pain assessed by visual analogue scale was reduced by dexamethasone by 50% (Schmelzeisen & Frolich, 1993).

In a randomised double-blind study of fifty adult patients, a single dose of 8mg dexamethasone administered orally two hours preoperatively resulted in a significant reduction in pain four hours postoperatively, and eliminated the need for opioid analgesia in the postoperative period. The incidence of severe swelling was also reduced significantly but there was no effect on trismus when compared to placebo (Baxendale et al., 1993).

In a randomised, double-blind, placebo-controlled, within-subject study to quantify the effects of a preoperative dose of 4mg of dexamethasone given
intravenously, no difference in swelling and daily pain was noted, however, trismus and global pain were significantly reduced by the steroid (Neupert et al., 1992).

In a single-blind, controlled trial, the administration of dexamethasone 10mg both pre- and postoperatively resulted in a significant reduction in trismus and a mean reduction in swelling volume of 66% twenty-four hours after surgery when compared with placebo (ElHag et al., 1985).

Other studies have also demonstrated that the analgesic and anti-inflammatory action is potentiated when a corticosteroid like methylprednisolone is administered in combination with another analgesic like ibuprofen (Troullos et al., 1990; Sisk & Bonnington, 1985).

Holland performed a crossover study on twenty patients using 40mg of intravenous methylprednisolone immediately preoperatively. Holland reported a 56% reduction of swelling twenty-four hours later, with no difference at seven days. Pain was favourably affected by the steroid only on the first postoperative day. Trismus was not assessed (Holland, 1987).

The preoperative intramuscular administration of 80mg methylprednisolone led to a reduction in the incidence of wound oedema from 88.6% to 61.4% after the removal of impacted third molars and also produced a significant reduction in pain and swelling after Le Fort I osteotomy (Nordstrom & Nordstrom, 1987).

Beirne and Hollander used a single dose of 125mg of methylprednisolone intravenously immediately preoperatively. They reported a significant reduction in pain and swelling as assessed by photographic measurements, but no difference in the degree of trismus compared with the placebo group (Beirne & Hollander, 1986).

Bystedt and Nordenram investigated the use of oral methylprednisolone and its effects on postoperative sequelae. Their preoperative oral dose of 12mg was
followed with 12mg doses six and twelve hours later postoperatively, followed by 4mg three times a day for two days. This regimen demonstrated no statistically significant differences between study and control groups two, five, and seven days postoperatively in respect to oedema, trismus, or pain (Bystedt & Nordenram, 1985).

In an evaluation of methylprednisolone and flurbiprofen for inhibition of the postoperative inflammatory response, corticosteroid pre-treatment did not result in significantly greater analgesia than placebo. The percentage change in measured facial width was significantly less seventy-two hours postoperatively in the corticosteroid group (Sisk & Bonnington, 1985).

In a randomised, placebo-controlled, double-blind trial, evaluating the efficacy of single doses of preoperative methylprednisolone acetate 80mg and postoperative aspirin 1000mg and ibuprofen 400mg together with codeine phosphate 30mg, pre-treatment with the corticosteroid produced no significant difference in the postoperative pain scores in each treatment group. Similarly, swelling did not differ significantly between treatment groups, but patients pre-treated with methylprednisolone had a significantly reduced period of postoperative trismus (Mitchell et al., 1985).

The administration of methylprednisolone alone in orthodontic operations has produced a significant reduction in swelling (Schaberg et al., 1984).

Skjelbred and Lokken administered 40mg of intravenous methylprednisolone two hours after surgery. They reported a 46% reduction in swelling compared with placebo on day three and a 60% reduction on day six (Skjelbred & Lokken, 1983). In two other studies, Skjelbred and Lokken evaluated the effects of 9mg intramuscular betamethasone given at different perioperative times. Immediate preoperative administration produced a 55% reduction of swelling on day three and a 69%
reduction of swelling on day six (Skjelbred & Lokken, 1982c). When the same regimen was administered three hours postoperatively a swelling reduction of 47% on day three and 14% on day six was reported (Skjelbred & Lokken, 1982b).

Huffman compared single doses of 40mg and 125mg of methylprednisolone to intravenous placebo immediately preoperatively. Huffman’s clinical assessment of postoperative oedema revealed a statistically significant reduction in oedema both 24 and 48 hours postoperatively; no difference between the 40mg and 125mg doses was reported. Huffman did not record postoperative pain or trismus (Huffman, 1977).

Messer and Keller removed a single mandibular third molar under local anaesthesia after injecting 4mg dexamethasone into the masseter muscle immediately beforehand. Using the patients as their own controls, subsequent extractions were associated with a 50% reduction in swelling and trismus, and a 30% reduction in pain in the dexamethasone group when assessed forty-eight hours postoperatively. No correlation was found between degree of swelling and trismus or postoperative pain (Messer & Keller, 1975).

Hooley and Francis, in a double-blind trial found that oral betamethasone 1.2mg prior to operation, then 1.2mg four times daily for three days reduced oedema, pain, and trismus following third molar removal (Hooley & Francis, 1969).

As can be noted from the above review of the relevant literature, corticosteroids are potent inhibitors of inflammation, and they have been widely used in different routes and regimens to lessen the inflammatory sequelae after oral surgery. Based on these studies, the use of perioperative corticosteroids appears to be a rational method for reducing postoperative complications of oedema and possibly trismus and pain following the surgical removal of mandibular third molars (Alexander & Thrandson, 2000; Esen et al., 1999; Gersema & Baker, 1992; Montgomery et al.,

However, widespread acceptance of their use in oral surgery has been impaired due to some inconsistent findings regarding their efficacy and potential side effects (Esen et al., 1999), the advent of newer NSAIDs (Neupert et al., 1992), and because recommendations for their use are rarely accompanied by definitive guidelines regarding the type of steroid, dosage, or duration of administration (Alexander & Throndonson, 2000).

Overdosage or prolonged use may exaggerate some of the normal physiological actions of corticosteroids leading to undesirable side-effects, most of which are relative to their mineralocorticoid activity and/or chronic dosing regimens (British Dental Association, 2002a; Montgomery et al., 1990). However, in most studies no clinically apparent infection, disturbance of wound healing, or other corticosteroid-related complications were noted, and significant suppression of the hypothalamus-pituitary-adrenal (HPA) axis and endogenous cortisol production can be largely excluded with short-term administration (Esen et al., 1999; Neupert et al., 1992; Gersema & Baker, 1992; Montgomery et al., 1990).

1.4.2. Choice of dexamethasone

Currently there are many corticosteroids to choose from, with different potencies, biological half-lives, and glucocorticoid and mineralocorticoid effects (Table 1.1). Hydrocortisone (cortisol) is the standard against which the clinical pharmacological properties of the various corticosteroids are judged. Since the isolation and early use of hydrocortisone as an anti-inflammatory drug, many synthetic
agents have been developed which are more potent, have longer acting anti-inflammatory activity, and elicit fewer undesirable mineralocorticoid side-effects (British Dental Association, 2002a; Alexander & Thondson, 2000; Neupert et al., 1992; Beirne, 1992; Montgomery et al., 1990).

<table>
<thead>
<tr>
<th>Corticosteroid</th>
<th>Equivalent dose (mg)</th>
<th>Anti-inflammatory potency</th>
<th>Sodium-retaining potency</th>
<th>Plasma half-life* (minutes)</th>
<th>Biological half-life* (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>betamethasone</td>
<td>0.60-0.75</td>
<td>25</td>
<td>0</td>
<td>100-300</td>
<td>36-72</td>
</tr>
<tr>
<td>cortisone</td>
<td>25</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>8-12</td>
</tr>
<tr>
<td>deflazacort</td>
<td>6</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>dexamethasone</td>
<td>0.75</td>
<td>30</td>
<td>0</td>
<td>100-300</td>
<td>36-72</td>
</tr>
<tr>
<td>hydrocortisone</td>
<td>20</td>
<td>1</td>
<td>1-2</td>
<td>90</td>
<td>8-12</td>
</tr>
<tr>
<td>methylprednisolone</td>
<td>4</td>
<td>5</td>
<td>0.5</td>
<td>180-200</td>
<td>12-36</td>
</tr>
<tr>
<td>prednisolone</td>
<td>5</td>
<td>4</td>
<td>0.8-1.0</td>
<td>200</td>
<td>12-36</td>
</tr>
<tr>
<td>prednisone</td>
<td>5</td>
<td>3.5</td>
<td>0.8-1.0</td>
<td>60-200</td>
<td>12-36</td>
</tr>
<tr>
<td>triamcinolone</td>
<td>4</td>
<td>5</td>
<td>0</td>
<td>300</td>
<td>18-36</td>
</tr>
</tbody>
</table>

*plasma half-life is the time it takes for the plasma level to reach 50% of its initial concentration; whereas the biological half-life is the time it takes a measured metabolic activity to decrease to half its initial level.

Table 1.1. Properties of various corticosteroids.

High anti-inflammatory (glucocorticoid) activity, minimal mineralocorticoid activity and extended biological activity are the desirable characteristics in selection of the appropriate corticosteroid for use in oral surgery (Montgomery et al., 1990).

In comparing the relative potencies of corticosteroids in terms of their anti-inflammatory effects it should be borne in mind that high glucocorticoid activity in itself is of no advantage unless it is accompanied by relatively low mineralocorticoid activity (British Dental Association, 2002a).

The synthetic glucocorticosteroids dexamethasone and methylprednisolone have been used extensively in oral surgery for their active anti-inflammatory and low mineralocorticoid effects. In this study, dexamethasone was chosen because of its higher potency, lower sodium-retaining ability, and longer half-life (Neupert et al., 1992; Beirne, 1992; Montgomery et al., 1990). Theoretically, this drug should block
all aspects of the inflammatory response, thus leading to a reduction in swelling and trismus and therefore a reduction in pain. Favourable clinical impressions have resulted in the drug being widely used, but better confirmation of its efficacy by well-controlled studies is still required (Baxendale et al., 1993).

1.4.3. Choice of the dexamethasone dosage regimen

The next step was to determine an appropriate dosage regimen of dexamethasone for this study. Unlike for paracetamol there was no single recommended optimal dosage regimen for dexamethasone. Various investigators have used different dosage regimens with greater or lesser success and the latest edition of the Dental Practitioners’ Formulary (British Dental Association, 2002a) describes a usual range of 0.5-10mg daily without specifying a particular indication. The package insert provided by the manufacturer (Medochemie Ltd, 2003) recommends to use the lowest possible dosage adequate to control the disease process and quotes an initial dose varying from 0.5-9mg a day, followed by one to two 0.5mg tablets twice a day, depending on the disease process being treated.

In determining an optimal dosage regimen for this study a number of issues derived from the literature review and some points of practical significance were taken into consideration.

Higher doses should yield more satisfactory results and generally speaking, for inflammation to be suppressed, exogenous corticosteroids must be administered in doses exceeding the normal amounts of cortisol released, which ranges from physiological levels of about 30mg up to a daily maximum output of 300mg during periods of physiological stress (Gersema & Baker, 1992; Montgomery et al., 1990).
This range is equivalent to 1.125-11.250mg of dexamethasone. In fact, in a study by Bystedt and Nordenram, oral methylprednisolone 12mg (equivalent to 2.25mg dexamethasone) preoperatively, followed by 12mg doses six and twelve hours later postoperatively, then by 4mg (equivalent to 0.75mg dexamethasone) three times a day for two days, demonstrated no statistically significant differences between study and control groups two, five, and seven days postoperatively with respect to oedema, trismus, or pain (Bystedt & Nordenram, 1985).

In a later study, Milles and Desjardins administered only a slightly greater dose of 16mg methylprednisolone the night before surgery, followed by a single intravenous dose of 20mg immediately preoperatively, corresponding to only 3mg and 3.75mg of dexamethasone respectively. They claimed that the dose of corticosteroid used in their study to achieve a 42% reduction in postoperative swelling on the second day after the surgical removal of impacted third molars, was considerably less than that used in most previous studies (Milles & Desjardins, 1993).

Also, the Dental Practitioners’ Formulary recommends gradual withdrawal of systemic corticosteroids in patients receiving the equivalent of 40mg prednisolone (i.e. 6mg dexamethasone) daily (British Dental Association, 2002a). This is undesirable as it adds greater complexity and difficulty with respect to patient instruction and compliance.

Therefore for this study a dose of 4mg dexamethasone daily was chosen. This dose lies within the dosage range suggested in the manufacturer’s instructions (Medochemie Ltd, 2003) and in the Dental Practitioners’ Formulary (British Dental Association, 2002a); it should be high enough to yield a satisfactory result and is possibly the lowest possible dosage to adequately do so. Also Messer and Keller
recorded no side effects when up to 12mg of dexamethasone were administered (Messer & Keller, 1975).

Swelling in patients treated with steroids does not appear to peak until the third day after surgery and rebound swelling can occur if the duration of use of the corticosteroids is inadequate; therefore it is important to maintain levels of short-duration steroid formulations for more than one day (Alexander & Thronson, 2000; Milles & Desjardins, 1993; Neupert et al., 1992; Montgomery et al., 1990; Koerner, 1987; Schaberg et al., 1984). In the study by Milles and Desjardins, described earlier, the dosage regimen used did not sustain a meaningful reduction in facial swelling past the third postoperative day, nor did it significantly affect trismus or the need for postoperative pain analgesic medication during the week following surgery. They in fact suggest that that a sustained release formulation or a multi-day course may be preferable to sustain the effect on oedema formation (Milles & Desjardins, 1993). Hyrakas et al. also state that more effective resumption of normal masticatory function would probably require repeated corticosteroid administration or the use of a longer-acting compound (Hyrkas et al., 1993).

In a similar study, the duration of postoperative oedema averaged 5.3 days in a group of oral surgery patients treated with oral dexamethasone pre- and postoperatively versus 7.5 days in a control group that was not receiving corticosteroids (Sisk & Bonnington, 1985). It was therefore decided to use multi-day therapy in this study and administer all the drugs for seven consecutive days, that is, from the day of the operation till the day the sutures were to be removed. This does not exceed the three week maximum period beyond which administration of systemic corticosteroids should be withdrawn gradually (British Dental Association, 2002a).
Considering that 0.5mg dexamethasone tablets were used in this study, it was decided to conveniently divide the daily 4mg dose into 1mg four times daily, so as to simply instruct the patients in the study group to take two tablets of each drug (i.e. 2×500mg paracetamol and 2×0.5mg dexamethasone) every six hours (q.d.s).

1.5. **CHOICE OF THE NSAID AND ITS DOSAGE REGIMEN**

1.5.1 Choice of an NSAID

In order to properly assess the therapeutic value of the paracetamol and corticosteroid combination, this study required the use of a control group. Although placebos were extensively used in previous studies of this kind (see sections 1.3 and 1.4), such an option was not even considered for this study. It was thought to be unacceptable for ethical reasons to deprive patients of postoperative analgesia following this kind of surgery. Also, as previously discussed, there have been a large number of studies demonstrating the effectiveness of various drugs in controlling the postoperative sequelae following oral surgery. Therefore, the aim of this study was primarily to find a suitable alternative when the more effective and popular drugs, for example the NSAIDs (see below), are contraindicated, and possibly to demonstrate the potential superiority of the paracetamol and corticosteroid combination over what is currently considered to be the best common practice. Hence the control drug selected for this study should be a good analgesic and anti-inflammatory agent that is very commonly used after oral surgery.

In surgery, NSAIDs have been shown to be effective analgesics, as judged by either a reduction in pain scores and/or by an opioid sparing effect. Some NSAIDs
alone, notably diclofenac and ketorolac, may be adequate or even preferred analgesic agents after minor surgery. In oral surgery, NSAIDs produce greater initial analgesia than steroids and NSAID pre-treatment also results in suppression of swelling compared with placebo (Mather, 1992).

NSAIDs have been demonstrated to be particularly effective for relief of pain following third molar removal (Amin & Laskin, 1983; van der Zwan J. et al., 1982; Cooper et al., 1979; Henrikson et al., 1979; Lokken et al., 1975). NSAIDs have been shown to be more useful in this situation than combined dextropropoxyphene and paracetamol (Rosen et al., 1985), and in another similar study the preoperative administration of 50mg diclofenac relieved pain and swelling more than placebo (Lin et al., 1996).

Preoperative administration of NSAIDs has also been demonstrated to suppress pain postoperatively in comparison with aspirin, paracetamol, paracetamol plus codeine, and paracetamol plus oxycodone (Troullos et al., 1990). Other investigators who used NSAIDs for the prevention of pain after surgical procedures demonstrated the superiority of 400mg ibuprofen over 600mg paracetamol (Forbes et al., 1990b), 650mg acetylsalicylic acid (Brogden, 1986; Forbes et al., 1984a), and 30mg codeine phosphate (Frame et al., 1989).

Amin and Laskin reported that the NSAID indometacin, administered both preoperatively and postoperatively, resulted in a decrease in objectively evaluated facial swelling forty-eight hours postoperatively compared to a paracetamol and codeine combination (Amin & Laskin, 1983). Petersen in another comparison of indometacin and placebo treatment, reported reduction in post-extraction pain and trismus with indometacin (Petersen, 1975). LaDow and Henefer also compared indometacin, administered preoperatively and for three days postoperatively, with a
placebo. Post-extraction oedema, pain, trismus, and local tenderness were all reduced by the NSAID treatment (LaDow & Henefer, 1966). Skjelbred and Lokken, in a comparison of the NSAID phenazone with placebo, reported that both oedema and pain were reduced by treatment with the NSAID (Skjelbred & Lokken, 1980).

Postoperative administration of NSAIDs has also been shown to result in postoperative analgesia superior to that achieved with opioid analgesics administered either preoperatively or postoperatively (Dionne et al., 1983; Dionne & Cooper, 1978). It is assumed that this analgesic effect is due partly to the anti-inflammatory activity of the NSAIDs (Sisk & Bonnington, 1985).

In a comparison of NSAIDs ibuprofen and flurbiprofen, with methylprednisolone and placebo for acute pain, swelling and trismus, Troullos et al. showed that the NSAIDs produced suppression of swelling in comparison with placebo, and greater initial analgesia than the corticosteroid (Troullos et al., 1990). In a similar study, the NSAID flurbiprofen, given preoperatively in a 50mg dose, resulted in significantly less pain than the intravenously administered corticosteroid methylprednisolone or than placebo. This study also showed that NSAIDs may provide better pain relief than corticosteroids (Sisk & Bonnington, 1985).

1.5.2 Choice of diclofenac sodium

Diclofenac sodium is the most commonly prescribed non-steroidal anti-inflammatory drug worldwide (Chang et al., 2002). Studies indicated that diclofenac sodium can be recommended for the prophylaxis of swelling and pain resulting from dental procedures (Mayer & Weiss, 1980) and in a fixed dosage it offers an effective solution against such postoperative sequelae (Henrikson et al., 1985). In a study using
the third molar surgery model, Hyrkas et al. commented that pain levels with diclofenac sodium were so low that it was very difficult to achieve lower values (Hyrkas et al., 1993).

Comparisons with other NSAIDs or with opioid analgesics, demonstrate that symptom relief with diclofenac sodium was either comparable to or better than that obtained with these agents (Kantor, 1986). In one study, patients receiving the NSAID tenoxicam experienced significantly more pain than those receiving diclofenac sodium (Roelofse et al., 1993). Even with respect to recovery in postoperative trismus, diclofenac sodium revealed a statistically significant advantage over another NSAID such as tiaprofenic acid (van der Westhuijzen et al., 1994).

Therefore diclofenac sodium provides a suitable control for this study, in that it should effectively manage the postoperative sequelae following the surgical removal of mandibular third molars in the control subjects, and it is a very popular gold-standard against which the paracetamol and corticosteroid combination can be compared.

1.5.3. Choice of the diclofenac sodium dosage regimen

The generally recommended dosage of diclofenac sodium in the Dental Practitioner's Formulary (British Dental Association, 2002c) and in the package insert provided by the manufacturer (Mepha Ltd, 1999) is 75-150mg daily in two to three divided doses. However, for an NSAID to have both a lasting analgesic and anti-inflammatory effect, as would be desirable following the surgical removal of mandibular third molars, full regular dosage is recommended (British Dental Association, 2002c). Therefore for this study the usual maximum daily dose of 150mg was chosen. As recommended, this was divided into three 50mg doses per day, to be
taken 8-hourly (t.d.s.). Such a dosage regimen was used successfully in a number of similar studies (Chang et al., 2004; Lin et al., 1996; Roelofse et al., 1996; Bakshi et al., 1994; Bailey et al., 1993; Ahlstrom et al., 1993; Roelofse et al., 1993; Kantor, 1986; Henrikson et al., 1985; Hultin & Olander, 1978). As was decided for the paracetamol and corticosteroid combination, the diclofenac sodium tablets were to be taken for the seven consecutive days from the day of the operation till the day the sutures were to be removed.

1.6. TIMING AND ROUTE OF ADMINISTRATION

1.6.1. Timing of the first dose

With respect to the time of administration of the first dose of both paracetamol and glucocorticosteroids, almost the same reductions were recorded in swelling and pain whether the drug was administered prior to surgery or two to three hours afterwards (Skjelbred & Lokken, 1993). Therefore, it was empirically decided to start administration of these drugs just before the operation. This was done mainly for convenience and to demonstrate to patients exactly how many tablets they had to take each time they were to take the drugs.

