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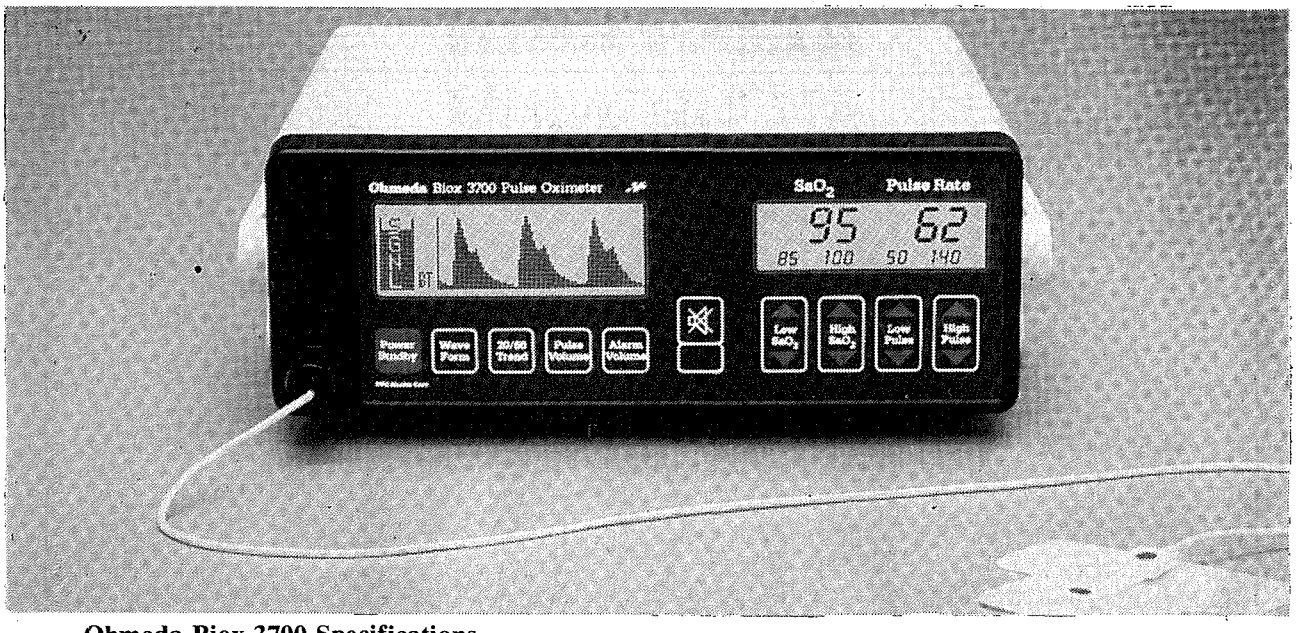

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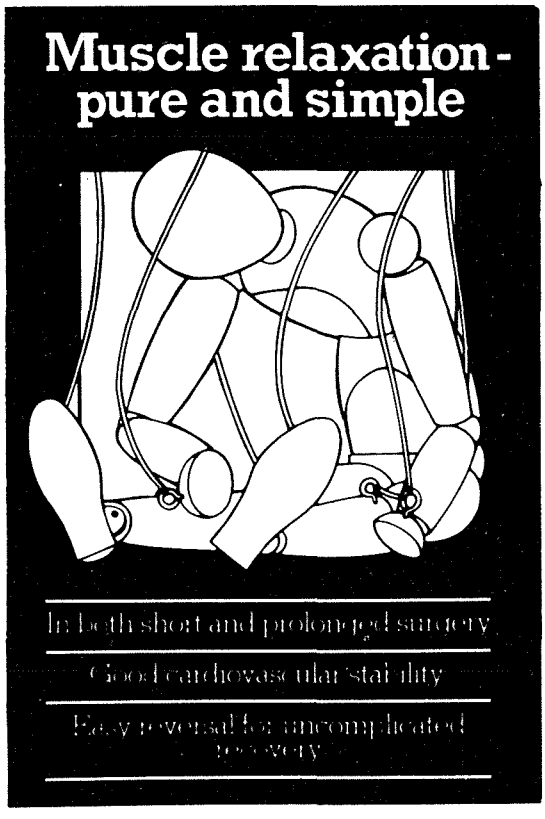

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Editor's Preface

This is the fifth Acta in the sixth year of the Association of Anaesthesiologists in the small Mediterranean island of Malta. Made up of all the anaesthetists on the Island the twenty two members of our Association have registered their mark in the World Federation of Societies of Anaesthesiologists and the European Society of Paediatric Anaesthesia.

With the aim of improving standards in Anaesthesia our Association this year is organising a conference and a video session on "Intravenous Anaesthesia". The participation of Belgian, Czechoslovak and U.K. colleagues enhances the knowledge about this subject, enlivens the discussion and enables cross fertilisation of ideas so essential in an island based Association.

As a means of reaching out to the lay public the Association has launched an essay competition dividing it in two categories, the over and the under eighteen years of age and entitled "Encountering Anaesthesia". The winning essays will be published in the next Acta. The Association thanks the local Banks for offering, prizes and book tokens to the winners.

A proposal by the Association for a World Anaesthetic Day is to be discussed by the World Federation later this year. The Association proposes that during this day October 11 of each year (the day the dentist WTG Morton gave ether anaesthesia) an effort will be made by all Associations of Anaesthesiologists to meet the lay public in order to remove fears and misconception about modern anaesthetic techniques and also to attract bright young doctors to our demanding speciality.