This was also the case with the diclofenac sodium, which when tested in patients undergoing third molar extractions in a double-blind, randomised, cross-over, trial, did not show any differences between pre- and postoperative oral administration, in pain scores and mouth opening observed for one week after the operation (Bridgman et al., 1996).
1.6.2 Route of administration

Selecting a route of administration can be influenced by both operator/patient convenience and operator experience. In most instances, parenteral dosing must be restricted to the immediate pre- and postoperative periods. The intravenous route offers instantaneous blood levels, but requires provider expertise and additional armamentarium. The intramuscular route may permit the use of repository drug forms; however, operator experience, patient discomfort, and added armamentarium may be hindrances. The convenience of oral dosing has general appeal with both operators and patients and although patient compliance must be relied upon for it to be effective (Montgomery et al., 1990), it was chosen for all the drugs used in this study. This spared patients the discomfort associated with injections and let them take the drugs unassisted at home for a whole week, enabling the repeated dosing required to maintain adequate blood levels during the postoperative period (Esen et al., 1999).

1.7. Measurement tools

In this section, the rationale behind the methodologies used for determining pain, facial swelling and trismus are explained.
1.7.1. Pain

Out of the many pain measurement instruments available, the visual analogue scale (VAS) appears to fulfil most of the properties of the ideal pain measurement system proposed by Gracely and Dubner (Gracely & Dubner, 1981).

The VAS has the advantage of simplicity (Ong & Seymour, 2004). It is widely used and independent of language (Ong & Seymour, 2004). It is easily understood by most patients and can be readily reproduced on successive presentations (Ong & Seymour, 2004). It is sensitive to pharmacological and non-pharmacological procedures which alter the experience of pain (Seymour, 1982; Joyce et al., 1975). A major advantage of the VAS is its ratio scale properties and so may be treated as such statistically (Price et al., 1994). In contrast to many other pain measurement tools, equality of ratios is implied, making it appropriate to speak meaningfully about percentage differences between VAS scores obtained either at multiple points in time, or from independent samples of subjects (Ong & Seymour, 2004). The VAS has a high number of response categories, making it potentially more sensitive to changes in pain intensity than measures with limited numbers of response categories (Seymour, 1982; Downie et al., 1978; Joyce et al., 1975).

The addition of descriptions along the length of the line may affect the distribution of results, causing the majority of the results to be grouped around the descriptions and so reducing the sensitivity of the scale (Ong & Seymour, 2004; Scott & Huskisson, 1976). The plain unmarked line VAS running from left to right is recommended as the most unbiased pain scale (Carlsson, 1983; Scott & Huskisson, 1976), and is probably the most reliable and sensitive tool for measuring pain (Ong & Seymour, 2004). In fact visual analogue scales have be used for the assessment of pain.
in a number of similar studies (Schultze-Mosgau et al., 1995; Berge & Boe, 1994; Baxendale et al., 1993; Hyrkas et al., 1993; Troullos et al., 1990; Berge, 1989; Berge, 1988; Mitchell et al., 1985; Sisk & Bonnington, 1985).

1.7.2. Swelling

Clinical observation and subjective scoring of facial swelling has been a common method for assessing drug effect in the impacted mandibular third molar model (Berge & Boe, 1994; Baxendale et al., 1993; Berge, 1989; Berge, 1988; Huffman, 1977; Messer & Keller, 1975). However, quantitative measurement of facial swelling is required to evaluate the effectiveness of a drug in an objective manner (Esen et al., 1999; Breytenbach, 1978). Various devices such as callipers (Breytenbach, 1978), lateral plates (Cameron, 1980), facebows (Troullos et al., 1990; Beirne & Hollander, 1986; Sisk & Bonnington, 1985; Holland, 1979; Lokken et al., 1975), photographs (Beirne & Hollander, 1986; Van Gool et al., 1975; Hooley & Francis, 1969), stereo-photographs (Pedersen & Maersk-Moller, 1985; Dixon & Newton, 1972), ultrasound (Esen et al., 1999; Schultze-Mosgau et al., 1995; Wilson & Crocker, 1985), a facial plethysmograph (Milles & Desjardins, 1993; Milles et al., 1985), and a facial oedemometer (ElHag et al., 1985), have all been used by different investigators to quantify facial swelling. In general these methods are too complex and expensive for routine postoperative use to check the progress of swellings (Schultze-Mosgau et al., 1995).

Invasive and potentially harmful computerised axial tomographic scan techniques (Esen et al., 1999; Schaberg et al., 1984) have also been used but are
difficult to justify in clinical trials requiring clinical observations (Milles & Desjardins, 1993).

No technique has proved superior or more accurate in analysing swelling (Neupert et al., 1992). The desire to include a large number of patients and the practicality of a low-cost reliable technique made linear measurements a feasible choice (Neupert et al., 1992). Determination of facial swelling using various adaptations of the measuring tape method was used in a number of similar studies (Schultze-Mosgau et al., 1995; Neupert et al., 1992; Mitchell et al., 1985). This method is non-invasive, cheap, quick, highly reproducible and easy to use.

1.7.3. Trismus

The direct linear measurement of maximum interincisal distance is the most commonly used method for determining drug effect on trismus (limitation of opening) in the impacted mandibular third molar model (Esen et al., 1999; Schultze-Mosgau et al., 1995; Baxendale et al., 1993; Hyrkas et al., 1993; Milles & Desjardins, 1993; Neupert et al., 1992; Troullos et al., 1990; Beirne & Hollander, 1986; Mitchell et al., 1985; ElHag et al., 1985; Såsk & Bonnington, 1985). Maximum mouth opening by the patient, taken as the maximum distance between the upper and lower central incisors (interincisal distance), can be measured directly. Trismus or limitation of opening is then calculated by subtracting the postoperative maximum interincisal distance from a preoperative baseline value.
1.8. Aims of the study

The aim of this double-blind randomised controlled clinical trial was to evaluate a combination of paracetamol and dexamethasone against diclofenac sodium, in controlling the postoperative pain, swelling and trismus following the surgical removal of mandibular third molars under local anaesthesia. The purpose for such a study was to find an alternative drug regimen for the control of the common postoperative sequelae of oral surgery, especially for those patients in whom the usual drug regimens (e.g. NSAIDs) are contraindicated. This may also obviate the need for the common hospital practice to admit patients overnight in order to allow parenteral administration of opioid analgesia if necessary, thus containing healthcare costs and avoiding opioid-associated adverse effects. Following a literature review, it was determined that such a study has not been published to date.
CHAPTER 2

THE PHARMACOLOGY OF INFLAMMATION AND PAIN
2. **The Pharmacology of Inflammation and Pain**

2.1. **The Pharmacology of Inflammation**

2.1.1. **Introduction**

Inflammation is a complex process that can be defined as 'the reaction of the vascular and supporting elements of a tissue to injury, and results in the formation of a protein-rich exudate, provided the injury has not been so severe as to destroy the area'.

The clinical features that accompany inflammation have been known since antiquity. They include pain, swelling, alteration of function, redness and heat. Inflammation is under the control of a variety of endogenous biochemical mediators produced at or near the site of injury. The biochemical and pharmacological properties of these mediators and their roles in inflammation will be considered in this section (Seymour *et al.*, 1999c).

2.1.2. **The Eicosanoids**

The term eicosanoids has been used to denote the metabolites of certain 20-carbon polyunsaturated fatty acids, mainly arachidonic acid. These precursors can be converted into compounds that act as regulators and mediators of the functions of various cells.

Many different products of arachidonic acid metabolism have been identified, but they can be conveniently divided into two main groups on the basis that they are ultimately derived from the action of one of two enzymes systems (cyclo-oxygenase
and lipoxygenase) on arachidonic acid (Fig. 2.1).

Cyclo-oxygenase products can be further subdivided into three groups – the prostaglandins, the thromboxanes, and prostacyclin. Lipoxygenase products consist mainly of the leukotrienes and various compounds based on eicosatetraenoic acid (Seymour et al., 1999c).

![Figure 2.1. The metabolic pathways of arachidonic acid and the synthesis of the eicosanoids (reproduced from Seymour et al., 1999c)](image)

2.1.2.1. Arachidonic acid

This is a 20-carbon polyunsaturated fatty acid. It has been suggested that there are two sources – the metabolic pool and the cell membrane pool. The endogenous synthesis of arachidonic acid appears to be from the metabolic pool by metabolism of dietary linoleic acid, whereas stimulated synthesis (for example after trauma) comes from the cell membrane pool. The membrane pool seems to be the major source of the eicosanoid precursor in inflammation.
In most cells and tissues it is thought that phospholipids are the major source of arachidonic acid. The first step in eicosanoid synthesis is the liberation of arachidonic acid from cell membrane phospholipids (phosphate fraction) by the action of a group of enzymes known as the phospholipases. In particular, phospholipase A2 is responsible for the bulk of arachidonic acid synthesis (Seymour et al., 1999c).

2.1.2.2. Cyclo-oxygenase products – the prostanoids

The next step in the formation of cyclo-oxygenase products is the action of the enzyme cyclo-oxygenase (COX) on free arachidonic acid. This action results in the insertion of two oxygen molecules into the fatty-acid carbon chain to form prostaglandin G2 (PGG2), which is rapidly transformed by the peroxidase-like activity of cyclo-oxygenase into the hydroxyperoxide prostaglandin H2 (PGH2). Following this, and depending on the particular cell and circumstances involved, one or more of the three groups of prostanoids – the prostaglandins, thromboxane, or prostacyclin – may be formed (Seymour et al., 1999c).

The cyclo-oxygenase enzyme exists in more than one form. COX-1 is a constitutive enzyme expressed in most cells, whereas COX-2 is induced by various cytokines and growth factors. Cytokine-induced COX-2 activity is suppressed by glucocorticosteroids and thus may account for some of the anti-inflammatory properties of these drugs. COX-2 also differs in its sensitivity to inhibition by other anti-inflammatory agents. Selective inhibition of COX-2 may be of clinical significance, especially in the propagation of dental pain. This enzyme is probably involved in prostaglandin production at the site of inflammation (e.g. a third molar tooth socket during and after extraction), but not at other sites such as the
gastrointestinal tract. Thus inhibition of COX-2 may be anti-inflammatory without the unwanted effects of gastric irritation (Seymour et al., 1999c).

A third variant of the cyclo-oxygenase enzyme has been identified. COX-3 is selectively inhibited by analgesic and antipyretic drugs such as paracetamol and phenacetin, and is potently inhibited by some non-steroidal anti-inflammatory drugs. It seems likely that inhibition of COX-3 could represent a primary central mechanism by which these drugs decrease pain and possibly fever (Senior, 2002).

Further enzyme activity (thromboxane synthetase and prostacyclin synthetase) on PGH₂ results in the formation of thromboxane A₂ (TXA₂) and prostacyclin (prostaglandin I₂; PGI₂). The main synthesis of thromboxane occurs in platelets, whereas prostacyclin is synthesised in vessel walls. Thromboxane A₂ plays an important role in platelet aggregation. Prostacyclin is a potent vasodilator and acts as an antagonist of platelet aggregation. Thromboxane A₂ and prostacyclin are therefore biologically opposite poles of the mechanism for regulating the platelet-vessel-wall interaction and the formation of a haemostatic plug. Both thromboxane A₂ and prostacyclin are unstable, with very short half-lives. Thromboxane A₂ is broken down to thromboxane B₂, whereas prostacyclin is further metabolized to 6-keto-PGF-la (Seymour et al., 1999c).

2.1.2.3. Lipoxygenase products – the leukotrienes

The action of the lipoxygenase enzyme system on arachidonic acid forms a range of hydroperoxyeicosatetraenoic acids (HPETEs), which may then be reduced to form the corresponding hydroxyeicosatetraenoic acids (HETEs). The leukotrienes are derived from 5-lipoxygenase acting on arachidonic acid to form 5-HPETE, which may
then be reduced to 5-HETE or rearranged to form lipoteichoic acid A₄ (LTA₄). LTA₄ can be hydrolysed enzymatically to produce LTB₄, or non-enzymatically to produce various di-HETEs. Alternatively, LTA₄ may undergo nucleophilic attack by glutathione to produce LTC₄ from which LTD₄ and LTE₄ are generated (Seymour et al., 1999c).

### 2.1.2.4. The role of eicosanoids in inflammation

An inflammatory response is always accompanied by the release of eicosanoids. In areas of acute inflammation PGE₂ and PGI₂ are generated by the local tissues and blood vessels, and mast cells release PGD₂. In chronic inflammation, cells of the monocyte-macrophage series also release PGE₂ and TXA₂ (Rang et al., 1999b).

PGE₂, PGI₂ and PGD₂ are powerful vasodilators in their own right and synergise with other inflammatory vasodilators such as histamine and bradykinin. It is this combined dilator action on precapillary arterioles which contributes to the redness and increased blood flow in areas of acute inflammation. These prostanoids do not directly increase the permeability of the postcapillary venules, but they potentiate this effect of histamine and bradykinin. Similarly, they do not themselves produce pain, but potentiate the effect of bradykinin by sensitising afferent C fibres. The anti-inflammatory effects of the NSAIDs are due largely to prevention of these actions of the prostaglandins (Rang et al., 1999b). PGE₁ appears to regulate the function of B lymphocytes and to inhibit the production and release of lymphokines from sensitised T lymphocytes (Seymour et al., 1999c).

Prostaglandins of the E series are also implicated in the production of fever and there is evidence that the increase in temperature generated by endogenous fever-
inducing cytokines is mediated by PGE$_2$. The antipyretic action of NSAIDs is due partly to inhibition of the synthesis of PGE$_2$ in the hypothalamus (Rang et al., 1999b).

Leukotriene B$_4$ is a powerful chemotactic attractant for polymorphonuclear leucocytes (PMNs) and other white blood cells. Leukotrienes C$_4$ and D$_4$ have a potent action on the endothelial lining of the postcapillary venules and cause leakage of plasma proteins and oedema formation (Seymour et al., 1999c).

2.1.3. Platelet-activating factor

Platelet-activating factor (PAF), which is also variously termed PAF-acether or acetyl-glyceryl-ether-phosphorylcholine (AGEPC), is a biologically active lipid which can produce effects at exceedingly low concentrations. The name platelet-activating factor is misleading, since PAF has actions on a variety of different target cells and is believed to be an important mediator in both acute and persisting allergic and inflammatory phenomena. PAF is derived from its precursor, acyl-PAF, by phospholipase A$_2$ activity, resulting in lyso-PAF which is then acetylated to give PAF, which in turn can be deacetylated to lyso-PAF. PAF is generated and released from most inflammatory cells when these are stimulated. Thus it is released from neutrophil polymorphs on phagocytosis of opsonised particles, from activated macrophages and eosinophils, from mast cells and basophils on interaction with antigen and from platelets on stimulation with thrombin (Rang et al., 1999b).
2.1.3.1. The role of PAF in inflammation

Acting on specific receptors, PAF has a wide range of pathophysiological actions and is capable of producing many of the phenomena of inflammation. In doses of 0.02-200 pmol injected locally, it produces not only local vasodilatation and thus erythema, but also increased vascular permeability and wheal formation. Higher doses produce hyperalgesia. It is a potent chemotaxin for neutrophils, eosinophils and monocytes and it can also activate phospholipase A2 with generation of eicosanoids. On platelets, it causes shape change and the release of the contents of dense granules and of α1 and α2 granules. This effect is associated with metabolism of arachidonic acid and thromboxane A2 generation and is important in haemostasis and thrombosis (Rang et al., 1999b).

2.1.4. Bradykinin and kallidin

These two kinins are polypeptides formed from the plasma α2-globulins by a complex series of proteolytic reactions. The precursors of bradykinin and kallidin (lysyl-bradykinin) are high and low molecular weight kininogens, respectively. Low molecular weight kininogen can be activated by tissue kallikrein which can be activated by a variety of factors, including the Hageman factor (factor XII) in the blood clotting cascade, and plasmin. Bradykinin and kallidin have very short half-lives (t₁/₂ 15s) and are inactivated by carboxypeptidases (kinases I and II) and angiotensin-converting enzyme (Seymour et al., 1999c).
2.1.4.1. The role of bradykinin and kallidin in inflammation

Both bradykinin and kallidin are potent vasodilators and increase capillary permeability, leading to oedema formation. In this respect, bradykinin is approximately ten times more active than histamine on a molar basis. The effects of the kinins, including bradykinin, are mediated by receptors designated B₁ and B₂. The B₂ receptors mediate most of the pharmacological activities of bradykinin and kallidin. Trauma appears to increase the rate of formation of B₁ receptors (Seymour et al., 1999c).

2.1.5. Histamine

This vasoactive amine is found in most tissues of the body, but the major source is the granules of mast cells. Histamine is formed by the decarboxylation of the amino acid histidine. Trauma, either mechanical or chemical, causes the release of histamine from the mast cells into the extracellular fluid. Once released, histamine is rapidly metabolised by one of two enzyme systems (histamine-N-methyltransferase or diamine oxidase) to metabolites with little or no pharmacological activity.

Many of the properties of histamine are related to its action on smooth muscles, including relaxation of the vascular smooth muscle and contraction of the bronchi and gut wall. It is also a very potent stimulus to secretion of the exocrine glands, particularly those in the gastric mucosa. Histamine also has a direct effect on free nerve endings and is important in the production of pain and itch. There is also evidence that histamine may function as a neurotransmitter in the central nervous system (CNS), being involved in the control of thirst, the secretion of anti-diuretic
hormone, the control of blood pressure, and pain perception (Seymour et al., 1999c).

2.1.6. 5-hydroxytryptamine

5-hydroxytryptamine (5-HT or serotonin) is an amine formed by the hydroxylation of tryptophan, which is then decarboxylated to form 5-HT. After release, 5-HT is oxidised by monoamine oxidases. The enterochromaffin cells of the gastric mucosa are the main storage site of 5-HT, and high concentrations are found in platelets.

The role of 5-HT in inflammation is uncertain and may be insignificant. However, it has a wide and variable range of pharmacological properties that not only vary between species but also in the same individual. An important property of 5-HT is its effect on blood vessels – dilatation of arteries and constriction of veins. These effects are mediated via receptors, of which seven main types and several subtypes have been isolated (Seymour et al., 1999c).

2.1.7. Complement

The complement system consists of a series of proteins that react in a cascade fashion. One stimulus for the cascade reaction is the combination of antigen with antibody on a cell surface (this is known as the classical pathway). An alternate pathway can be triggered by bacterial toxins or large polysaccharides.

Fragments produced during the complement cascade are important in the inflammatory process. Fragments C3a and C5a induce the release of histamine from mast cells which causes increased capillary permeability. Other components of the
complement cascade are chemotactic to white blood cells (C5a, C5b, C567 complex) and enhance phagocytosis (C3b, C5b). Damage to cell membranes followed by cell lysis occurs when factors C8 and C9 are activated (Seymour et al., 1999c).

2.1.8. Interleukins

Interleukins (IL) are cytokines released from macrophages and lymphocytes during inflammation and the immune response. At least sixteen interleukins have been identified: referred to as interleukins 1-16. They are mainly involved in communication between lymphocytes. Interleukin-1 is produced by macrophages whilst processing antigen. It exerts a number of inflammatory actions, which include the stimulation of prostaglandin and collagenase production, chemoattraction for white blood cells, and enhancement of the hepatic synthesis of acute-phase proteins (Seymour et al., 1999c).

2.2. THE PHARMACOLOGY OF PAIN

2.2.1. Introduction

There is no single nerve pathway that is devoted exclusively to transmitting and processing information concerned with pain. The detection and signalling of tissue damage or nociception (from the Greek nocere, to damage) plays a primary role in protecting the organism. It is hardly surprising that such a system is elaborate and uses complex neural pathways, both excitatory and inhibitory. Some of the inhibitory pathways include feedback loops which can reduce pain (Seymour et al., 1999b).
2.2.2. Peripheral mediators of pain

When tissue is damaged either as a result of an infection, trauma, or an operative procedure, an inflammatory response is initiated. As a consequence, various cytokines and other inflammatory mediators are released from circulating leucocytes and platelets, by vascular endothelial cells, from mast cells, and other immune cells present in the tissues and from the nerve fibres themselves. The various mediators considered to be hyperalgesic include serotonin, adenosine, histamine, bradykinin, interleukins, nerve growth factor, substance P and the metabolites of arachidonic acid.

Arachidonic acid is derived from cell-membrane phospholipids by the action of the enzyme phospholipase A2. This enzyme is activated by trauma or infection. Once released, arachidonic acid is acted on by two further enzyme systems. Cyclooxygenase activity results in the formation of prostaglandins, thromboxane, and prostacyclin, whereas lipo-oxygenase activity results in the production of the leukotrienes (Seymour et al., 1999b).

2.2.2.1. Prostaglandins

Prostaglandins of the E series (e.g. PGE2) are particularly associated with the production of pain that accompanies trauma, infection, and injury. Intravenous and intramuscular injections of prostaglandins of the E series cause headache and long-lasting pain, respectively. The intradermal administration of histamine, bradykinin, or PGE2 produces pain of short duration, but only PGE2 causes hyperalgesia. Histamine, bradykinin, or PGE2 do not produce pain when given singly via the subcutaneous route. However, the addition of PGE2 to bradykinin or to histamine is overtly painful,
whereas the further addition of bradykinin or histamine is not. In areas already
sensitised by prostaglandins, subsequent infusions of bradykinin or histamine cause
pain. These findings suggest that prostaglandins, particularly of the E series, are able
to sensitise nociceptors to both chemical and mechanical stimulation.

Initially, it was thought that prostaglandins lowered the threshold of the
polymodal nociceptors of C fibres. However, it is now speculated that distinct
prostaglandin receptors may exist in a variety of tissues. The interaction between
PGE\textsubscript{2} and polymodal nociceptors on C fibres may be due to a direct binding of these
agonists to receptors on the free nerve fibre. Such binding may alter the sensitivity of
the nerve ending to other mediators of pain and inflammation, notably histamine and
bradykinin (Seymour \textit{et al.}, 1999b).

2.2.2.2. Leukotrienes

An intradermal injection of leukotriene B\textsubscript{4} (LTB\textsubscript{4}) decreases the mechanical
and thermal thresholds for nociception. The mode of action of LTB\textsubscript{4} in sensitising
nerve fibres appears to be similar to that produced by PGE\textsubscript{2}. LTB\textsubscript{4} causes the release
from polymorphonuclear leucocytes of a compound identified as 8R, 155-
dihydroxyeicosatetraenoic acid. This compound also decreases the mechanical and
thermal thresholds of C-fibre mechanonoceptors and produces mechanical
hyperalgesia. Another leukotriene, LTD\textsubscript{4}, can also sensitise sensory neurones
indirectly by stimulating the synthesis and release of other leukotrienes and
prostaglandins (Seymour \textit{et al.}, 1999b).
2.2.2.3. 5-hydroxytryptamine

5-hydroxytryptamine (5-HT or serotonin) is an amine that is released from platelets and mast cells during tissue damage. When 5-HT is applied to raw skin (e.g. a blister base) is causes a mild and transient pain. This is due to activation of 5-HT\textsubscript{3} receptors found on some small-diameter neurones. In addition, 5-HT also sensitises free nerve endings to the nociceptive actions of bradykinin (Seymour \textit{et al.}, 1999b).

2.2.2.4. Adenosine triphosphate and adenosine

Adenosine triphosphate (ATP) is present in all cells and when released by tissue damage it can act on the surrounding cells including the sensory neurones. An intradermal injection of micromolar concentrations of ATP produces a sharp, transient pain. This action is thought to be due to an opening of ion channels permeable to both Na\textsuperscript{+} and Ca\textsuperscript{2+}. Adenosine, the breakdown product of ATP, can also produce hyperalgesia. The mechanisms of action of adenosine are not well understood, but are thought to be due to a direct effect on sensory neurones (Seymour \textit{et al.}, 1999b).

2.2.2.5. Histamine

This is a vasoactive amine released from mast cells when subjected to either mechanical or chemical trauma. In general, low concentrations of histamine induce itch, whereas higher concentrations produce pain. The mechanism of histamine-induced pain is uncertain. Some sensory neurones possess H\textsubscript{1} receptors. Activation of these receptors increases membrane Ca\textsuperscript{2+} permeability (Seymour \textit{et al.}, 1999b).
2.2.2.6. Bradykinin

Bradykinin is a polypeptide formed from plasma $\alpha_2$-globulins by a complex series of proteolytic reactions. It is one of the most potent endogenous pain-producing (algogenic) substances released during inflammation. Bradykinin directly stimulates nociceptive nerve terminals and also sensitises them to other stimuli including those of a mechanical and chemical nature. There is also synergism between the excitatory action of bradykinin and other endogenous mediators associated with pain (e.g. prostaglandins and 5-HT). The pharmacological effects of bradykinin are mediated via two main classes of bradykinin receptor, $B_1$ and $B_2$. The $B_2$ receptors are the most pharmacologically active. When bradykinin activates a $B_2$ receptor on nerve fibres, an inward (depolarising) current is generated which results in an increase in membrane conductance to sodium ions (Seymour et al., 1999b).

2.2.2.7. Interleukins

A variety of cytokines (interleukins, interferons, tumour necrosis factor) are released by phagocytic and various immunocompetent cells. These molecules have a variety of fundamental functions in the inflammatory responses. They can also influence the activity of sensory neurones, probably by indirect routes. For example, interleukin-1$\beta$ (IL-1$\beta$) and interleukin-6 (IL-6) can stimulate the release of prostaglandins. Thus, these cytokines enhance the important relationship between pain and inflammation (Seymour et al., 1999b).
2.2.2.8. Nerve growth factor

Nerve growth factor (NGF) is a neurotrophic factor, produced in limited amounts by a range of cell types (e.g. fibroblasts and Schwann cells). NGF may be of considerable importance in inflammatory pain. Animal studies have shown that an injection of NGF leads to increased sensitivity to noxious stimuli, whereas animals exposed to antibodies to NGF have a reduced response to painful and inflammatory stimuli. It also stimulates the release of histamine and leukotriene C₄ from human basophils. In inflammatory-induced hyperalgesia, there is likely to be a subtle interplay between the nerves, inflammatory cells, and resident tissue cells at sites of tissue damage. NGF may have a significant role in co-ordinating such interplay (Seymour et al., 1999b).

2.2.2.9. Substance P

This neurotransmitter (so-called because it is a powder) is located in 10-33% of dorsal root ganglion neurones and is transported to the peripheral primary afferent terminals. When released, it contributes to the inflammatory response by causing vasodilatation, increased vascular permeability, increased production and release of lysosomal enzymes, release of PGE₂, interleukins 1 and 6 (IL-1, and IL-6). Substance P does not have a direct effect on cutaneous nociceptors, but due to its pro-inflammatory effect it makes a significant contribution to hyperalgesia (Seymour et al., 1999b).
2.2.3. Central mediators of pain

Transmission of nociceptive information from the primary afferent neurone to secondary, tertiary, and higher order neurones is achieved by chemical transmitters called neurotransmitters. Knowledge of central neurotransmitters is still relatively sparse and they are under intense study; consequently the picture is in a state of flux. It has become clear that, at any particular synapse, two or more transmitters may be simultaneously released (co-release), each performing a particular role. The resultant effect is due to the blend of the pharmacological soup released from the nerve endings that act on the nerve membrane of the neurone with which the neurotransmitter is communicating. This may be the postsynaptic membrane of the nerve cell of the next order (for example, transmission from primary to secondary neurone) or it may be the adjacent presynaptic endings of a neurone whose nerve cell is in a remote site. The former is an example of a neurotransmitter acting as a direct link between two neurones; the latter is an example of a neurotransmitter modulating transmission at an adjacent synapse by altering the release of neurotransmitter(s) from its presynaptic endings (Seymour et al., 1999b).

2.2.3.1. Amino acids

Aspartate and glutamate are ubiquitous and excite most nerve cells in the dorsal horn. Therefore, they are unlikely to be involved exclusively in the transmission of nociceptive information; presumably they operate in conjunction with other neurotransmitters and neuromodulators. There is now strong evidence that these amino acids act on receptors specific for the exogenous chemical substance N-methyl-D-
aspartate (NMDA) and which are therefore called NMDA receptors. These are now thought to play an important role in chronic neuropathic pain including some forms of chronic orofacial pain, for example post-herpetic neuralgia of the face (Seymour et al., 1999b).

By contrast, γ-aminobutyric acid (GABA) and glycine are endogenous inhibitory amino acids. GABA probably acts as an important postsynaptic inhibitor of the cell bodies of second order neurones in the substantia gelatinosa. This explains the well-known phenomenon where rubbing a painful part of the body relieves the local pain. Rubbing stimulates tactile receptors and hence A nerve fibres. In turn, these probably activate an interneurone in the dorsal horn, which releases GABA. GABA inhibits firing of the second-order neurone, thereby blocking the onward transmission of nociceptive information to the brain (Duggan & Foong, 1985).

2.2.3.2. Enkephalins

These peptides were originally identified in pig brain extracts. Two structurally similar peptides were found — methionine enkephalin (Met-enkephalin) and leucine enkephalin (Leu-enkephalin) — each of which is derived by enzymatic cleavage from a larger and independent precursor, proenkephalin A (Hughes et al., 1975). It was then discovered that the Met-enkephalin amino-acid sequence is present in pituitary peptide, β-lipotropin, as residues 61-65. Soon afterwards, it was shown that the C-fragment of β-lipotropin (residues 61-91) interacts specifically with opioid receptors: it is now known as β-endorphin (Seymour et al., 1999b).

All these peptides have properties in common with morphine, such as production of analgesia, physical dependence and tolerance, and the contraction of
There is now evidence that the enkephalins are neurotransmitters of specific (enkephalinergic) nerve fibres in the brain that modulate sensory information pertaining to pain and emotional behaviour. Regional variations in enkephalin levels parallel the distribution of opioid receptors. The levels of enkephalins are highest in brain fractions that contain nerve terminals, and their concentration profile is similar to the distribution of opioid receptors (Akil et al., 1984). Opioid receptors are found throughout the central nervous system: there are high concentrations in the limbic system, the substantia gelatinosa, periaqueductal grey matter, the nucleus raphe magnus, the spinal nucleus of the fifth cranial nerve, and the thalamus. The receptors appear to be the site of action of these endogenous opioid peptides (Martin, 1983; Chang & Cuatrecasas, 1981).

2.2.3.3. Dynorphins

These may act as neurotransmitters or neurohormones; they are produced by enzymatic cleavage from the precursor, prodynorphin. The dynorphins are larger peptides than the enkephalins but their physiological role is uncertain (Seymour et al., 1999b).

2.2.3.4. Endorphins

There are at least four endorphins – peptides designated α-, β-, γ-, and δ-endorphins – of which β-endorphin is the most significant. All are derived by enzymatic cleavage from the precursor pro-opiomelanocortin, which is also the precursor for β-lipotropin and corticotropin.
The endorphins are neurohormones that are released into the bloodstream and have a variable duration of action. They are found mainly in the anterior pituitary gland, in the same cells as corticotropin and β-lipotropin. All these hormones are secreted in parallel during stress, possibly as an adaptive mechanism: the endorphins may help to relieve any pain might then incur (Seymour et al., 1999b).

2.2.3.5. Substance P

Substance P (so-called because it was a powder) is a polypeptide, discovered by von Euler and Gaddum in 1931. Evidence suggests that substance P is a neurotransmitter in small-diameter fibres, particularly C fibres. That substance P is specifically related to pain is indicated by the disappearance of nerve endings containing it (sited in the caudal division of the trigeminal nerve) after removal of tooth pulps in cats. The tooth pulp is innervated almost exclusively by pain fibres (Seymour et al., 1999b).

In general, endogenous opioid peptides suppress pain, whereas substance P promotes it (Sweet, 1980). However, application of substance P to exposed tooth pulp does not excite sensory neurones and its role in the pulp is still obscure. Substance P and enkephalins do interact: the release of substance P is inhibited not only by Met-enkephalin, but also by β-endorphin and morphine (Seymour et al., 1999b).
CHAPTER 3

DRUG PHARMACOLOGY
3. **DRUG PHARMACOLOGY**

3.1. **PARACETAMOL**

3.1.1. Introduction

Paracetamol (\(N\)-acetyl-\(p\)-aminophenol; acetaminophen) is the active metabolite of phenacetin, a so-called coal tar analgesic. Paracetamol is an effective alternative to aspirin as an analgesic-antipyretic agent; however, unlike aspirin, its anti-inflammatory activity is weak and thus it is not a useful agent to treat inflammatory conditions. Because paracetamol is well tolerated, lacks many of the side effects of NSAIDs, and is available without prescription, it has earned a prominent place as a common household analgesic. However, acute overdosage causes fatal hepatic damage, and the number of self-poisonings and suicides with paracetamol has grown alarmingly in recent years.

Acetanilide is the parent member of this group of drugs. It was introduced into medicine in 1886 under the name of Antifebrin by Cahn and Hepp, who had accidentally discovered its antipyretic action. However, acetanilide proved to be excessively toxic. In the search for less toxic compounds, para-aminophenol was tried in the belief that the body oxidised acetanilide to this compound. Toxicity was not lessened, however, and a number of chemical derivatives of para-aminophenol were then tested. One of the more satisfactory of these was phenacetin (acetophenetidin). It was introduced into therapy in 1887 and was extensively employed in analgesic mixtures until it was implicated in analgesic-abuse nephropathy. Paracetamol was first used in medicine by von Mering in 1893. However, it has gained popularity only since
1949, after it was recognized as the major active metabolite of both acetanilide and phenacetin (Insel, 1995).

### 3.1.2. Pharmacokinetics and metabolism

Paracetamol is rapidly and almost completely absorbed from the gastrointestinal tract. The concentration in plasma reaches a peak in 30 to 60 minutes, and the half-life in plasma is about 2 hours after therapeutic doses. Paracetamol is relatively uniformly distributed throughout most body fluids. Binding of the drug to plasma proteins is variable; only 20% to 50% may be bound at the concentrations encountered during acute intoxication. After therapeutic doses, 90% to 100% of the drug may be recovered in the urine within the first day, primarily after hepatic conjugation with glucuronic acid (about 60%), sulfuric acid (about 35%), or cysteine (about 3%); small amounts of hydroxylated and deacetylated metabolites also have been detected (Fig. 3.1). Children have less capacity for glucuronidation of the drug than do adults. A small proportion of paracetamol undergoes cytochrome P450-mediated N-hydroxylation to form N-acetyl-benzoquinoneimine, a highly reactive intermediate. This metabolite normally reacts with sulfhydryl groups in glutathione. However, after ingestion of large doses of paracetamol, the metabolite is formed in amounts sufficient to deplete hepatic glutathione; under these circumstances, reaction with sulfhydryl groups in hepatic proteins is increased and hepatic necrosis can result, perhaps in part as a result of intracellular accumulation of \( \text{Ca}^{2+} \), activation of \( \text{Ca}^{2+} \)-dependent endonuclease, and resultant DNA fragmentation (Rang et al., 1999a; Insel, 1995).
3.1.3. Pharmacodynamics and pharmacological properties

Paracetamol has both analgesic and antipyretic properties similar to those of aspirin; however, the drug has little or no anti-inflammatory action (Seymour et al., 1999d). The failure of paracetamol to exert significant anti-inflammatory activity may be attributed to the fact that it is only a weak inhibitor of cyclo-oxygenase in the presence of the high concentrations of peroxides that are found in inflammatory lesions (Marshall et al., 1987; Hanel & Lands, 1982). Further, paracetamol does not inhibit neutrophil activation as do other NSAIDs (Abramson & Weissmann, 1989). Neither the site nor the mechanisms of the analgesic action of paracetamol have been clearly established. Different workers have concluded that the site of action is purely peripheral, purely central, or both. It is very much less effective than aspirin as a
peripheral cyclo-oxygenase inhibitor, but has the same potency as aspirin in inhibiting brain prostaglandin synthetase. The antipyretic property of paracetamol probably has a similar mechanism to that of aspirin (Seymour et al., 1999d).

Single or repeated therapeutic doses of paracetamol have no effect on the cardiovascular and respiratory systems. Acid-base changes do not occur, nor does the drug produce the gastric irritation, erosion, or bleeding that may occur after administration of salicylates. Paracetamol has no effects on platelets, bleeding time, or the excretion of uric acid (Insel, 1995).

3.1.4. Adverse effects and overdose

Paracetamol has remarkably few unwanted effects and at normal therapeutic doses is probably the safest analgesic. Skin rashes and white blood cell disorders have occasionally been reported. However, the most serious problem with paracetamol is hepatotoxicity after overdose. At normal doses, paracetamol is broken down in the liver to metabolites that are normally innocuous. In overdose, one of the metabolites (probably \( N \)-acetyl-\( p \)-benzoquinone), which is usually reduced by conjugation with glutathione and then eliminated, accumulates and renders liver cells incapable of synthesising protein. Acute liver damage can occur after a single dose of 10-15g; a dose of 25g is invariably fatal. The problem of overdose is compounded by the absence of untoward effects in the first twenty-four hours after overdose, during which time serious and perhaps fatal liver damage will have occurred. The overdose victim may therefore take further tablets, but their relations or friends will have seen little obvious signs of illness and so may not seek help. Signs and symptoms of liver damage manifest themselves between two and six days after overdose. Jaundice and
coagulation disorders accompany the hepatotoxicity, which leads to coma and death (Rang et al., 1999a; Seymour et al., 1999d; Insel, 1995).

Early treatment is essential in paracetamol overdose. Gastric lavage followed by oral activated charcoal will prevent further absorption, provided it is in the first hour after dosage. If less than twelve hours have elapsed, then N-acetylcysteine is the treatment of choice. This can be given orally and treatment should continue until there is a significant reduction of plasma paracetamol concentrations. Minimal hepatic damage can be anticipated when the plasma concentration is less than 120μg/mL at 4 hours, or 30μg/mL at twelve hours after ingestion. N-acetylcysteine conjugates with the metabolite, protecting the liver cells from further damage. If the patient is seen after twenty-four hours, the success of treatment depends on the magnitude of the initial overdose. If large quantities of paracetamol have been consumed, the patient will suffer a slow and distressing death (Rang et al., 1999a; Seymour et al., 1999d; Insel, 1995).

3.2. GLUCOCORTICOSTEROIDS

3.2.1. Introduction

There are two types of steroids synthesised in the adrenal cortex – the 19-carbon androgens and the 21-carbon corticosteroids. Both are derived from cholesterol. The 21-carbon corticosteroids can be further classified into: (1) glucocorticoids (hydrocortisone, also known as cortisol or corticosterone), because of their action on carbohydrate metabolism; and (2) mineralocorticoids (aldosterone), because of their effect on sodium retention. These actions are not mutually exclusive.
as glucocorticoids have considerable effects on electrolyte balance. Secretion of glucocorticoids is under the control of adrenocorticotrophic hormone (ACTH), whereas the secretion of mineralocorticoids is controlled by the renin-angiotensin system.

Corticosteroids, via an interaction with DNA-linked receptors, have a diverse range of properties and functions. They are involved in carbohydrate, fat, and protein metabolism; they affect electrolyte and water balance; and they are essential for the normal function of the cardiovascular system, kidney, skeletal muscle, and nervous system. They also enable the organism to withstand changes in the environment and cope with stressful events. The many different properties of the corticosteroids are due to their action on protein synthesis, especially DNA transcription and the production of specific proteins (Seymour et al., 1999a).

3.2.2. Pharmacological properties

The pharmacological actions of the glucocorticoids may be considered under three main headings (Rang et al., 1999c):

- General effects on metabolism, water and electrolyte balance and organ systems.
- Negative feedback effects on the anterior pituitary and hypothalamus.
- Anti-inflammatory and immunosuppressive effects.

3.2.2.1. General metabolic and systemic effects

The main metabolic effects are on carbohydrate and protein metabolism. The hormones cause both a decrease in the uptake and utilisation of glucose and an
increase in gluconeogenesis, resulting in a tendency to hyperglycaemia. There is a concomitant increase in glycogen storage which may be due to insulin secretion in response to the increase in blood sugar. There is decreased protein synthesis and increased protein breakdown, particularly in muscle. Glucocorticoids have a 'permissive' effect on the lipolytic response to catecholamines and other hormones, which act by increasing intracellular cyclic adenosine monophosphate (cAMP) concentration. Such hormones cause lipase activation through a cAMP-dependent kinase, the synthesis of which requires the presence of glucocorticoids. Large doses of glucocorticoids given over a long period result in the redistribution of fat characteristic of Cushing's syndrome. The glucocorticoids, in non-physiological concentrations, have some mineralocorticoid actions, causing sodium retention and potassium loss—possibly by occupying mineralocorticoid receptors. Glucocorticoids tend to produce a negative calcium balance by decreasing calcium absorption in the gastrointestinal tract and increasing its excretion by the kidney. This can result in osteoporosis (Rang et al., 1999c).

3.2.2.2. Negative feedback effects on the anterior pituitary and hypothalamus

Both endogenous and exogenous glucocorticoids have a negative feedback effect on the secretion of corticotrophin-releasing factor (CRF) and ACTH. Administration of exogenous glucocorticoids depresses the secretion of CRF and ACTH thus inhibiting the secretion of endogenous glucocorticoids and causing atrophy of the adrenal cortex. If therapy is prolonged, it may take many months to return to normal function when the drugs are stopped (Rang et al., 1999c).
3.2.2.3. Anti-inflammatory and immunosuppressive effects

When given therapeutically, glucocorticoids have powerful anti-inflammatory and immunosuppressive effects. They inhibit both the early and the late manifestations of inflammation, i.e. the initial redness, heat, pain and swelling, but also the later stages of wound healing and repair and the proliferative reactions seen in chronic inflammation. They affect all types of inflammatory reactions whether caused by invading pathogens, by chemical or physical stimuli or by inappropriately deployed immune responses such as are seen in hypersensitivity or autoimmune disease (Rang et al., 1999c).

In the early stages they reduce the capillary permeability caused by histamine and bradykinin, which in turn reduces oedema. They also inhibit both bradykinin formation and the migration of white blood cells into the site of inflammation. In its later stages, steroids reduce granulation tissue formation by inhibiting the proliferation of fibroblasts and blood vessels (Seymour et al., 1999c).

It is now established that steroids can affect eicosanoid synthesis by several possible mechanisms (Fig. 3.2). These include:

- Inhibition of the cyclo-oxygenase enzyme COX-2 by inhibiting transcription of the relevant gene.

- Inhibition of the transcription of the gene for the enzyme phospholipase A2. This enzyme acts on cell-membrane phospholipids and converts them to arachidonic acid.

- Corticosteroids also induce the formation of an anti-inflammatory protein known as lipocortin-1, which also has an inhibitory effect on phospholipase A2.
Other effects on the mediators of inflammatory and immune responses:

- Decreased production of platelet-activation factor.
- Decreased generation of cytokines – IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, TNF-γ, cell adhesion factors and granulocyte-macrophage-colony stimulating factor (GM-CSF) – due to inhibition of transcription of the relevant genes.
- Reduction in the concentration of complement components in the plasma.
- Decreased generation of induced nitric oxide.
- Decreased histamine release from basophils.
- Decreased IgG production.

Actions on inflammatory cells:

- Decreased egress of neutrophils from blood vessels and reduced activity of neutrophils and macrophages due to decreased transcription of the genes for cell adhesion factors and the relevant cytokines.
- Reduced clonal proliferation of T cells, mainly through decreased transcription of the genes for IL-2 and the IL-2 receptor and decreased action of cytokine-secreting T lymphocytes.
- Decreased fibroblast function and therefore less production of collagen and glycosaminoglycans; the contribution of these events to chronic inflammation is reduced but so also is healing and repair.
- Reduced function of osteoblasts and increased activity of osteoclasts – and thus a tendency to develop osteoporosis.
Figure 3.2. The effect of glucocorticosteroids on eicosanoid synthesis (adapted from Rang et al., 1999b).

These anti-inflammatory and immunosuppressive actions of the glucocorticoids have generally been considered to be ‘pharmaceutical’ actions only, i.e. to be qualitatively different from the physiological effects (namely the metabolic and regulatory actions) of endogenously produced glucocorticoids. It is now understood that the anti-inflammatory and immunosuppressive actions do have a physiological role in that they prevent ‘overshoot’ of the body’s powerful defence reactions, which might otherwise themselves threaten homeostasis (Munck et al., 1984).

The consequence of these powerful actions of the glucocorticoids is that they can be of great value when used to treat certain conditions in which there is hypersensitivity and unwanted inflammation, but they carry the hazard that they can suppress the necessary protective responses to infection and can decrease essential healing processes (Rang et al., 1999c).
3.2.3. Mechanism of action

Glucocorticoid effects involve interactions between the steroids and intracellular receptors that belong to the superfamily of receptors that control gene transcription. This superfamily also includes the receptors for mineralocorticoids, the sex steroids, thyroid hormones, vitamin D₃ and retinoic acid. There are believed to be 10-100 steroid-responsive genes in each cell.

The glucocorticoids, after entering cells, bind to specific receptors in the cytoplasm. These receptors, which have a high affinity for glucocorticoids, are found in virtually all tissues – about 3000 to 10 000 per cell, the number varying in different tissues. After interaction with the steroid, the receptor becomes ‘activated’, i.e. it undergoes a conformational change which exposes a DNA-binding domain. The steroid-receptor complexes form dimers (pairs), then move to the nucleus and bind to steroid-response elements in the DNA. The effect is either to repress (prevent transcription of) or induce (i.e. initiate transcription of) particular genes (Rang et al., 1999c).

Repression is brought about in part by inhibition of the action of various transcription factors such as AP-1 and NF-κB (Marx, 1995). These transcription factors normally switch on the genes for COX-2, various cytokines, and the inducible form of nitric oxide synthase. Basal and induced transcription of the genes for collagenase are modified and vitamin D₃ induction of the ostecalcin gene in osteoblasts is inhibited (Funder, 1997; Marx, 1995; Krane, 1993; Landers & Spelsberg, 1992).

Induction involves the formation of specific messenger RNAs, which direct the synthesis of specific proteins. In addition to the enzymes involved in their
metabolic action (e.g. the cAMP-dependent kinase), the glucocorticoids induce the formation of lipocortin-l, a member of the family of calcium-regulated phospholipid-binding proteins termed ‘annexins’. Lipocortin-l is important in the negative feedback action of glucocorticoids on the hypothalamus and anterior pituitary and has an anti-inflammatory effect by inhibiting phospholipase A2 (Rang et al., 1999c).

Much is now known about the anti-inflammatory and immunosuppressive actions of the glucocorticoids, but their metabolic actions are less well understood. Several relevant enzymes can be shown, in vitro, to be induced by glucocorticoids (e.g. the cAMP-dependent kinase), but these do not as yet explain all of the metabolic actions seen in vivo (Rang et al., 1999c).

3.2.4. Pharmacokinetics

Glucocorticosteroids may be given by a variety of routes. Most are active when given orally. Certain water-soluble esters of hydrocortisone and its synthetic congeners are administered intravenously to achieve high concentrations of drug rapidly in body fluids. More prolonged effects are obtained by intramuscular injection of suspensions of hydrocortisone, its congeners, and its esters. Minor changes in chemical structure may markedly alter the rate of absorption, time of onset of effect, and duration of action. Glucocorticosteroids may also be given topically, injected intra-articularly, given by aerosol into the respiratory tract, administered as drops into the eye or the nose, or applied in creams or ointments to the skin.

Following absorption, 90% or more of cortisol in plasma is reversibly bound to protein under normal circumstances. Only the fraction of corticosteroid that is unbound can enter cells to mediate corticosteroid effects. Two plasma proteins account
for almost all of the steroid-binding capacity: corticosteroid-binding globulin (CBG; also called transcortin), and albumin. CBG is an α-globulin secreted by the liver that has high affinity for steroids but relatively low total binding capacity, whereas albumin, also produced by the liver, has low affinity but relatively large binding capacity. At normal or low concentrations of corticosteroids, most of the hormone is protein-bound. At higher steroid concentrations, the capacity of protein binding is exceeded, and a significantly greater fraction of the steroid exists in the free state. Corticosteroids compete with each other for binding sites on CBG. CBG has relatively high affinity for cortisol and most of its synthetic congeners and low affinity for aldosterone and glucuronide-conjugated steroid metabolites; thus, greater percentages of these latter steroids are found in the free form.

All of the biologically active adrenocortical steroids and their synthetic congeners have a double bond in the 4,5 position and a ketone group at C 3. As a general rule, the metabolism of steroid hormones involves sequential additions of oxygen or hydrogen atoms, followed by conjugation to form water-soluble derivatives. Reduction of the 4,5 double bond occurs at both hepatic and extrahepatic sites, yielding inactive compounds. Subsequent reduction of the 3-ketone substituent to the 3-hydroxyl derivative, forming tetrahydrocortisol, occurs only in the liver. Most of these reduced steroids are conjugated through the 3-hydroxyl group with sulfate or glucuronide by enzymatic reactions that take place in the liver and, to a lesser extent, in the kidney. The resultant sulfate esters and glucuronides form water-soluble derivatives and are the predominant forms excreted in the urine. Neither biliary nor fecal excretion is of quantitative importance in human beings.

Although it is established that the specificity of steroid hormones is determined by interactions with their cognate steroid hormone receptors, recent studies
have revealed an important role for the steroid-metabolising enzyme 11β-
hydroxysteroid dehydrogenase in mineralocorticoid-responsive tissues. This enzyme
protects the mineralocorticoid receptor by oxidizing the 11-hydroxyl group of cortisol
to generate cortisone, an inactive metabolite. Synthetic steroids with an 11-keto
substituent, such as cortisone and prednisone, must be enzymatically reduced to the
corresponding 11β-hydroxy derivative before they are biologically active. This
reaction is carried out by a distinct 11β-hydroxysteroid dehydrogenase isozyme in the
liver that operates in a reductive mode; in settings where this enzymatic activity is
impaired, such as severe hepatic disease, it is prudent to use 11β-hydroxy steroids that
do not require enzymatic activation (such as cortisol and prednisolone) rather than
those that require metabolic conversion (Davis & Granner, 1995).

3.2.5. Adverse effects

Unwanted effects are likely to occur with large doses or prolonged
administration but should not occur with short-term or replacement therapy. These
effects are inherent in the three categories of pharmacological actions associated with
the drugs (Rang et al., 1999c):

- Suppression of the response to infection or injury: An intercurrent infection can be
  potentially very serious unless recognised and treated with antimicrobial agents
  along with an increase in the dose of steroid. Wound healing may be impaired, but
  peptic ulceration is probably not the problem it has been considered to be in the
  past, the incidence being only slightly higher in patients treated with steroids than
  in controls. However, patients on concurrent high doses of NSAIDs are more at
  hazard from peptic ulceration.
• **Suppression of the patients’ capacity to synthesise corticosteroids:** Sudden withdrawal of the drugs after prolonged therapy may result in acute adrenal insufficiency. Careful procedures for phased withdrawal should be followed. Recovery of full adrenal function usually takes about two months, though it can take eighteen months or more.

• **Metabolic effects:** When the drugs are used in anti-inflammatory and immunosuppressive therapy, the metabolic actions and the effects on water and electrolyte balance and organ systems are unwanted side-effects and iatrogenic Cushing's syndrome may occur.

    Osteoporosis, with the attendant hazard of fractures, is probably one of the main limitations to long-term glucocorticoid therapy. Glucocorticoids influence bone by regulation of calcium and phosphate metabolism and through effects on collagen synthesis by osteoblasts and collagen degradation by collagenase. Glucocorticoids modify transcription of the collagenase genes and inhibit vitamin D₃-mediated induction of genes in osteoblasts. Given long-term, glucocorticoids reduce the function of osteoblasts (which lay down bone matrix) and increase the activity of osteoclasts (which digest bone matrix). The effect on osteoclasts is indirect – through decreasing the intestinal absorption of calcium, resulting in increased parathormone secretion, which in turn stimulates these cells.

    The tendency to hyperglycaemia which occurs with exogenous glucocorticoids may develop into actual diabetes. Another limitation is the development of muscle wasting and weakness. In children, the metabolic effects (particularly those on protein metabolism) may result in inhibition of growth, even with fairly low doses, though this is not likely to occur unless treatment is continued for more than six months. A depressant effect on DNA synthesis and cell division in
some tissues may also be implicated in this effect. There is often euphoria, but some patients may become depressed or develop psychotic symptoms. An effect on the blood supply to bone can result in avascular necrosis of the head of the femur. The incidence of cataracts is higher after prolonged administration of the glucocorticoids in patients with rheumatoid arthritis, and cataracts have occurred in children as well. Other toxic effects that have been reported are glaucoma, raised intracranial pressure, hypercoagulability of the blood, fever and disorders of menstruation. Oral candidosis (thrush – a fungal infection) frequently occurs when glucocorticoids are taken by inhalation (Rang et al., 1999c).

3.2.6. Dexamethasone

Chemical modifications to the hydrocortisone (cortisol) molecule have generated derivatives with greater separations of glucocorticoid and mineralocorticoid activity; for a number of synthetic glucocorticoids, such as dexamethasone, the effects on electrolytes are minimal even at the highest doses used. In addition, these modifications have led to derivatives with greater potencies and with longer durations of action. However, because the anti-inflammatory and metabolic effects of glucocorticoids are mediated by the same glucocorticoid receptor, the various derivatives do not effectively separate anti-inflammatory effects from effects on carbohydrate, protein, and fat metabolism or from suppressive effects on the HPA axis.

The structures of hydrocortisone (cortisol) and dexamethasone are shown in figure 3.3. Differences in chemical structure may bring about changes in specificity and/or potency as a result of changes in affinity and intrinsic activity at corticosteroid
receptors, alterations in absorption, protein binding, rate of metabolic transformation, rate of excretion, or membrane permeability. The 4,5 double bond and the 3-keto group on ring A are essential for both glucocorticoid and mineralocorticoid activity; an 11β-hydroxyl group on ring C is required for glucocorticoid activity but not mineralocorticoid activity; a hydroxyl group at C 21 on ring D is present on all natural corticosteroids and on most of the active synthetic analogs and seems to be an absolute requirement for mineralocorticoid activity, but not glucocorticoid activity. The 17α-hydroxyl group on ring D is a substituent on cortisol and on all of the currently used synthetic glucocorticoids. While steroids without the 17α-hydroxyl group have appreciable glucocorticoid activity, the 17α-hydroxyl group gives optimal potency.

Introduction of an additional double bond in the 1,2 position of ring A, selectively increases glucocorticoid activity, resulting in an enhanced glucocorticoid to mineralocorticoid potency ratio. This modification also results in a compound that is metabolised more slowly than hydrocortisone.

Fluorination at the 9α position on ring B enhances both glucocorticoid and mineralocorticoid activity and possibly is related to an electron-withdrawing effect on the nearby 11β-hydroxyl group. When combined with the 1,2 double bond in ring A and other substitutions at C 16 on ring D, the 9α-fluoro derivative formed (i.e. dexamethasone) has even more marked glucocorticoid activity. These substitutions at C 16 also virtually eliminate mineralocorticoid activity (Davis & Granner, 1995).
Figure 3.3. Molecular structure of hydrocortisone and dexamethasone (adapted from Davis & Granner, 1995).

The pharmacokinetic and pharmacological properties of dexamethasone have already been discussed in section 1.4.1 (Table 1.1).

3.3. **Non-Steroidal Anti-Inflammatory Drugs**

3.3.1. **Introduction**

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely used of all therapeutic agents. They are frequently prescribed for musculoskeletal complaints and are often taken without prescription for various aches and pains. There are now more than fifty different NSAIDs on the market. Virtually all currently available NSAIDs can have significant unwanted effects, especially in the elderly. This situation is likely to improve as a result of recent research findings (Rang et al., 1999a).
3.3.2. Pharmacological actions

NSAIDs include a variety of different agents of different chemical classes. Most of these drugs have three major types of effect:

- *Anti-inflammatory effects*: modification of the inflammatory reaction.
- *Analgesic effect*: reduction of certain sorts of pain.
- *Antipyretic effect*: lowering of a raised temperature.

In general, all of these effects are related to the primary action of the drugs – inhibition of arachidonate cyclo-oxygenase (COX) and thus inhibition of the production of prostaglandins and thromboxanes – though some aspects of the action of individual drugs may occur by different mechanisms (Rang *et al.*, 1999a).

There is more than one type of COX enzyme. COX-1 is a constitutive enzyme expressed in most tissues, including blood platelets, and is involved in cell-cell signalling and in tissue homeostasis. COX-2 is induced in inflammatory cells when they are activated and the primary inflammatory cytokines – interleukin-1 and tumour necrosis factor-α – are important in this regard. Thus COX-2 is responsible for the production of the prostanoid mediators of inflammation (Vane & Botting, 1996). Most NSAIDs in current use are inhibitors of both these isoenzymes, though they vary in the degree of inhibition of each (Griswold & Adams, 1996). Clearly the anti-inflammatory action of the NSAIDs is mainly related to their inhibition of COX-2 and it is probable that, when used as anti-inflammatory agents, their unwanted effects are due largely to their inhibition of COX-1. The main pharmacological actions and the common side-effects of the NSAIDs are outlined below.
3.3.2.1. Antipyretic effect

Normal body temperature is regulated by a centre in the hypothalamus which ensures a balance between heat loss and heat production. Fever occurs when there is a disturbance of this hypothalamic ‘thermostat’ that leads to the set-point of body temperature being raised. NSAIDs reset the thermostat. Once there has been a return to the normal set-point, the temperature-regulating mechanisms (dilatation of superficial blood vessels, sweating, etc.) then operate to reduce temperature. Normal temperature is not affected by NSAIDs.

The mechanism of the antipyretic action of the NSAIDs is thought to be due largely to inhibition of prostaglandin production in the hypothalamus. During an inflammatory reaction, bacterial endotoxins cause the release from macrophages of a pyrogen – interleukin-1 (IL-1) – which stimulates the generation, in the hypothalamus, of E-type prostaglandins and these, in turn, cause the elevation of the set-point for temperature. There is some evidence that prostaglandins are not the only mediators of fever; hence NSAIDs may have an additional antipyretic effect by mechanisms as yet unknown (Rang et al., 1999a).

3.3.2.2. Analgesic effect

NSAIDs are mainly effective against pain associated with inflammation or tissue damage because they decrease production of the prostaglandins that sensitise nociceptors to inflammatory mediators such as bradykinin. Therefore they are effective in arthritis, bursitis, pain of muscular and vascular origin, toothache, dysmenorrhea, the pain of postpartum states, postoperative pain and the pain of
cancer metastases in bone – all conditions that are associated with increased prostaglandin synthesis. Their ability to relieve headache may be related to the abrogation of the vasodilator effect of prostaglandins on the cerebral vasculature.

There is some evidence that they have a central effect – by an action mainly in the spinal cord (Rang et al., 1999a).

3.3.2.3. Anti-inflammatory effects

As has been described in section 2.1, there are many chemical mediators of inflammation. Each facet of the response – vasodilatation, increased vascular permeability, cell accumulation, etc. – can be produced by several different mechanisms.

Drugs such as the NSAIDs reduce mainly those components of the inflammatory and immune response in which the products of COX-2 action play a significant part (Rang et al., 1999a), namely:

- Pain.
- Vasodilatation.
- Oedema (by an indirect action – the vasodilatation facilitates and potentiates the action of mediators such as histamine which increase the permeability of postcapillary venules).
3.3.3. Mechanism of action

The main action of NSAIDs is, as stated above, inhibition of arachidonate cyclo-oxygenase, as described originally by Vane in 1971. COX is a bifunctional enzyme, having two distinct activities – the main cyclo-oxygenase action (steps 1 and 2 in Fig. 3.4) which gives PGG\textsubscript{2}, and a peroxidase action which converts PGG\textsubscript{2} to PGH\textsubscript{2}. Different NSAIDs inhibit the enzyme by different mechanisms, but all act at the first of the two sites (Rang et al., 1999a).

![Figure 3.4. The inhibition of arachidonate cyclo-oxygenase by NSAIDs (adapted from Rang et al., 1999b).](image)

Other actions besides inhibition of cyclo-oxygenase may contribute to the anti-inflammatory effects of some NSAIDs. Reactive oxygen radicals produced by neutrophils and macrophages are implicated in tissue damage in some conditions, and NSAIDs that have particularly strong O\textsubscript{2}-radical-scavenging effects as well as cyclo-oxygenase inhibitory activity may decrease tissue damage (Rang et al., 1999a).
3.3.4. Adverse effects

NSAIDs are responsible for nearly a quarter of the adverse drug reactions reported officially in the United Kingdom, and they also feature in the reports of drug-related deaths. Although this may be partly because NSAIDs are used extensively in the elderly, the inherent toxicity of these drugs is clearly a contributory factor. When NSAIDs are used in joint diseases (which usually necessitate fairly large doses and long-continued use) there is a high incidence of side-effects – more particularly in the gastrointestinal tract but also in liver, kidney, spleen, blood and bone marrow (Rang et al., 1999a).

3.3.4.1. Gastrointestinal disturbances

Adverse gastrointestinal events are the commonest unwanted effects of the NSAIDs, the relative risk being on average three times that in the population of non-NSAID users. Common gastrointestinal side effects are dyspepsia, diarrhoea (but sometimes constipation), nausea and vomiting. It has been estimated that one in five chronic users of NSAIDs will have gastric damage, which can be silent but which carries a small but definite risk of serious haemorrhage and/or perforation. Patients using piroxicam have the highest risk of gastric bleeding; there is less risk with diclofenac, meloxicam and naproxen, less still with ibuprofen and least with nimuselide (Bateman, 1994).

NSAID-induced gastric damage is due mainly to the inhibition of COX-1 which is responsible for the synthesis of the prostaglandins that normally inhibit acid secretion, as well as having a protective action on the mucosa and modulating its
blood flow. Oral administration of prostaglandin analogues such as misoprostol can diminish NSAID-induced gastric damage (Rang et al., 1999a).

3.3.4.2. Skin reactions

Skin reactions are the second most common unwanted effects of NSAIDs, particularly with mefenamic acid (10-15% frequency) and sulindac (5-10% frequency). The type of skin condition seen varies from mild rashes, urticaria, and photosensitivity reactions to more serious and potentially fatal rare diseases (Rang et al., 1999b).

3.3.4.3. Adverse renal effects

Therapeutic doses of NSAIDs in healthy individuals pose little threat to kidney function, but in some, susceptible patients, they cause acute renal insufficiency, which is reversible on stopping the drug. The basis of this effect is the inhibition of the biosynthesis of those prostanoids, \( \text{PGE}_{2} \), \( \text{PGI}_{2} \) involved in the maintenance of renal blood dynamics, and more particularly in the \( \text{PGE}_{2} \)-mediated compensatory vasodilatation that occurs in response to the action of noradrenaline or angiotensin II. NSAIDs taken regularly in high doses over a long period can also cause 'analgesic nephropathy' which comprises chronic nephritis and renal papillary necrosis (De Broe & Elseviers, 1998).
3.3.4.4. Other unwanted effects

Other, much less common, unwanted effects of NSAIDs include bone marrow disturbances and liver disorders, the latter more likely if there is already renal impairment. NSAIDs (in particular, aspirin) may precipitate asthma in NSAID-sensitive asthmatic patients (Rang et al., 1999a).

3.3.5. Diclofenac

Diclofenac (Fig. 3.5) is a derivative of phenylacetic acid that shares all the pharmacological properties of the other NSAIDs. It has analgesic, anti-pyretic, and anti-inflammatory activities. Diclofenac is an inhibitor of cyclo-oxygenase, and its potency is substantially greater than that of indomethacin, naproxen, or several other agents. In addition, diclofenac appears to reduce intracellular concentrations of free arachidonic acid in leukocytes, perhaps by altering the release or uptake of the fatty acid (Seymour et al., 1999d; Insel, 1995).

Figure 3.5. Molecular structure of diclofenac (adapted from Insel, 1995).
Diclofenac is rapidly and completely absorbed after oral administration; peak concentrations in plasma are reached within two to three hours. Administration with food slows the rate but does not alter the extent of absorption. There is a substantial first-pass effect, such that only about 50% of diclofenac is available systemically. The drug is extensively bound to plasma proteins (99%), and its half-life in plasma is one to two hours. Diclofenac is metabolised in the liver by a cytochrome P450 isozyme of the CYP2C subfamily to 4-hydroxydiclofenac, the principal metabolite, and other hydroxylated forms; after glucuronidation and sulfation, the metabolites are excreted in the urine (65%) and bile (35%) (Insel, 1995).

Diclofenac produces side effects in about 20% of patients, and approximately 2% of patients discontinue therapy as a result. Gastrointestinal effects are the most common; bleeding and ulceration or perforations of the intestinal wall have been observed. Elevation of hepatic aminotransferase activities in plasma occurs in about 15% of patients. The elevations in aminotransferase usually are reversible and only rarely are associated with clinical evidence of hepatic disease. Other untoward responses to diclofenac include CNS effects, skin rashes, allergic reactions, fluid retention and edema, and rarely, impairment of renal function. The drug is not recommended for children, nursing mothers, or pregnant women (Insel, 1995).
CHAPTER 4

PATIENTS, MATERIALS AND METHOD
4. **Patients, Materials and Method**

4.1. **Introduction**

The study received ethical approval from the Research Ethics Committee of the University of Malta in March 2003 (see Appendix I) and was conducted in accordance with the Declaration of Helsinki (41st World Medical Assembly, 1989). The study was carried out at the Dental Outpatients Department, St. Luke’s Hospital, Gwardamangia, Malta and designed to fit within the usual operating procedures of the Department. The Dental Outpatients Department is the only state-funded institution where surgical removal of mandibular third molars is carried out and this type of treatment is covered by National Insurance at no cost to patients.

4.2. **Patient Selection – Inclusion and Exclusion Criteria**

Patients are usually referred to the Dental Department from Health Centres or private practices or may be self-referred. Patients are first assessed clinically and radiographically by means of an orthopantomograph (OPT) radiograph taken at the Department and are then given the next available appointment with one of the two oral surgeons on a Tuesday or Thursday morning.

All the booked patients were assessed for participation in the study. Stringent patient inclusion and exclusion criteria (Table 4.1 and Appendix III) were used in attempt to minimise the risk of confounding factors.
### Patient inclusion and exclusion criteria:

<table>
<thead>
<tr>
<th>Criteria</th>
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<tbody>
<tr>
<td>Presence of an impacted mandibular third molar indicated for removal</td>
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<tr>
<td>Recent (≤ 6 months) good quality OPT radiograph available</td>
</tr>
<tr>
<td>Adjacent fully erupted non-carious or restorable mandibular second molar present</td>
</tr>
<tr>
<td>Opposing maxillary third molar absent</td>
</tr>
<tr>
<td>Pell and Gregory relationships 1 or 2 and A or B</td>
</tr>
<tr>
<td>Patient is not pregnant and does not suffer from any medical condition</td>
</tr>
<tr>
<td>Patient is not taking any other medication</td>
</tr>
<tr>
<td>No contraindications to any of the drugs being used</td>
</tr>
<tr>
<td>Patient is able and willing to take the tablets as prescribed</td>
</tr>
<tr>
<td>Patient is able and willing to complete the pain chart and attend for all the follow-up visits</td>
</tr>
<tr>
<td>Patient has undergone a dental prophylaxis 1 week before the procedure</td>
</tr>
<tr>
<td>Any other dental treatment completed at least 1 week before the procedure</td>
</tr>
<tr>
<td>Patient did not experience any pain, swelling or infection in the week before the procedure</td>
</tr>
<tr>
<td>Patient has not taken any medication in the week before the procedure</td>
</tr>
<tr>
<td>No other procedure carried out on the day of the operation</td>
</tr>
<tr>
<td>Surgical procedure did not last more than 30 minutes</td>
</tr>
<tr>
<td>No intraoperative or immediate postoperative complications</td>
</tr>
<tr>
<td>Patient took drugs as instructed</td>
</tr>
<tr>
<td>Patient did not take any other medication in the week after the procedure</td>
</tr>
<tr>
<td>Patient complied with standard postoperative instructions</td>
</tr>
<tr>
<td>Healing took place uneventfully and with no postoperative complications</td>
</tr>
<tr>
<td>Patient attended for all the follow-up visits</td>
</tr>
</tbody>
</table>

*Table 4.1. Summary of patient inclusion and exclusion criteria.*

### 4.2.1. OPT radiograph

The consistency and availability of a recent (6 months) good quality OPT radiograph taken with the same radiographic machine (*Orthoralix S®*, Dentsply Italia srl, Divisione Gendex, Milan, Italy) and developed with the same developer (*Clarimat 300®*, Dentsply Italia srl, Divisione Gendex, Milan, Italy) under the same conditions was considered essential as this radiograph is the principle means by which an impaction is classified and by which the difficulty and complexity of the procedure is assessed. The impaction angle (Fig. 4.1), impaction type, number of roots, root
morphology (Fig. 4.2), the Pell and Gregory classification (see section 4.2.2) and the relationship with the inferior dental (alveolar) nerve (Fig. 4.3) of the mandibular third molar are determined from the OPT radiograph (Bell, 2004; Bell et al., 2003; Whaites, 1996). It is also the radiograph used by the oral surgeon as a guide while performing the procedure.

![Figure 4.1. Impaction angle of the mandibular third molar (reproduced from Whaites, 1996).](image)

![Figure 4.2. Root morphology of the mandibular third molar. (reproduced from Whaites, 1996).](image)
4.2.2. Pell and Gregory classification

The severity of the postoperative sequelae is directly related to the difficulty of the procedure. The impacted mandibular third molars were classified according the Pell and Gregory Classification (Table 4.2) (Peterson, 1998c).

<table>
<thead>
<tr>
<th>Pell and Gregory Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Relationship between the impacted third molar and the anterior part of the ramus of the mandible</strong></td>
</tr>
<tr>
<td><strong>Class 1</strong> <em>(Fig. 4.4)</em></td>
</tr>
<tr>
<td><strong>Class 2</strong> <em>(Fig. 4.5)</em></td>
</tr>
<tr>
<td><strong>Class 3</strong> <em>(Fig. 4.6)</em></td>
</tr>
</tbody>
</table>

Table 4.2. Pell and Gregory classification system (figures reproduced from Peterson, 1998c).
The first part of this method for classifying impacted mandibular third molars is based on the amount of impacted tooth that is covered with the bone of the mandibular ramus. This part of the classification refers to the Pell and Gregory Classes 1, 2 and 3. It should be obvious that the class 1 relationship will provide the greatest accessibility to the impacted tooth and therefore will be easiest to remove. The class 3 relationship provides the least accessibility and therefore presents the greatest difficulty.
The depth of the impacted tooth compared with the height of the adjacent second molar provides the other part of the classification system for determining the difficulty of impaction removal. This part of the classification system refers to the Pell and Gregory Classes A, B and C. In this classification the degree of difficulty is measured by the thickness of the overlying bone; that is, the degree of difficulty increases as the depth of the impacted tooth increases. As the tooth becomes less accessible and it becomes more difficult to section the tooth and to prepare points for elevation, the overall difficulty of the operation increases substantially.

In this study, the much more complex and rarer classes 3 and C were excluded. Any exceptionally simple cases that happened not to require the removal of bone during the procedure were also excluded. This was done to ensure similarity between cases, therefore consisting only of classes 1A, 1B, 2A and 2B, and requiring bone removal.

4.2.3. Duration

The difficulty of the procedure is also reflected in its duration (Hill & Walker, 2001; Pedersen, 1985), so it was decided to exclude all patients in whom the procedure lasted more than 30 minutes.

4.2.4. Adjacent mandibular second molar

The presence of the adjacent fully erupted non-carious or restorable mandibular second molar was also considered necessary as the absence of the second molar usually allows a more direct approach to the surgical site, necessitating no or
less bone removal and therefore a potentially less invasive and much simpler procedure.

4.2.5. Opposing maxillary third molar

The opposing maxillary third molar was required to be absent at the time of the procedure as its presence during the postoperative period could give rise to a confounding source of pain and swelling from the tooth biting directly on the inflamed surgical site and traumatising the flap. This tooth is usually absent, either having been extracted at an earlier occasion for other reasons or being congenitally missing or unerupted. However, if it was present and erupted, and without a valid reason for being retained it was extracted at least one week before the procedure.

4.2.6. Medical, behavioural and drug history

Eligible patients were also required to be in good health, not pregnant, not taking any medications or other drugs, and having no contraindication to any of the drugs being used in the study, and the ability to take the tablets as prescribed, complete the pain chart and attend for all the follow-up visits.

4.2.7. Oral hygiene

All participants were also booked for oral hygiene instructions and a dental prophylaxis with the same dental hygienist a week before the procedure so as ensure a similar good level of oral hygiene in all the study subjects.
4.2.8. **Other dental treatment**

If patients required any other dental treatment (except surgical removal of the contralateral mandibular third molar) this was completed at least a week before the procedure, so as to eliminate confounding sources of pain from untreated dental conditions or postoperatively from the treatment itself. Eligible contralateral mandibular third molars were included in the study as separate cases.

4.2.9. **Preoperative factors**

It was also decided from beforehand to exclude all patients that had experienced any pain, swelling or infection or had taken any medication in the week preceding the procedure.

4.2.10. **Complications, compliance and follow-up**

Patients who experienced any complications (Robinson, 2000a; Peterson, 1998a), required any additional medication, did not attend for all the follow-up visits, did not comply exactly with the postoperative instructions or did not take only the given drugs as instructed were also excluded.
4.3. **DRUGS USED**

For the study group, the 500mg paracetamol tablets used were *Panadol® Tablets*, (GlaxoSmithKline Consumer Healthcare, Brentford, UK, batch 4TP864) and the 0.5mg dexamethasone tablets used were *Dexamed® 0.5 tablets* (Medochemie Ltd, Limassol, Cyprus, lot 70422), while for the control group the 50mg diclofenac sodium tablets used were *Olsen®-50 Lactabs®* (Mepha Ltd, Aesch-Basel, Switzerland, batch 652495).

For all patients the 0.2% chlorhexidine gluconate mouthwash used was *Corsodyl Mouthwash®* (GlaxoSmithKline Consumer Healthcare, Brentford, UK) and the only type of anaesthetic used was *Lignospan special®* (Septodont, Saint-Maur-des-Fossés Cedex, France), a 2% lidocaine hydrochloride with adrenaline 1:80,000 local anaesthetic in 1.8mL dental cartridges.

4.4. **MEASUREMENTS**

In this section, the instruments and methods used for determining pain, facial swelling and trismus are explained.
4.4.1. Pain

The pain was recorded by the patients on a pain chart that consisted of twenty-one visual analogue scales. Each VAS consisted of an unmarked 100mm long horizontal line, the opposite ends of which were labelled ‘©’ and ‘®’ and explained to the patients as representing “no pain” and “unbearable pain” respectively (see Appendix III) (Ong & Seymour, 2004). Patients were asked to indicate which point on the line best represents their current pain intensity. The distance (from 0 to 100mm) from the ‘©’ end to the mark made by the patient measured with a ruler (to the nearest mm) was taken to be that patient’s pain score (from 0 to 100) (Fig. 4.10).

Fig. 4.10. Recording the patient’s pain scores from the pain chart.
4.4.2. Swelling

Facial swelling was determined by the same examiner measuring an easily reproducible facial dimension with a measuring tape (to the nearest mm), from the inferior-most point of attachment of the left ear lobe to the head, through a point known as point B or supramentale, that is the deepest point on the midline of the mandible between the lower lip and the chin point, to inferior-most point of attachment of the right ear lobe to the head (Fig. 4.11). For each record, measurements were repeated three times and the mean calculated. Values for facial swelling were obtained by subtracting the preoperative baseline facial dimension from the postoperative values.

![Fig. 4.11. Measuring facial swelling.](image)
4.4.3. Trismus

Maximum mouth opening by the patient, taken as the maximum distance between the upper and lower central incisors (interincisal distance), was measured with a simple purpose-built measuring device (to the nearest mm), by the same examiner. At each visit, measurements were repeated three times and the mean recorded. Trismus or limitation of opening was calculated by subtracting the postoperative maximum interincisal distances from the preoperative baseline value.

The measuring device was an equilateral triangular piece of flat Perspex with sides measuring 100mm. Two of the sides had identical 100mm scales along the edges, starting from the same angle. The triangle was placed between the patients’ upper and lower central incisors at the incisal interproximal point. The triangle was then tilted in the sagittal plane to obtain the same value at the point of contact of the incisors with both scales. This value was recorded as the interincisal distance (Fig. 4.12).

Fig. 4.12. Measuring trismus.
4.5. **Randomisation and Control**

The patients were randomly allocated into the study group and the control group (Fig. 4.13), by an independent assistant tossing a coin (Von Arx & Simpson, 1989).

*Figure 4.13. Patient selection and group allocation flowchart.*
4.6. **Double Blind Methodology**

A double-blind methodology was used. The tablets were not marked and the packs, containing the exact number of tablets for the seven days were only labelled with simple instructions on how to take the tablets (Fig. 4.14) so that none of the patients were in fact able to identify what they were given from the appearance or from the dosing regimen.

![The drug packaging used in the study.](image)

The oral surgeon and the examiner taking the measurements left the room while the nurse gave the tablets to the patients, and patients were instructed not to ever discuss their medications with the examiner or any other health professional, but to refer any later queries only to the oral surgeon or to the nurse involved with the study.
4.7. **Method**

The first dose of the drugs and a 1-minute preoperative mouthrinse with 10mL of the 0.2% chlorhexidine gluconate mouthwash were given to the patients by the nurse just before the examiner took the preoperative baseline measurements for mouth opening and facial dimension, and then the oral surgeon injected the local anaesthetic using a dental syringe. Local anaesthesia was achieved by inferior alveolar nerve block at the mandibular foramen and buccal infiltration using the minimum necessary number of whole cartridges of local anaesthetic (Robinson *et al.*, 2000). The number of cartridges of local anaesthetic solution administered was recorded.

The only treatment carried out on the day of the procedure was the surgical removal of one mandibular third molar. The mandibular third molars (Fig. 4.15) were all surgically removed using a standard aseptic technique (Hill & Walker, 2001; Robinson, 2000b; Peterson, 1998c; Koerner, 1994): access via a three-sided buccal mucoperiosteal flap (Figs. 4.16 and 4.17), protection of the lingual nerve with a periosteal elevator (Fig. 4.18), bone removal using stainless steel burs in a surgical slow-speed handpiece with sterile physiological saline irrigation (Figs. 4.19 and 4.20), tooth sectioning when required, elevation (Figs. 4.21 and 4.22), wound irrigation and closure with 3/0 black silk sutures (Figs. 4.23 and 4.24). No haemostatic agent or electrosurgery unit were used.
Figure 4.15. A partially erupted impacted mandibular third molar.

Figure 4.16. Cervical, mesial and distal incisions made.
Figure 4.17. Three-sided buccal mucoperiosteal flap raised.

Figure 4.18. Lingual flap raised and lingual nerve protected with a periosteal elevator.
Figure 4.19. Bone removed using stainless steel burs in a surgical slow-speed handpiece.

Figure 4.20. Bone removal completed.
Figure 4.21. Tooth elevated.

Figure 4.22. Tooth delivered.
Figure 4.23. Closure with 3/0 black silk sutures.

Figure 4.24. Wound closed primarily.
The duration of the procedure from the beginning of the first incision to the completion of the last suture was recorded by the nurse to the nearest minute. The side, impaction angle, impaction type, crown status, number of roots, root morphology, the Pell and Gregory Classification and the relationship with the inferior dental (alveolar) nerve of the mandibular third molar (see sections 4.2.1 and 4.2.2) were recorded (Bell, 2004; Bell et al., 2003; Whaites, 1996). Any immediate local and systemic complications were also noted.

Patients were given a pain chart and standard postoperative instructions by the examiner and then discharged. All patients were also instructed to rinse their mouth for one minute with one undiluted measure Corsodyl Mouthwash® (i.e. 10mL of 0.2% chlorhexidine gluconate solution) every 12 hours for 7 days (Hermesch et al., 1998; Peterson, 1998b; Ragno, Jr. & Szkutnik, 1991; Larsen, 1991; Larsen, 1990). No prophylactic antibiotics were prescribed (Peterson, 1998c; Seymour & Walton, 1984; Van Gool et al., 1977).

Patients were advised to rest and not to return to work before they had the sutures removed on the seventh postoperative day and were provided with a sick leave certificate when necessary.
4.8. **Follow-up**

The patients were reviewed on the second, fourth and seventh postoperative days (Table 4.3). This combination of days was chosen for practical reasons, that is, irrespective of whether the surgical procedure was carried out on a Tuesday or on a Thursday, and considering that the Dental Department does not open on Sundays. This combination of days allows for a sufficiently long and well-distributed follow-up of three visits throughout the seven days immediately following the procedure.

<table>
<thead>
<tr>
<th>Tuesday Patients</th>
<th>Day</th>
<th>Thursday Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1 week</strong></td>
<td><strong>Tuesday</strong></td>
<td><strong>1 week</strong></td>
</tr>
<tr>
<td><em>preoperatively</em></td>
<td></td>
<td><em>preoperatively</em></td>
</tr>
<tr>
<td>Dental prophylaxis.</td>
<td></td>
<td>Dental prophylaxis.</td>
</tr>
<tr>
<td><strong>Wednesday</strong></td>
<td></td>
<td><strong>Friday</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Saturday</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Sunday</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Day 1</strong></td>
</tr>
<tr>
<td><strong>Operation</strong></td>
<td><strong>Baseline facial swelling and trismus measurements taken preoperatively; pain chart given.</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Day 2</strong></td>
<td><strong>Wednesday</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Day 3</strong></td>
</tr>
<tr>
<td><strong>1st follow-up visit</strong></td>
<td><strong>Facial swelling and trismus measurements taken; pain chart checked.</strong></td>
<td><strong>Day 1</strong></td>
</tr>
<tr>
<td><strong>Day 3</strong></td>
<td><strong>Thursday</strong></td>
<td><strong>Day 2</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Saturday</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Day 5</strong></td>
<td><strong>Facial swelling and trismus measurements taken; pain chart checked.</strong></td>
<td><strong>Day 3</strong></td>
</tr>
<tr>
<td><strong>2nd follow-up visit</strong></td>
<td></td>
<td><strong>Day 4</strong></td>
</tr>
<tr>
<td><strong>Day 6</strong></td>
<td><strong>Department closed.</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Day 7</strong></td>
<td></td>
</tr>
<tr>
<td></td>
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<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Table 4.3. Follow-up schedule.*
During each visit values for mouth opening and facial swelling were recorded by the same examiner and the pain chart checked for proper completion. The pain was recorded by the patients on the pain chart 8-hourly for seven days, at 7.00am, 3.00pm and 11.00pm. On the day of the procedure only, patients were to record the first pain score immediately following full recovery of nerve sensation (usually one to three hours postoperatively), instead of at 7.00am (Mitchell et al., 1985). The 8-hourly scores were recorded, from which the daily means were then calculated.

At each visit the patients were also thoroughly assessed by the examiner who was a trained dental surgeon, so that any delayed local and systemic complications (Robinson, 2000a; Peterson, 1998a) as well as any adverse drug reactions could be noted. The sutures were removed by the examiner on the last visit, and the pain chart collected.
CHAPTER 5

RESULTS
5. **RESULTS**

5.1. **INTRODUCTION**

The results were processed using SPSS® 12.0 for Windows® statistical analysis software (SPSS Inc., Chicago, USA) and Microsoft® Excel 2002 SP3 spreadsheet software (Microsoft Corporation, Redmond, USA) on a Fujitsu Siemens Amilo D 1840W computer (Fujitsu Siemens Computers GmbH, Munich, Germany) running Microsoft® Windows® XP 2002 SP2 operating system (Microsoft Corporation, Redmond, USA) following the advice of a qualified statistician.
5.2. **Sample Descriptive Statistics**

Of the 68 patients eligible to participate in the study, one 26-year-old female did not consent. Of the remaining 67 participating patients, 4 were retrospectively excluded from the study:

- One 21-year-old male in the paracetamol and dexamethasone group experienced severe haemorrhage from the surgical wound a few hours following the procedure; this was later identified to have originated from a large intraosseous feeder artery, which had to be electro-cauterised.

- One 26-year-old female in the diclofenac sodium group suffered inferior dental nerve paraesthesia; this was transient in nature and resolved completely a few weeks later.

- One 26-year-old male in the diclofenac sodium group developed localised alveolar osteitis of the surgical wound (dry socket) and a concurrent upper respiratory tract infection, for which he was prescribed antimicrobials by his general medical practitioner.

- One 31-year-old female in the diclofenac sodium group did not take the drug as prescribed and switched to a self-prescribed over-the-counter analgesic on the first day.

The data and results of the remaining 63 patients were processed and subjected to statistical analysis.
5.2.1. Patient distribution by drug group

A total of 63 valid patients participated in the study. These were evenly distributed between the paracetamol and dexamethasone study group and the diclofenac sodium control group (Table 5.1; Fig. 5.1).

<table>
<thead>
<tr>
<th>Statistic</th>
<th>Drug group</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Paracetamol &amp; Dexamethasone</td>
<td></td>
</tr>
<tr>
<td>count</td>
<td>31</td>
<td>32</td>
</tr>
<tr>
<td>percentage</td>
<td>49.2%</td>
<td>50.8%</td>
</tr>
</tbody>
</table>

*Table 5.1. Patient distribution by drug group.*

*Figure 5.1. Patient distribution by drug group.*
5.2.2. Patients descriptive statistics

There were a total of 26 male and 37 female participants in the study. A Pearson Chi-Squared Test ($\chi^2$-test) showed that the gender distribution between the two drug groups was not statistically significant ($p>0.05$) (Table 5.2; Fig. 5.2).

<table>
<thead>
<tr>
<th>Gender</th>
<th>Statistic</th>
<th>Drug group</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Paracetamol &amp; Dexamethasone</td>
<td>Diclofenac sodium</td>
</tr>
<tr>
<td>Male</td>
<td>count</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>percentage</td>
<td>42.3%</td>
<td>57.7%</td>
</tr>
<tr>
<td>Female</td>
<td>count</td>
<td>20</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>percentage</td>
<td>54.1%</td>
<td>45.9%</td>
</tr>
<tr>
<td>Total</td>
<td>count</td>
<td>31</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>percentage</td>
<td>49.2%</td>
<td>50.8%</td>
</tr>
</tbody>
</table>

Table 5.2. Gender distribution by drug group.

Figure 5.2. Gender distribution by drug group.
The age of the patients ranged from 16 to 61 years, with a mean age (± standard error of the mean) of 27.59 ±1.10 years. A Student’s t-test for independent samples showed that the two drug groups did not differ significantly in terms of age ($p>0.05$) (Table 5.3; Fig. 5.3).

<table>
<thead>
<tr>
<th>Age statistics</th>
<th>Drug group</th>
<th>Whole sample</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Paracetamol &amp; Dexamethasone</td>
<td>Diclofenac sodium</td>
</tr>
<tr>
<td>Mean ±SEM (years)</td>
<td>26.42 ±1.25</td>
<td>28.72 ±1.79</td>
</tr>
<tr>
<td>Range (years)</td>
<td>16 – 46</td>
<td>16 – 61</td>
</tr>
</tbody>
</table>

*Table 5.3. Age distribution by drug group.*

*Figure 5.3. Boxplot of the age distribution by drug group.*

104
5.2.3. Impacted mandibular third molars descriptive statistics

The impacted mandibular third molar cases were not significantly different between the two drug groups with respect to side of the mouth, Pell and Gregory class, impaction angle and type, crown status, number of roots, root anatomy and relationship to the inferior dental nerve ($\chi^2$-test $p>0.05$). Pell and Gregory classes 3 and C were prospectively excluded and there were no inverted or transversely impacted mandibular third molars. None of the mandibular third molars had an absent crown or more than three roots (Table 5.4).

<table>
<thead>
<tr>
<th>Factor</th>
<th>Variants</th>
<th>Statistic</th>
<th>Drug group</th>
<th>Total</th>
</tr>
</thead>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Paracetamol &amp; Dexamethasone</td>
<td>Diclofenac sodium</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Side</td>
<td>right</td>
<td>count</td>
<td>14</td>
<td>12</td>
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<tr>
<td></td>
<td></td>
<td>percentage</td>
<td>45.2%</td>
<td>37.5%</td>
</tr>
<tr>
<td></td>
<td>left</td>
<td>count</td>
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<td>20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>percentage</td>
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<td>62.5%</td>
</tr>
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<td>Pell &amp; Gregory classification</td>
<td>1A</td>
<td>count</td>
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<td>1</td>
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<tr>
<td></td>
<td></td>
<td>percentage</td>
<td>9.7%</td>
<td>3.1%</td>
</tr>
<tr>
<td></td>
<td>1B</td>
<td>count</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>percentage</td>
<td>9.7%</td>
<td>12.5%</td>
</tr>
<tr>
<td></td>
<td>2A</td>
<td>count</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>percentage</td>
<td>29.0%</td>
<td>25.0%</td>
</tr>
<tr>
<td></td>
<td>2B</td>
<td>count</td>
<td>16</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>percentage</td>
<td>51.6%</td>
<td>59.4%</td>
</tr>
<tr>
<td>Impaction angle</td>
<td>mesioangular</td>
<td>count</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>percentage</td>
<td>45.2%</td>
<td>46.9%</td>
</tr>
<tr>
<td></td>
<td>distoangular</td>
<td>count</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>percentage</td>
<td>29.0%</td>
<td>28.1%</td>
</tr>
<tr>
<td></td>
<td>vertical</td>
<td>count</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>percentage</td>
<td>16.1%</td>
<td>9.4%</td>
</tr>
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<td></td>
<td>horizontal</td>
<td>count</td>
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<td>5</td>
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<td>15.6%</td>
</tr>
<tr>
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<td>inverted</td>
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<td>0.0%</td>
</tr>
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<td>0.0%</td>
</tr>
<tr>
<td>Impaction type</td>
<td>partial bony</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------</td>
<td>--------------</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>count</td>
<td>15</td>
<td>12</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>percentage</td>
<td>48.4%</td>
<td>37.5%</td>
<td>42.9%</td>
<td></td>
</tr>
<tr>
<td>full bony</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>percentage</td>
<td>3.2%</td>
<td>3.1%</td>
<td>3.2%</td>
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<tr>
<td>dental</td>
<td>15</td>
<td>19</td>
<td>34</td>
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<td>59.4%</td>
<td>54.0%</td>
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<table>
<thead>
<tr>
<th>Crown status</th>
<th>intact</th>
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</thead>
<tbody>
<tr>
<td>count</td>
<td>30</td>
<td>29</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>percentage</td>
<td>96.8%</td>
<td>90.6%</td>
<td>93.7%</td>
<td></td>
</tr>
<tr>
<td>broken down</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>percentage</td>
<td>3.2%</td>
<td>9.4%</td>
<td>6.3%</td>
<td></td>
</tr>
<tr>
<td>absent</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>percentage</td>
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<td>0.0%</td>
<td>0.0%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of roots</th>
<th>one</th>
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<th></th>
<th></th>
</tr>
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<tbody>
<tr>
<td>count</td>
<td>10</td>
<td>14</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>percentage</td>
<td>32.3%</td>
<td>43.8%</td>
<td>38.1%</td>
<td></td>
</tr>
<tr>
<td>two</td>
<td>19</td>
<td>18</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>percentage</td>
<td>61.3%</td>
<td>56.3%</td>
<td>58.7%</td>
<td></td>
</tr>
<tr>
<td>three</td>
<td>2</td>
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<td>2</td>
<td></td>
</tr>
<tr>
<td>percentage</td>
<td>6.5%</td>
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<td>3.2%</td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Root anatomy</th>
<th>straight or favourably curved</th>
<th></th>
<th></th>
<th></th>
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<tr>
<td>count</td>
<td>20</td>
<td>22</td>
<td>42</td>
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</tr>
<tr>
<td>percentage</td>
<td>64.5%</td>
<td>68.8%</td>
<td>66.7%</td>
<td></td>
</tr>
<tr>
<td>curved, dilacerated or hooked</td>
<td>11</td>
<td>10</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>percentage</td>
<td>35.5%</td>
<td>31.3%</td>
<td>33.3%</td>
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<table>
<thead>
<tr>
<th>Relationship to the inferior dental nerve</th>
<th>non-intimate</th>
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<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>count</td>
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</tr>
<tr>
<td>percentage</td>
<td>38.7%</td>
<td>46.9%</td>
<td>42.9%</td>
<td></td>
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<tr>
<td>loss of tramlines</td>
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<td>9</td>
<td>17</td>
<td></td>
</tr>
<tr>
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<td>25.8%</td>
<td>28.1%</td>
<td>27.0%</td>
<td></td>
</tr>
<tr>
<td>narrowing of tramlines</td>
<td>8</td>
<td>4</td>
<td>12</td>
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</tr>
<tr>
<td>percentage</td>
<td>25.8%</td>
<td>12.5%</td>
<td>19.0%</td>
<td></td>
</tr>
<tr>
<td>change in direction of tramlines</td>
<td>1</td>
<td>0</td>
<td>1</td>
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</tr>
<tr>
<td>percentage</td>
<td>3.2%</td>
<td>0.0%</td>
<td>1.6%</td>
<td></td>
</tr>
<tr>
<td>radiolucent band across the roots</td>
<td>2</td>
<td>4</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>percentage</td>
<td>6.5%</td>
<td>12.5%</td>
<td>9.5%</td>
<td></td>
</tr>
</tbody>
</table>

| Totals                                   | 31           | 32 | 63 |
| percentage                               | 49.2%        | 50.8% | 100.0% |

Table 5.4. Impacted mandibular third molars descriptive statistics by drug group.
5.2.4. Surgical procedure descriptive statistics

With respect to the surgical procedures there were no significant differences between the two drug groups in terms of the number of procedures performed by the two operators and in the distribution of cases between the two groups per month ($\chi^2$-test $p>0.05$). The surgical procedures in the two drug groups did not significantly differ in number of local anaesthetic cartridges and sutures used, and in whether tooth division was performed ($\chi^2$-test $p>0.05$) (Table 5.5).

<table>
<thead>
<tr>
<th>Factor</th>
<th>Variants</th>
<th>Statistic</th>
<th>Drug group</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Paracetamol &amp; Dexamethasone</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Diclofenac sodium</td>
<td></td>
</tr>
<tr>
<td>Operator</td>
<td>Oral Surgeon A</td>
<td>count</td>
<td>16</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>percentage</td>
<td>51.6%</td>
<td>47.6%</td>
</tr>
<tr>
<td></td>
<td>Oral Surgeon B</td>
<td>count</td>
<td>15</td>
<td>33</td>
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<td></td>
<td></td>
<td>percentage</td>
<td>48.4%</td>
<td>52.4%</td>
</tr>
<tr>
<td>Month</td>
<td>November</td>
<td>count</td>
<td>4</td>
<td>8</td>
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<td></td>
<td></td>
<td>percentage</td>
<td>12.9%</td>
<td>12.7%</td>
</tr>
<tr>
<td></td>
<td>December</td>
<td>count</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>percentage</td>
<td>9.7%</td>
<td>9.5%</td>
</tr>
<tr>
<td></td>
<td>January</td>
<td>count</td>
<td>3</td>
<td>6</td>
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<tr>
<td></td>
<td></td>
<td>percentage</td>
<td>9.7%</td>
<td>9.5%</td>
</tr>
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<td>February</td>
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<td>percentage</td>
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<td>6.3%</td>
</tr>
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<td>March</td>
<td>count</td>
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<td>15</td>
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<td></td>
<td></td>
<td>percentage</td>
<td>25.8%</td>
<td>23.8%</td>
</tr>
<tr>
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<td>count</td>
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<td>percentage</td>
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<td>20.6%</td>
</tr>
<tr>
<td></td>
<td>May</td>
<td>count</td>
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<td>8</td>
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<td></td>
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<td>percentage</td>
<td>12.9%</td>
<td>12.7%</td>
</tr>
<tr>
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<td>June</td>
<td>count</td>
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<td>3</td>
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<td></td>
<td></td>
<td>percentage</td>
<td>3.2%</td>
<td>4.8%</td>
</tr>
<tr>
<td>Number of local anaesthetic cartridges used</td>
<td>count</td>
<td>percentage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>-------</td>
<td>------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>two</td>
<td>19</td>
<td>61.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>59.4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>38</td>
<td>60.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>three</td>
<td>11</td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>34.4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>34.9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>four</td>
<td>1</td>
<td>3.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>3.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>3.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>five</td>
<td>0</td>
<td>0.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>3.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1.6%</td>
<td></td>
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<table>
<thead>
<tr>
<th>Tooth division</th>
<th>count</th>
<th>percentage</th>
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<td>yes</td>
<td>16</td>
<td>51.6%</td>
</tr>
<tr>
<td></td>
<td>23</td>
<td>71.9%</td>
</tr>
<tr>
<td></td>
<td>39</td>
<td>61.9%</td>
</tr>
<tr>
<td>no</td>
<td>15</td>
<td>48.4%</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>28.1%</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>38.1%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of sutures</th>
<th>count</th>
<th>percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>two</td>
<td>6</td>
<td>19.4%</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>15.6%</td>
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<tr>
<td></td>
<td>11</td>
<td>17.5%</td>
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<tr>
<td>three</td>
<td>17</td>
<td>54.8%</td>
</tr>
<tr>
<td></td>
<td>21</td>
<td>65.6%</td>
</tr>
<tr>
<td></td>
<td>38</td>
<td>60.3%</td>
</tr>
<tr>
<td>four</td>
<td>6</td>
<td>19.4%</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>15.6%</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>17.5%</td>
</tr>
<tr>
<td>five</td>
<td>2</td>
<td>6.5%</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>3.1%</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>4.8%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total</th>
<th>count</th>
<th>percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>31</td>
<td>49.2%</td>
</tr>
<tr>
<td></td>
<td>32</td>
<td>50.8%</td>
</tr>
<tr>
<td></td>
<td>63</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

*Table 5.5. Surgical procedure descriptive statistics by drug group.*
There was no significant difference (Student’s t-test $p>0.05$) in operating times between the two drug groups (Table 5.6; Fig 5.4).

<table>
<thead>
<tr>
<th>Duration statistics</th>
<th>Drug Group</th>
<th>Whole sample</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Paracetamol &amp; Dexamethasone</td>
<td>Diclofenac sodium</td>
</tr>
<tr>
<td>Mean ±SEM (minutes)</td>
<td>12.45 ±0.61</td>
<td>13.31 ±0.73</td>
</tr>
<tr>
<td>Range (minutes)</td>
<td>8 – 25</td>
<td>6 – 28</td>
</tr>
</tbody>
</table>

*Table 5.6. Duration of the surgical procedure by drug group.*

![Boxplot of the duration of the surgical procedure by drug group.](image)

It was therefore shown that there were no statistically significant differences in any of the variables between the cases in the two groups except for the drug or drugs they had received (see above).
5.3. **MEASUREMENT REPRODUCIBILITY**

All readings for pain scores, facial dimension and mouth opening were measured by the same investigator always using the same instruments. In the week before the start of the study, a set of repeated readings on five volunteers (not taking part in the study) were taken on the four days when measurements had to be taken during the study (i.e. Monday, Tuesday, Thursday and Saturday). This test was then repeated in the week after the whole study was completed. A mean percentage value for measurement reproducibility (intra-operator reliability) was estimated from the coefficient of variation (CV) of the test results (100-CV), for each of the three variables.

The value obtained for the reproducibility of measuring a pain score from the visual analogue scale was 100.00%, while the reproducibility for measuring subject facial dimension and mouth opening were 99.85% and 99.28% respectively. These values indicate very high intra-operator reliability and measurement reproducibility for all the readings obtained. Inter-operator reliability was not applicable as there was only one investigator.
5.4. **EXPERIMENTAL RESULTS**

5.4.1. **Pain**

The patients in the paracetamol and dexamethasone experienced an overall mean reduction in pain of 36% as compared to the patients in the diclofenac sodium control group (Tables 5.7 and 5.8; Figs. 5.5 and 5.6). Analysis of variance (ANOVA) for repeated measures showed that this difference was statistically significant \((p<0.05)\). The patients in the paracetamol and dexamethasone group always experienced less pain than the patients in the diclofenac sodium group. However, when considering the daily means this difference was not statistically significant \((t\text{-test } p>0.05)\) on the first two days (Table 5.7). This is confirmed by the 8-hourly pain scores as only the difference between the last of the first six scores is statistical significant \((t\text{-test } p<0.05)\). However, when considering the next fifteen 8-hourly scores for days three to seven, the difference was significant \((t\text{-test } p<0.05)\) in nine of them (Table 5.8).

As can be seen in figure 5.5 the pain experienced in both drug groups continuously decreased over the seven days. However, when the daily means are expressed as 8-hourly scores in figure 5.6 it can be seen that although the overall trend in pain reduction was maintained, pain levels tended to increase in the evenings (except on day one) in the diclofenac sodium group. This only happened occasionally and less markedly in the paracetamol and dexamethasone group.

Also worth noting is that the variance in pain experienced in the paracetamol and dexamethasone group was almost always less than that in the diclofenac sodium group and this difference tended to be significant (Levene's test for equality of
variances $p<0.05$) when the difference in pain was more clinically and statistically significant (Tables 5.7 and 5.8).

<table>
<thead>
<tr>
<th>Day</th>
<th>Statistic</th>
<th>Pain (daily)</th>
<th>Paracetamol &amp; Dexamethasone</th>
<th>Diclofenac sodium</th>
<th>Difference</th>
<th>Percentage difference</th>
<th>$p$-values†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>mean ±SEM</td>
<td>64.8 ±4.6</td>
<td>71.3 ±4.8</td>
<td>-6.5 ±6.7</td>
<td>-9.1%</td>
<td>&gt;0.05</td>
<td></td>
</tr>
<tr>
<td></td>
<td>variance</td>
<td>661.8</td>
<td>732.0</td>
<td></td>
<td></td>
<td></td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>2</td>
<td>mean ±SEM</td>
<td>36.4 ±4.7</td>
<td>47.1 ±5.4</td>
<td>-10.7 ±7.2</td>
<td>-22.8%</td>
<td>&gt;0.05</td>
<td></td>
</tr>
<tr>
<td></td>
<td>variance</td>
<td>678.4</td>
<td>938.9</td>
<td></td>
<td></td>
<td></td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>3</td>
<td>mean ±SEM</td>
<td>23.3 ±3.8</td>
<td>40.4 ±4.9</td>
<td>-17.1 ±6.1</td>
<td>-42.3%</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td></td>
<td>variance</td>
<td>439.8</td>
<td>753.6</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>4</td>
<td>mean ±SEM</td>
<td>19.4 ±3.5</td>
<td>34.5 ±4.4</td>
<td>-15.2 ±5.7</td>
<td>-43.9%</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td></td>
<td>variance</td>
<td>378.0</td>
<td>631.8</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>5</td>
<td>mean ±SEM</td>
<td>14.0 ±3.1</td>
<td>25.9 ±3.9</td>
<td>-11.9 ±5.0</td>
<td>-46.0%</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td></td>
<td>variance</td>
<td>298.4</td>
<td>485.7</td>
<td></td>
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<td>&lt;0.05</td>
</tr>
<tr>
<td>6</td>
<td>mean ±SEM</td>
<td>13.9 ±3.3</td>
<td>24.1 ±3.8</td>
<td>-10.2 ±5.1</td>
<td>-42.4%</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td></td>
<td>variance</td>
<td>332.7</td>
<td>468.5</td>
<td></td>
<td></td>
<td></td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>7</td>
<td>mean ±SEM</td>
<td>9.0 ±2.6</td>
<td>16.5 ±3.8</td>
<td>-7.5 ±4.6</td>
<td>-45.4%</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td></td>
<td>variance</td>
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<td>459.8</td>
<td></td>
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<td>&gt;0.05</td>
</tr>
<tr>
<td>Overall mean</td>
<td>mean ±SEM</td>
<td>9.0 ±2.6</td>
<td>16.5 ±3.8</td>
<td>-7.5 ±4.6</td>
<td>-45.4%</td>
<td>&lt;0.05</td>
<td></td>
</tr>
</tbody>
</table>

†The Student's t-test for independent samples was used to estimate the statistical significance of the reductions in pain, and Levene's test for equality of variances was used to estimate the statistical significance of the difference between the variances of the two drug groups.

The overall statistical significance for average reduction in pain was estimated using ANOVA for repeated measures.

Table 5.7. Daily pain scores by drug group.
Figure 5.5. Daily pain scores by drug group (error bars represent the SEM).

<table>
<thead>
<tr>
<th>Time</th>
<th>Statistic</th>
<th>Pain (8-hourly)</th>
<th>p-values†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Paracetamol &amp; Dexamethasone</td>
<td>Diclofenac sodium</td>
</tr>
<tr>
<td>1</td>
<td>mean ±SEM</td>
<td>64.7 ±5.8</td>
<td>73.5 ±5.1</td>
</tr>
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<td></td>
<td>variance</td>
<td>1025.8</td>
<td>848.1</td>
</tr>
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<td>2</td>
<td>mean ±SEM</td>
<td>69.9 ±5.2</td>
<td>72.7 ±5.5</td>
</tr>
<tr>
<td></td>
<td>variance</td>
<td>838.9</td>
<td>951.2</td>
</tr>
<tr>
<td>3</td>
<td>mean ±SEM</td>
<td>59.8 ±5.5</td>
<td>67.7 ±5.4</td>
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<td>variance</td>
<td>944.9</td>
<td>941.7</td>
</tr>
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<td>4</td>
<td>mean ±SEM</td>
<td>40.9 ±5.0</td>
<td>45.2 ±6.1</td>
</tr>
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<td>variance</td>
<td>766.0</td>
<td>1173.5</td>
</tr>
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<td>mean ±SEM</td>
<td>36.6 ±5.0</td>
<td>45.0 ±5.6</td>
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<td>variance</td>
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<td>1015.0</td>
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<td>31.7 ±5.1</td>
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<td>mean ±SEM</td>
<td>variance</td>
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<td>-----------</td>
<td>-----------</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>22.7 ±3.8</td>
<td>448.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>36.6 ±5.1</td>
<td>848.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-13.9 ±6.4</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-38.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>22.7 ±3.7</td>
<td>429.9</td>
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</tr>
<tr>
<td></td>
<td>41.4 ±5.3</td>
<td>904.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-18.8 ±6.5</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-45.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>24.6 ±4.6</td>
<td>663.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>43.3 ±5.4</td>
<td>937.7</td>
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<td>-18.7 ±7.1</td>
<td>&gt;0.05</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-38.5%</td>
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<td></td>
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<tr>
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<td>19.3 ±3.7</td>
<td>416.0</td>
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<td>681.5</td>
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</tr>
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<td>-12.1 ±5.9</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-35.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>20.2 ±3.8</td>
<td>446.7</td>
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<td>34.3 ±4.9</td>
<td>762.3</td>
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<td>-14.1 ±6.2</td>
<td>&gt;0.05</td>
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<tr>
<td></td>
<td>-41.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>18.6 ±3.8</td>
<td>454.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>37.9 ±5.0</td>
<td>806.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-19.3 ±6.3</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-50.9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>14.0 ±3.1</td>
<td>304.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>24.4 ±4.0</td>
<td>514.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-10.4 ±5.1</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-42.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>14.2 ±3.4</td>
<td>365.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>23.0 ±3.9</td>
<td>482.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-8.7 ±5.2</td>
<td>&gt;0.05</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-38.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>13.7 ±3.1</td>
<td>290.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>30.3 ±5.0</td>
<td>793.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-16.5 ±5.8</td>
<td>&gt;0.05</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-54.6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>13.4 ±3.5</td>
<td>375.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>21.8 ±3.7</td>
<td>447.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-8.5 ±5.1</td>
<td>&gt;0.05</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-38.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>13.8 ±3.4</td>
<td>352.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>23.3 ±4.2</td>
<td>567.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-9.4 ±5.4</td>
<td>&gt;0.05</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-40.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>14.5 ±3.8</td>
<td>437.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>27.3 ±5.0</td>
<td>801.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-12.9 ±6.3</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-47.0%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The Student’s t-test for independent samples was used to estimate the statistical significance of the percentage reduction in pain, and Levene’s test for equality of variances was used to estimate the statistical significance of the difference between the variances of the two drug groups. The overall statistical significance for average reduction in pain was estimated using ANOVA for repeated measures.

Table 5.8. 8-hourly pain scores by drug group.

<table>
<thead>
<tr>
<th></th>
<th>mean ±SEM</th>
<th>variance</th>
<th>mean ±SEM</th>
<th>variance</th>
<th>mean ±SEM</th>
<th>variance</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>9.3 ±2.9</td>
<td>260.4</td>
<td>15.3 ±3.4</td>
<td>365.7</td>
<td>-5.9 ±4.5</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>20</td>
<td>10.1 ±3.0</td>
<td>282.9</td>
<td>16.5 ±3.9</td>
<td>487.5</td>
<td>-6.4 ±5.0</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>21</td>
<td>7.6 ±2.7</td>
<td>220.0</td>
<td>17.7 ±4.7</td>
<td>715.8</td>
<td>-10.1 ±5.4</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

Overall mean ±SEM
-11.3 ±4.8
-35.6%
<0.05

The Student’s t-test for independent samples was used to estimate the statistical significance of the percentage reduction in pain, and Levene’s test for equality of variances was used to estimate the statistical significance of the difference between the variances of the two drug groups. The overall statistical significance for average reduction in pain was estimated using ANOVA for repeated measures.

Figure 5.6. 8-hourly pain scores by drug group (error bars represent the SEM).
5.4.2. Swelling

The patients in the paracetamol and dexamethasone experienced an overall mean reduction in facial swelling of 76% as compared to the patients in the diclofenac sodium control group (Table 5.9; Fig. 5.7). Analysis of variance (ANOVA) for repeated measures showed that this difference was very highly significant ($p<0.001$). The patients in the paracetamol and dexamethasone group always had less facial swelling than the patients in the diclofenac sodium group, and this difference was always very highly statistically significant (t-test $p>0.001$) (Table 5.9).

Also worth noting is that the variance in facial swelling in the paracetamol and dexamethasone group was always less than that in the diclofenac sodium group and this difference was always highly significant (Levene’s test for equality of variances $p<0.01$) (Table 5.9).

<table>
<thead>
<tr>
<th>Day</th>
<th>Statistic</th>
<th>Swelling (mm)</th>
<th>$p$-values$^+$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Paracetamol &amp; Dexamethasone</td>
<td>Diclofenac sodium</td>
</tr>
<tr>
<td>3</td>
<td>$mean \pm SEM$</td>
<td>3.9 ±0.4</td>
<td>9.3 ±1.0</td>
</tr>
<tr>
<td></td>
<td>variance</td>
<td>5.4</td>
<td>29.3</td>
</tr>
<tr>
<td>5</td>
<td>$mean \pm SEM$</td>
<td>1.2 ±0.3</td>
<td>4.4 ±0.6</td>
</tr>
<tr>
<td></td>
<td>variance</td>
<td>3.0</td>
<td>11.4</td>
</tr>
<tr>
<td>8</td>
<td>$mean \pm SEM$</td>
<td>0.1 ±0.1</td>
<td>1.7 ±0.4</td>
</tr>
<tr>
<td></td>
<td>variance</td>
<td>0.1</td>
<td>5.5</td>
</tr>
<tr>
<td></td>
<td><strong>Overall mean</strong> $\pm SEM$</td>
<td>0.1 ±0.1</td>
<td>1.7 ±0.4</td>
</tr>
</tbody>
</table>

$^+$The Student’s t-test for independent samples was used to estimate the statistical significance of the percentage reduction in pain, and Levene’s test for equality of variances was used to estimate the statistical significance of the difference between the variances of the two drug groups.

$^\dagger$The overall statistical significance for average reduction in pain was estimated using ANOVA for repeated measures.

*Table 5.9. Facial swelling measurements by drug group.*
5.4.3. Trismus

The patients in the paracetamol and dexamethasone experienced an overall mean reduction in trismus of 56% as compared to the patients in the diclofenac sodium control group (Table 5.10; Fig. 5.8). Analysis of variance (ANOVA) for repeated measures showed that this difference was very highly significant \( p<0.001 \). The patients in the paracetamol and dexamethasone group always had less trismus than the patients in the diclofenac sodium group, and this difference was always very highly statistically significant \( t\text{-test } p<0.001 \) (Table 5.10).

Also worth noting is that even the variance in trismus in the paracetamol and dexamethasone group was always less than that in the diclofenac sodium group and this difference was always significant (Levene’s test for equality of variances \( p<0.05 \)) (Table 5.10).
Table 5.10. Trismus measurements by drug group.

<table>
<thead>
<tr>
<th>Day</th>
<th>Statistic</th>
<th>Trismus (mm)</th>
<th>Paracetamol &amp; Dexamethasone</th>
<th>Diclofenac sodium</th>
<th>Difference</th>
<th>Percentage difference</th>
<th>p-values†</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>mean ±SEM</td>
<td>12.1 ±1.3</td>
<td>19.2 ±1.2</td>
<td>-7.1 ±1.8</td>
<td>-37.1%</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>variance</td>
<td>51.9</td>
<td>45.0</td>
<td></td>
<td></td>
<td>&gt;0.05</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>mean ±SEM</td>
<td>5.7 ±0.9</td>
<td>13.1 ±1.1</td>
<td>-7.4 ±1.5</td>
<td>-56.3%</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>variance</td>
<td>27.3</td>
<td>40.4</td>
<td></td>
<td></td>
<td>&gt;0.05</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>mean ±SEM</td>
<td>1.9 ±0.7</td>
<td>7.6 ±1.1</td>
<td>-5.7 ±1.3</td>
<td>-74.8%</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>variance</td>
<td>15.1</td>
<td>39.4</td>
<td></td>
<td></td>
<td>&gt;0.05</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Overall mean ±SEM</td>
<td>-6.7 ±1.1</td>
<td>-56.0</td>
<td></td>
<td>&lt;0.001†</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

†The Student’s t-test for independent samples was used to estimate the statistical significance of the percentage reduction in pain, and Levene’s test for equality of variances was used to estimate the statistical significance of the difference between the variances in the two drug groups.

‡The overall statistical significance for average reduction in pain was estimated using ANOVA for repeated measures.

Figure 5.8. Trismus measurements by drug group (error bars represent the SEM).
5.5. **Correlations**

In both drug groups, pain, swelling and trismus decrease over time (Figs. 5.5, 5.6, 5.7 and 5.8), however Pearson bivariate correlation tests show that these correlations are only always statistically significant between swelling and trismus \((p<0.05)\).

5.6 **Adverse Drug Reactions**

None of the patients participating in the study reported any adverse drug reactions, including side effects, overdose, drug interactions (applicable only for paracetamol and dexamethasone group), idiosyncratic reactions or allergies.
6. DISCUSSION

6.1 INTRODUCTION

The development of a painful, localised, acute inflammatory response occurs in all patients immediately after oral surgical procedures. It is recognised that there is a need to improve postoperative analgesia in ambulant day case patients. This may obviate the need for the common hospital practice to admit patients overnight in order to allow parenteral administration of opioid analgesia if necessary (Baxendale et al., 1993).

The acute postoperative sequelae of surgical procedures are manifestations of inflammation due to tissue injury. Strategy for managing these clinical symptoms is aimed at pharmacologically interfering with the inflammatory process in order to limit the intensity and shorten the duration of the clinical signs of inflammation: pain, oedema, and loss of function (see section 1.1).

The surgical removal of impacted mandibular third molars is often associated with specific inflammatory reactions, including pain, swelling (oedema) and trismus (limitation of opening/loss of function). Therefore, this procedure represents a good model for studying the therapeutic efficacy of analgesic and anti-inflammatory drugs (see section 1.2).

The selection of this surgical model proved to be very advantageous for the purposes of this study. A suitable number of cases were identified and included in the study in the limited time available, since this was a relatively common procedure, of short duration that is performed consistently on a regular basis in an outpatients' setting. Typically patients undergoing this procedure were young and of good physical
health – a requirement for inclusion. This and the other stringent selection criteria eliminate the confounding effects that concomitant systemic disease, medications and other factors may have on the study results (see section 4.2). The surgical procedure was adequately standardised without difficulty (see section 4.7).

The surgical mandibular third molar model also offers the possibility of using the popular cross-over or ‘split-mouth’ study design, in which only patients with bilateral impacted mandibular third molar are included in the study, so that patients can act as their own controls with one impacted third molar allocated to the study group, while its contralateral counterpart is allocated to the control group. Although this design is highly acclaimed, in that it should eliminate patient-related bias, it assumes that the two impactions in each patient are identical, which is rarely the case. Also randomisation cannot be used with such a study design and there is a risk of introducing recall bias, since patients experience the second surgical procedure in the light of what they had experienced in the first one (‘pain memory’). Therefore, it was decided not to use the cross-over study design in this case. This also had the advantage of having more patients with only one impacted mandibular third molar eligible for participation in the study (Jackson, 1999).

A considerable number of variable factors were categorised and recorded for each case, and it was confirmed that there were no statistically significant differences in any of the demographic, case-related and surgical variables between the two drug groups (see section 5.2). The records of these variable factors also help in determining the comparability of the study conditions with circumstances in which the drug regimens used in this study might be considered for use in daily clinical practice.

A randomised controlled trial (RCT) study design was used (see section 4.5). Diclofenac sodium was chosen as the control drug, primarily to provide the patients in
the control group with a suitable analgesic instead of a placebo; and also to enhance
the clinical value and generalisability of the study, in that the paracetamol and
dexamethasone combination were compared with what is considered to be the most
popular ‘gold standard’ drug used in these situations (see section 1.5). A double-blind
approach was also used to further reduce the risk of bias (see section 4.6).

All of the three postoperative sequelae of third molar surgery (i.e. pain,
swelling and trismus) were evaluated in this study. The methods used to determine and
quantify these events were relatively simple but highly reliable (see sections 1.7, 4.4
and 5.3). The experimental results were analysed both with the more commonly used
Student’s t-test for independent samples and also with ANOVA for repeated measures
tests (see section 5.4). This was done because the use of multiple t-tests to analyse data
obtained from a repeated measures study design (i.e. comparisons of data collected at
baseline, day 2, day 3, day 4, etc.), increases the likelihood of making a type I
statistical error (i.e. rejecting the null hypothesis when it is actually true). The extent
of variation between patients’ response to the drugs within each group was also
assessed using Levene’s test for equality of variances. Pearson bivariate correlation
statistics were used to assess the significance of any relationship between the three
different postoperative sequelae (see section 5.5).

From the original number of 67 participants, there were only 4 drop-outs
during the course of the study and none of the reasons for exclusion from the study
could be related to the patients’ particular drug group (see section 5.2).
6.2 THE ACTIONS OF PARACETAMOL AND DEXAMETHASONE

The patients in the paracetamol and dexamethasone group experienced an overall mean reduction of 36% in pain \( (p<0.05) \), of 76% in facial swelling \( (p>0.001) \) and of 56% in trismus \( (p>0.001) \) as compared to the patients in the diclofenac sodium control group. The greater reduction in swelling and trismus experienced by the patients in the paracetamol and dexamethasone group, was consistent with the findings of many previous studies that showed that corticosteroids were superior to NSAIDs in controlling such postoperative inflammatory sequelae (see section 1.4). However, the also greater reduction in pain differs from the results of earlier studies. A paracetamol and corticosteroid combination was not evaluated in any of the previous studies, however NSAIDs were consistently found to provide better analgesia than both paracetamol and corticosteroids when the latter were used separately (see section 1.5).

A possible explanation for these findings is that paracetamol is an effective analgesic, but because it lacks any significant anti-inflammatory properties (see section 3.1), it is usually ineffective in controlling postoperative pain due to the significant inflammation associated with this type of pain (see section 2.1). The additional use of a glucocorticosteroid such as dexamethasone, which is a potent anti-inflammatory agent (see section 3.2), effectively controls the inflammation and thus enables paracetamol to express its full analgesic potential. The corticosteroid could also have an indirect analgesic effect.

The tissue damage that is associated with the removal of impacted mandibular third molars initiates the synthesis or the local release of numerous endogenous pro-inflammatory compounds. The resultant postoperative pain and inflammation is under the control of these biochemical mediators produced at or near the site of injury. One
specific class of pro-inflammatory compounds is the metabolites of arachidonic acid. Many of the arachidonic acid metabolites have been implicated in the development of injury-induced oedema and hyperalgesia (Jackson, 1999). A group of these metabolites is the prostanoids (prostaglandins, thromboxane and prostacyclin), produced by the action of the cyclo-oxygenase enzyme on arachidonic acid. PGE₂ and PGI₂ are generated by the local tissues and blood vessels, mast cells release PGD₂, while cells of the monocyte-macrophage series also release PGE₂ and TXA₂. PGE₂, PGI₂ and PGD₂ are powerful vasodilators in their own right and synergise with other inflammatory vasodilators such as histamine and bradykinin. It is this combined dilator action on precapillary arterioles, which contributes to the redness and increased blood flow in areas of acute inflammation. These prostanoids do not directly increase the permeability of the postcapillary venules, but they potentiate this effect of histamine and bradykinin. Similarly, they do not themselves produce pain, but potentiate the effect of bradykinin by sensitising afferent C fibres (see section 2.1.2.4).

Like diclofenac sodium, paracetamol exerts its analgesic effect mainly by inhibiting cyclo-oxygenase. However, unlike diclofenac sodium, paracetamol is only a weak inhibitor of cyclo-oxygenase in the presence of the high concentrations of peroxides that are found in inflammatory lesions. It is very much less effective than other NSAIDs as a peripheral cyclo-oxygenase inhibitor, but has the same potency in inhibiting brain prostaglandin synthetase (see section 3.1.3). The cyclo-oxygenase enzyme exists in more than one form. COX-1 is a constitutive enzyme expressed in most cells, whereas COX-2 is induced by various cytokines and growth factors (see section 2.1.1.2). Diclofenac sodium is almost equipotent on both COX-1 and COX-2 (COX-2 to COX-1 ratio = 0.7), while paracetamol is much more selective for COX-2 (COX-2 to COX-1 ratio = 7.5) (Rang et al., 1999a). However, paracetamol also
selectively inhibits a third variant of the cyclo-oxygenase enzyme – COX-3. It seems likely that inhibition of COX-3 could represent a primary central mechanism by which this drug decreases pain (see section 2.1.2.2).

Cytokine-induced COX-2 activity is also suppressed by glucocorticosteroids and thus may account for some of the anti-inflammatory properties of dexamethasone. Selective inhibition of COX-2 may be of clinical significance, especially in the propagation of postoperative dental pain. This enzyme is probably involved in prostaglandin production at the site of inflammation (i.e. the surgical wound), but not at other sites such as the gastrointestinal tract. Thus, inhibition of COX-2 may be anti-inflammatory without the unwanted effects of gastric irritation associated with COX-1 inhibition (see section 2.1.2.2).

Glucocorticosteroids such as dexamethasone also decrease the production of prostanoids by inhibiting of the transcription of the gene for the enzyme phospholipase A_2. This enzyme acts on cell-membrane phospholipids and converts them to arachidonic acid, the parent compound of the prostanoids. Glucocorticosteroids also induce the formation of an anti-inflammatory protein known as lipocortin-1, which also has an inhibitory effect on phospholipase A_2. These effects on phospholipase A_2 also reduce the production PAF and of another group of eicosanoids – the leukotrienes (see section 3.2.2.3). PAF produces increased vascular permeability and local vasodilatation and thus oedema. It also produces hyperalgesia and it is a potent chemotaxin for neutrophils, eosinophils and monocytes (see section 2.1.3.1). Leukotriene B_4 is a powerful chemotactic attractant for polymorphonuclear leucocytes and other white blood cells. Leukotrienes C_4 and D_4 have a potent action on the endothelial lining of the postcapillary venules and cause leakage of plasma proteins and oedema formation (see section 2.1.2.4).
The eicosanoids and PAF are not the only endogenous pain-modulatory and pro-inflammatory compounds produced following oral surgery. The efficacy of dexamethasone also lies in inhibiting a number of other putative biochemical mediators of postoperative pain and inflammation. These include the kinins (bradykinin and kallidin), cytokines (interleukins, TNF-\(\gamma\), GM-CSF and other cell adhesion factors), histamine, nitric oxide and complement (see chapter 2 and section 3.2.2.3).

Bradykinin and kallidin are two kinins that act independently as well as synergistically with products of the arachidonic acid cascade to produce both hyperalgesia as well as tissue oedema. Both bradykinin and kallidin are potent vasodilators and increase capillary permeability, leading to oedema formation (see section 2.1.4.1). Bradykinin is also one of the most potent endogenous pain-producing (algogenic) substances released during inflammation. Bradykinin directly stimulates nociceptive nerve terminals and also sensitises them to other stimuli including those of a mechanical and chemical nature. There is also synergism between the excitatory action of bradykinin and other endogenous mediators associated with pain (e.g. prostaglandins and 5-HT) (see section 2.2.2.6).

Cytokines have a variety of fundamental functions in the inflammatory responses. Interleukins are mainly involved in communication between lymphocytes and may exert a number of inflammatory actions, which include the stimulation of prostaglandin and collagenase production, and chemoattraction for white blood cells (see section 2.1.8). They can also influence the activity of sensory neurones, probably by indirect routes. For example, IL-1\(\beta\) and IL-6 can stimulate the release of prostaglandins. Thus, these cytokines enhance the important relationship between pain and inflammation (see section 2.2.2.7)
Histamine, released by degranulation of mast cells, also plays a role in the development of acute pain and oedema. It causes relaxation of the vascular smooth muscle and has also a direct effect on free nerve endings, important in the production of pain. There is also evidence that histamine may function as a neurotransmitter in the CNS, being involved in the control of pain perception (see sections 2.1.5 and 2.2.2.5).

Complement fragments C3a and C5a induce the release of histamine from mast cells which causes increased capillary permeability. Other components of the complement cascade are chemotactic to white blood cells (C5a, C5b, C567 complex) and enhance phagocytosis (C3b, C5b). Damage to cell membranes followed by cell lysis occurs when factors C8 and C9 are activated (see section 2.1.7).

Glucocorticosteroids also have an effect on inflammatory cells. They decrease the egress of neutrophils from blood vessels and reduce the activity of neutrophils and macrophages. They reduce clonal proliferation of T cells and decrease the action of cytokine-secreting T lymphocytes. They also decrease fibroblast function and therefore less production of collagen and glycosaminoglycans (see section 3.2.2.3).

Glucocorticosteroids therefore exhibit very diverse and powerful anti-inflammatory effects. In the early stages they reduce the capillary permeability caused by histamine and bradykinin, which in turn reduces oedema. They also inhibit both bradykinin formation and the migration of white blood cells into the site of inflammation. In its later stages, steroids reduce granulation tissue formation by inhibiting the proliferation of fibroblasts and blood vessels.

Postoperative swelling is caused principally by the accumulation of tissue fluid and blood and is influenced predominantly by vascular permeability and blood flow (ElHag et al., 1985). Postoperative trismus is mainly due to muscle spasm
caused, in part, by local oedema formation between the muscles fibres (Mitchell et al., 1985). Dexamethasone reduces oedema formation, which may in turn reduce the duration of postoperative trismus (Mitchell et al., 1985). In fact, the results have shown a significant correlation between postoperative swelling and trismus (see section 5.5).

In selecting the ideal corticosteroid for this study, high glucocorticoid activity, minimal mineralocorticoid activity and extended biologic activity were sought. The results obtained showed that dexamethasone successfully fulfilled these requirements. Dexamethasone is thirty times as potent as hydrocortisone in terms of glucocorticoid activity, it has no mineralocorticoid activity and its biological half-life ranges from 36 to 72 hours. In fact, none of the patients reported any corticosteroid-related adverse drug reactions; as such side effects are usually associated with steroid mineralocorticoid activity (see section 1.4.2).

The pain experienced in both drug groups continuously decreased over the seven days (Fig. 5.5). However, when the daily means were expressed as 8-hourly scores in figure 5.6 it was noted that although the overall trend in pain reduction was maintained, pain levels tended to increase in the evenings (except on day one) in the diclofenac sodium group. This only happens occasionally, and less markedly in the paracetamol and dexamethasone group (see section 5.4.1). The importance of the role of corticosteroids in the modulation of pain has already been explained. The concentration of endogenous corticosteroids in the blood is high in the morning, and low at midnight (Rang et al., 1999c). In the patients receiving only diclofenac sodium, the lower levels of endogenous corticosteroids in the evenings could possibly result in an increased pain experience at this time of the day. This effect could be masked in the other patients who were receiving a dose of dexamethasone every 6 hours.
Another interesting finding of this study was that Levene’s test for equality of variances showed that the variance in pain experienced in the paracetamol and dexamethasone group was almost always less than that in the diclofenac sodium group and this difference tended to be significant ($p<0.05$) when the difference in pain is more clinically and statistically significant (see section 5.4.1). The variance in facial swelling and trismus in the paracetamol and dexamethasone group was also always less than that in the diclofenac sodium group and this difference was always statistically significant ($p<0.05$ and $p<0.01$ respectively). The means that the patients who received the diclofenac sodium exhibited a significantly greater inter-patient variation with respect to response to the drug therapy, and hence therapeutic outcome. This is consistent with what is stated in the Dental Practitioners’ Formulary – that although differences in anti-inflammatory activity between different NSAIDs may be small, there is considerable variation in individual patient response. Only about 60% of patients will respond to any NSAID (British Dental Association, 2002c). This means that up to 40% of patients may not respond adequately to treatment with diclofenac sodium. Hence the paracetamol and dexamethasone combination also proved to be superior on this front, in that a more predictable and consistent therapeutic outcome can be expected in most patients.
6.3 Limitations of the Study

Quantitative assessments of the postoperative sequelae represent a major difficulty in deriving meaningful conclusions from this kind of study. Evaluation of facial swelling resulting from surgical procedures has proven to be most problematic in similar studies. Swelling involves a three-dimensional volumetric change at the tissue and cellular level (Neupert et al., 1992). Methods used to evaluate swelling include computerised tomography, ultrasonography, photographic analysis, modified face bow, linear measurements, subjective assessment, and many others (see section 1.7.2). The desire to include a large number of patients and the practicality of a low-cost reliable technique made linear measurements a feasible choice. Whether a different format of measuring would yield similar results is a topic for future studies.

The timing of postoperative measurements in any drug trial depends upon the availability and willingness of patients to attend outside their normal return visit. It would have been ideal to physically review patients on a daily basis. However, it is unreasonable to expect patients to return on several occasions for repeated measurements (Mitchell et al., 1985). Also the weekend imposes further restrictions on patients’ availability. Thus the study was designed to clinically assess patients on the second, fourth and seventh postoperative days. The final visit was also for suture removal.

Effectiveness of the oral route of administration is dependent on patient compliance, but repeated dosing was required to maintain adequate blood levels during the postoperative period. However, this means that the study should be considered only on an intention-to-treat (ITT) basis (Esen et al., 1999).
Many drugs have been extensively evaluated in the treatment of postoperative sequelae after third molar surgery (Mitchell et al., 1985). However, exactly how the various drugs influence pain and inflammation is not completely understood and is a continuing area of investigation (Neupert et al., 1992). In this study, paracetamol and dexamethasone led to a significant reduction in the clinical manifestations of inflammation and a number of mechanisms by which this could have been achieved have been put forward (see section 6.2) Which of these mechanisms, if any, play important roles in decreasing postoperative swelling remains to be clarified (Milles & Desjardins, 1993).

Patients usually experience their most severe pain after surgery in the early postoperative period (Seymour et al., 1983a). In fact, the amount of pain experienced by the patients in this study was considerably high on the first day (Figs. 5.5 and 5.6) irrespective of drug group. None of the drug regimens used in this study managed to provide excellent pain relief on the first postoperative day.

As with the use of any medication, benefits must outweigh risks. Potential side effects and risks with the use of steroids include suppression of the immune system, hypertension, hyperglycemia, a sense of euphoria, glaucoma and many others (see section 3.2.5). Absolute contraindications noted are ocular herpes, tuberculosis, primary glaucoma, acute psychosis, and allergy (British Dental Association, 2002a; Neupert et al., 1992). Although no adverse drug reactions were reported in this study, this would be quite improbable in the general population, and could have been only because an insufficiently large number of selected (healthy) patients were included in the study.
Specific optimal dosages were recommended for both paracetamol and diclofenac sodium, but not for dexamethasone (see sections 1.3, 1.4 and 1.5). In this study only one of the many possible dexamethasone dosage regimens was evaluated, and although it proved to be superior to the control, this does not mean that it is the ideal dosage regimen for this drug. A thorough evaluation of dose-dependent effects is very important in the study of drug mechanisms. Increasing the dosage of compounds that rely on the binding of the ligand to a specific receptor to produce an effect usually results in an increase in the effect (Jackson, 1999).

Further studies to evaluate a range of doses are necessary to determine the 'floor' and the 'ceiling' doses of dexamethasone for this clinical application. The lower doses at which the drug response is no different from that produced by a placebo establish the 'floor' effect for the drug. Drug doses below this 'floor' have no efficacy in treating the condition. In contrast the higher drug doses at which there is no additional increase in efficacy establish the 'ceiling' effect. Although drug doses in excess of the 'ceiling' typically produce the maximal effect they are often associated with the development of an unacceptably high occurrence of unwanted side effects (Jackson, 1999).

The establishment of a dose-response relationship also allows for the determination of pharmacologically relevant doses, such as the ED$_{50}$ (median effective dose). The establishment of a dose-response relationship for dexamethasone and calculation of the ED$_{50}$ would be of great value for making recommendations about the dose of dexamethasone that is most effective in reducing postoperative inflammation. Determination of the ED$_{50}$ of dexamethasone in humans also would
facilitate comparisons of dexamethasone’s potency and efficacy with those of other corticosteroids used to reduce the postoperative inflammation associated with surgical third molar removal.

Perhaps the greatest concern about the use of corticosteroids in third molar surgery is suppression of the hypothalamus-pituitary adrenal axis (HPA). This may not be detected clinically during the course of such a study (Neupert et al., 1992). Further studies with blood sampling for the assessment of plasma cortisol levels and follow-up with HPA suppression tests would be required to investigate this effect.

As has already been mentioned in the previous section, none of the drug regimens used in this study managed to provide excellent pain relief on the first postoperative day. Well controlled studies using a combination of glucocorticosteroids, non-steroidal anti-inflammatory drugs, long-acting local anaesthetics and possibly opioid analgesics are needed to establish a protocol for maximum effectiveness in reducing postoperative discomfort in oral surgery.

Another improvement on the dosage regimen that has been used in this study would be to simply reduce the administration of paracetamol and dexamethasone from four times daily to twice daily, so as to enhance patient compliance. This is possible with dexamethasone because of its long half-life and a sustained-release paracetamol preparation has been formulated for this purpose, but this is not yet available locally.

This study was limited to the surgical removal of impacted mandibular third molars on a limited number of healthy patients. It would be worthwhile to carry out similar studies using different surgical models (e.g. periodontal surgery, maxillofacial surgery, periapical surgery), and/or on a larger and more diverse study population.
The aim of this study was to show that a combination of paracetamol and dexamethasone was at least just as effective as the commonly used diclofenac sodium 'gold standard', in controlling the sequelae of third molar surgery, so as to provide patients in whom NSAIDs are contraindicated, with a suitable alternative drug regimen. The findings in this study show a combination of oral paracetamol 1g and oral dexamethasone 1mg four times daily, was in fact, significantly superior to oral diclofenac sodium 50mg three times daily, in safely reducing the postoperative pain, swelling and trismus following the surgical removal of mandibular third molars under local anaesthesia in otherwise healthy patients. Also, a more predictable and consistent patient response could be expected with paracetamol and dexamethasone combination therapy than with the diclofenac sodium.

It is therefore concluded that, in the absence of contraindications the use of the paracetamol and dexamethasone combination appears to be safe and effective drugs for reducing the postoperative sequelae of third molar surgery. This may be especially beneficial for those patients in whom the usual drug regimens (e.g. NSAIDs) are contraindicated.

The use of paracetamol and dexamethasone combination therapy following this kind of oral surgical procedure, may also obviate the need for the common hospital practice to admit patients overnight in order to allow parenteral administration of opioid analgesia if necessary, thus reducing healthcare costs and avoiding opioid-associated adverse effects.
APPENDIX I.

ETHICAL APPROVAL
14th March 2003

Dr A Bartolo
Peprina A, 62
Triq Guzeppi Caruana
Tal-Virtu, Rabat RBT 02

Dear Dr Bartolo

Please refer to your application submitted to the Research Ethics Committee in connection with your postgraduate dissertation entitled:

THE EFFECTS OF PARACETAMOL WITH CORTICOSTEROID VS A NON-Steroidal Anti-Inflammatory Drug (NSAID) ON POST-OPERATIVE PAIN, SWELLING AND OTHER EVENTS FOLLOWING SURGICAL REMOVAL OF MANDIBULAR THIRD MOLARS

At the last meeting of the Research Ethics Committee held on 5th March 2003 members reviewed and approved the above-mentioned Protocol. Members advised to brief up the 'Patient Information Leaflet'.

You are kindly requested to submit to the Research Ethics Committee a brief report on completion of your research.

Yours sincerely

[Signature]

Professor A Serracino Inglott
Chairman
Research Ethics Committee

Cc: Dr J Mifsud
APPENDIX II A.

PATIENT INFORMATION LEAFLET AND CONSENT FORM (ENGLISH)
PATIENT INFORMATION LEAFLET

Following the surgical removal of wisdom teeth it is normal to expect some discomfort, pain and swelling. In order to reduce these symptoms, dentists generally advise their patients to take a particular drug(s) for the few days following the procedure. A number of drugs have been shown to be useful for this purpose.

In this study I want to see how some of these drugs compare to one another. Following the surgical removal of your wisdom tooth you will be given a suitable drug(s) to take for a few days, during which I will follow you up regularly to assess your level of pain and swelling by examining you clinically and asking you a few simple questions. This is a "controlled-blind" study, which means that you and some other patients will be given a particular drug(s), while another group of patients will be given another drug(s), and that you shall not be told the name of the drug(s) from beforehand.

Your cooperation may help us give patients the better type of drug to make them feel more comfortable following dental surgical procedures.

I thank you for your help and I wish you an uneventful recovery.

Dr Adam Bartolo B.Ch.D.
Dental Surgeon
CONSENT FORM

I am a Maltese citizen.

I have been asked to participate in a research study.

The purpose and details of the study have been explained to me by Dr. Adam P. T. C. D. and any difficulties which I raised have been adequately clarified.

I give my consent to the Principal Investigator and his delegate either make the appropriate observations/tests or both or take the necessary samples. I am aware of the inconveniences which this will cause.

I understand that the results of this study may be used for medical or scientific purposes and that the results achieved from this study in which I am participating may be reported or published; however, I shall not be personally identified in any way, either individually or collectively, without my express written permission.

I am under no obligation to participate in this study and am doing so voluntarily.

I may withdraw from the study at any time, without giving any reason. This will not influence in any way the care and attention and treatment normally given to me (applicable only in case of patients receiving treatment).

I understand that any complications and/or adverse effects which may arise during or as a consequence of the study will be recorded and any treatment which this may entail will be given within the Government Health Services.

I am not receiving any remuneration for participating in this study.

In case of queries during the study I may contact Dr. Adam P. T. C. D. Tel No 2973 886.

Signature of participant ____________________________

Name of participant __________________________________________

Id. No.: __________________________________________

Signature of Chief Investigator/Investigator ____________________________

Name of Chief Investigator/Investigator ____________________________

Id. No.: __________________________________________

DATE ____________________________

* delete where applicable
APPENDIX IIb.

PATIENT INFORMATION LEAFLET AND CONSENT FORM (MALTESE)
TAGHRIF GĦALL-PAZJENT


F' dan l-istudju, nixtieq inqabel xi wħud minn dawn il-medċini. Wara li tkun tnēh jiżqet id-darsa ta l-ġhaqal, se tingħata medċina(i) addattata(i) għalik sabiex teħodha(horn) għal ftit jiem. Matul dawn il-jiem, jien se narak regolarment u nistaqsik xi mistoqsijiet sempliċi sabiex nara kif tkun sejjer bl-uqieq u bin-nefha. Dan huwa “controlled-blind study”, jiġifieri, int u pazjenti oħra se tingħata medċina(i) partikulari, filwaqt li grupp ieħor ta' pajżenti sa jingħata medċina(i) differenti, u li ma tistax tkun ta' l-isem tal-medċina(i) minn qabel.

Il-koperazzjoni tieghek tista' tginna biex nagsiħtu l-aħjar medċina lill-pazjenti wara xi operazzjoni fil-halq.

Grazzi ta l-ġħainuna tieghek u nixtieqek fejqu mal-aqwa.

Dr. Adam Bartolo B.Ch.D.
Dentist
PROPOSTA GHALL-FORMULA TAL-KUNSENS

Jien/a cittadin/a Malta

Talbuni biex niehu sehem fl-studju ricerka

Il-ghan u d-dettagli ta' l-istudju aqegha homli li wkoll iccarrali xi mistoqsijiet li ghamilt.

Naghti l-kunsens tieghi lill-persuna responsabbli ghal din ir-ricerka u l-assistenti taghha biex jaghmu l-osservazzjonijiet li hemm biznn jew inkella jiehdu l-kampjuni u nifhem li dan jista' jkun ta' skomdu ghalija.

Jiena nifhem li r-rizultati ta' dan l-istudju jistgħu jintuzaw ghal skoqjiex xjetifizzi u jista' jji ppmubblikat rapport bil-miktub: jekk isir hekk b'ebda mod ma nista' nku identifikat/a, individualment jew bhalja parti mmin grup, minghajr il-kunsens tieghi bil-miktub.

Jiena ma għandi l-ebda damir li niehu sehem f'dan l-istudju u dan qed nagħmilu minn rajna.


Jiena nifhem li jekk ikun hemm xi kumplikazzjonij jew effetti mhux mistennija waqt l-istudju, dawn jigu mmizzla bil-miktub u jekk ikun hemm xi kura, kif jingħata fis-Servizz Nazjonali tas-Sahha.

Jiena qe4,gitallas/mhux qed nithallas* biex niehu sehem f'dan l-istudju. Jekk ikollli xi diffikulta' waqt l-istudju, nista' nistaqsi ghal:

<table>
<thead>
<tr>
<th>Dr. Adam Bartolo</th>
<th>Numru ta' telefon</th>
<th>32351536</th>
<th>jew</th>
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<td>Numru ta' telefon</td>
<td>39402845</td>
<td>jew</td>
</tr>
<tr>
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<td></td>
</tr>
<tr>
<td>Numru ta' l-identita</td>
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<tr>
<td>Isem tal-participant</td>
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<td></td>
</tr>
<tr>
<td>Firma tal-persuna responsabbli ghal din ir-ricerka</td>
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<tr>
<td>Numru ta' l-identita</td>
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DATA

*aqa' fejn ma jagapplikxas
APPENDIX III.

DATA COLLECTION FORMS
<table>
<thead>
<tr>
<th>Gender</th>
<th>Date</th>
<th>Age (years)</th>
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<tbody>
<tr>
<td>male</td>
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<td>female</td>
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<table>
<thead>
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<th>Side</th>
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<tbody>
<tr>
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<td>1A</td>
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<tr>
<td>left</td>
<td>1B</td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
<td>2B</td>
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<table>
<thead>
<tr>
<th>Impaction type</th>
<th>Impaction angle</th>
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<tr>
<td>partial bony</td>
<td>mesioangular</td>
</tr>
<tr>
<td>full bony</td>
<td>distoangular</td>
</tr>
<tr>
<td>dental</td>
<td>vertical</td>
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<tr>
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<td>horizontal</td>
</tr>
<tr>
<td></td>
<td>inverted</td>
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<tr>
<td></td>
<td>transverse</td>
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<table>
<thead>
<tr>
<th>Crown</th>
<th>Relationship to the ID nerve</th>
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<tbody>
<tr>
<td>intact</td>
<td>non-intimate</td>
</tr>
<tr>
<td>broken down</td>
<td>loss of tramlines</td>
</tr>
<tr>
<td>absent</td>
<td>narrowing of tramlines</td>
</tr>
<tr>
<td></td>
<td>change in direction of tramlines</td>
</tr>
<tr>
<td></td>
<td>radiolucent band across the roots</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of roots</th>
<th>Number of LA cartridges used</th>
<th>Tooth Division</th>
<th>Duration (minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>Adam Bartolo</td>
</tr>
<tr>
<td>Roots</td>
<td></td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>straight or favourably curved</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>curved, dilacerated or hooked</td>
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<table>
<thead>
<tr>
<th>Operator</th>
<th></th>
</tr>
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<tbody>
<tr>
<td>Oral surgeon A</td>
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</tr>
<tr>
<td>Oral surgeon B</td>
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</tr>
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</table>

<table>
<thead>
<tr>
<th>Group</th>
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</thead>
<tbody>
<tr>
<td>paracetamol &amp; dexamethasone</td>
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<tr>
<td>diclofenac sodium</td>
</tr>
<tr>
<td>No.</td>
</tr>
<tr>
<td>-----</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>3</td>
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<tr>
<td>7</td>
</tr>
<tr>
<td>Day</td>
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<td>7</td>
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</tbody>
</table>
### Immediate local complications:

- Failure of local anaesthesia
- Failure to extract the tooth
- Fracture of the tooth or root being extracted
- Fracture of the alveolus
- Displacement of the tooth or a root into the tissues
- Loss of a tooth or part of a tooth into the pharynx and so to the lung or stomach
- Fracture or subluxation of an adjacent tooth
- Collateral damage to surrounding soft tissues
- Thermal injury
- Haemorrhage
- Dislocation of the temporomandibular joint
- Fracture of the mandible
- Damage to branches of the trigeminal nerve

### Immediate systemic complications:

- Faint (vaso-vagal attack)
- Hypoglycaemia
- Panic attack/hyperventilation
- Convulsions/fits
- Myocardial infarction
- Addisonian crisis
- Respiratory obstruction
- Failure to proceed with procedure under local anaesthesia

### Delayed/late local complications:

- Excessive pain, swelling and/or trismus
- Haemorrhage
- Localised osteitis (dry socket)
- Acute osteomyelitis
- Infection of soft tissues
- Failure of the socket to heal
- Nerve damage
- Chronic osteomyelitis
- Osteoradionecrosis
- Chronic pain

### Delayed/late systemic complications:

- Infective endocarditis
- Transmissible viral infections (e.g., hepatitis)

### Adverse drug reactions:

1. 
2. 
3. 
4.

Adam Bartolo
**Patient selection and standardisation criteria:**

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of an impacted mandibular third molar indicated for removal</td>
<td></td>
</tr>
<tr>
<td>Recent (≤ 6 months) good quality OPT radiograph available</td>
<td></td>
</tr>
<tr>
<td>Adjacent fully erupted non-carious or restorable mandibular second molar present</td>
<td></td>
</tr>
<tr>
<td>Opposing maxillary third molar absent</td>
<td></td>
</tr>
<tr>
<td>Pell and Gregory relationships 1 or 2 and A or B</td>
<td></td>
</tr>
<tr>
<td>Patient is not pregnant and does not suffer from any medical condition</td>
<td></td>
</tr>
<tr>
<td>Patient is not taking any other medication</td>
<td></td>
</tr>
<tr>
<td>No contraindications to any of the drugs being used</td>
<td></td>
</tr>
<tr>
<td>Patient is able and willing to take the tablets as prescribed</td>
<td></td>
</tr>
<tr>
<td>Patient is able and willing to complete the pain chart and attend for all the follow-up visits</td>
<td></td>
</tr>
<tr>
<td>Patient has undergone a dental prophylaxis 1 week before the procedure</td>
<td></td>
</tr>
<tr>
<td>Any other dental treatment completed at least 1 week before the procedure</td>
<td></td>
</tr>
<tr>
<td>Patient did not experience any pain, swelling or infection in the week before the procedure</td>
<td></td>
</tr>
<tr>
<td>Patient has not taken any medication in the week before the procedure</td>
<td></td>
</tr>
<tr>
<td>No other procedure carried out on the day of the operation</td>
<td></td>
</tr>
<tr>
<td>Lignospan special® dental local anaesthetic used</td>
<td></td>
</tr>
<tr>
<td>1-minute preoperative mouthrinse with Corsodyl Mouthwash® given</td>
<td></td>
</tr>
<tr>
<td>Surgical procedure carried out using standard aseptic technique</td>
<td></td>
</tr>
<tr>
<td>Bone removal using rotary cutting instruments performed</td>
<td></td>
</tr>
<tr>
<td>3/0 black silk sutures used</td>
<td></td>
</tr>
<tr>
<td>No other drugs, haemostatic agents or electrosurgery unit were used</td>
<td></td>
</tr>
<tr>
<td>Surgical procedure did not last more than 30 minutes</td>
<td></td>
</tr>
<tr>
<td>No intraoperative or immediate postoperative complications</td>
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</tr>
<tr>
<td>Patient attended for all the follow-up visits</td>
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<tr>
<td>Patient completed the pain chart properly</td>
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</tr>
<tr>
<td>Double-blind methodology preserved</td>
<td></td>
</tr>
<tr>
<td>Patient took drugs and Corsodyl Mouthwash® as instructed</td>
<td></td>
</tr>
<tr>
<td>Patient did not take any other medication in the week after the procedure</td>
<td></td>
</tr>
<tr>
<td>Patient complied with standard postoperative instructions</td>
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</tr>
<tr>
<td>Healing took place uneventfully and with no postoperative complications</td>
<td></td>
</tr>
</tbody>
</table>

*Adam Bartolo*
REFERENCES
REFERENCES

41st World Medical Assembly 1989, Declaration of Helsinki.


Bateman, D. N. (1994) NSAIDs: time to re-evaluate gut toxicity, Lancet, 343; 8905: 1051-1052.


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Rosen, M., Absi, E. G., & Webster, J. A. (1985) Suprofen compared to dextropropoxyphene hydrochloride and paracetamol (Cosalgesic) after extraction of wisdom teeth under general anaesthesia, Anaesthesia, 40; 7: 639-641.