September 1987
St. Luke's Hospital
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N. Azzopardi
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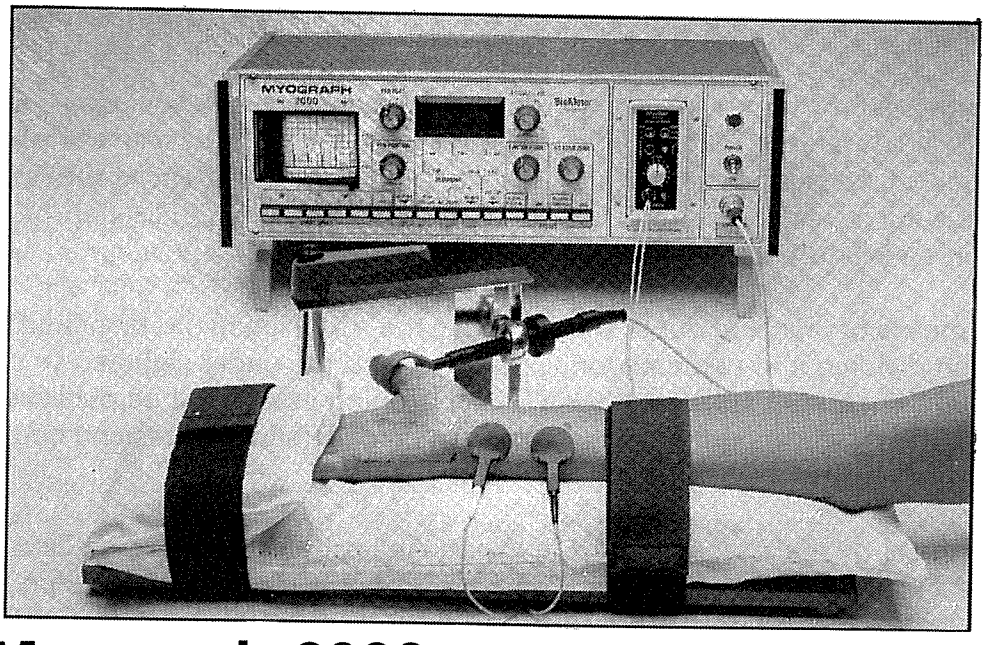

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Clinical Use of Peripheral Nerve Stimulators

D. OSTERGAARD, J. VIBY MOGENSEN

Introduction

Evaluation of degree of neuromuscular blockade during anaesthesia is often based solely upon clinical observations such as occurrence of spontaneous movements, bucking and swallowing, or testing of clinical signs such as the ability to open eyes and sustain headlift. The clinical evaluation is, however, not always adequate. Thus, in two studies on the frequency of residual curarisation in the recovery room it was found that the neuromuscular blockade was insufficiently reversed in 24-44% of patients given a non-depolarizing relaxant and not monitored with a nerve stimulator during anaesthesia[1,2].

The increased awareness of the risk of residual curarisation and the development of the new non-depolarizing relaxants, Atracurium and Vecuronium, with a rapid spontaneous recovery rate, have increased the interest in simple methods for evaluation of neuromuscular blockade. Equipment for mechanical and electromyografic (EMG) monitoring of the response to nerve stimulation has become commercially available[3,4]. Unfortunately, this equipment is expensive and rather cumbersome to use in daily clinical routine. However, one can manage quite well without such sophisticated equipment, i.e. with only a nerve stimulator.

The purpose of this review article is to discuss the principles of peripheral nerve stimulation and the clinical use of nerve stimulators without recording equipment.

Patterns of Nerve Stimulation

The neuromuscular function is monitored by stimulation of a peripheral motor nerve and evaluation of the response of the skeletal muscle innervated by that nerve.

Three different types of stimulation are used, i.e. single twitch, tetanic and train-of four (TOF) stimulation[5].

Single Twitch Stimulation

Single supramaximal current impulses are applied at frequencies of 0.1 to 1.0 Hz. The response to single twitch stimulation depends on the frequency with which the individual stimuli are applied. During a non-depolarizing block, the twitch response will decrease if the stimuli are given more than every 6-10 sec[6]. Therefore a 0.1 Hz frequency is often used during anaesthesia. The 1.0 Hz stimulation shortens the time necessary to obtain supramaximal stimulation and can be used during induction of anaesthesia. Supra-maximal stimulation is necessary to ensure activation of all muscle fibers.

Tetanic Stimulation

In clinical practice the frequency most commonly used is 50 Hz, given for 5 s. Some use higher frequencies e.g. 100Hz, but a frequency above 50 Hz is unphysiological, since a 50 Hz tetanic stimulation stresses the neuromuscular junction to the same extent as does a maximal voluntary effort[7]. During normal neuromuscular transmission the response to tetanic stimulation is sustained (fig.1). The decrement in acetylcholine release caused by the tetanic stimulation does not cause fade because the release of acetylcholine is many times greater than necessary to evoke a response (margin of safety). Following a non-depolarizing neuromuscular blocking agent the decrease in acetylcholine output during the tetanic stimulation will be manifested by a non-sustained response (fade). The degree of fade depends first of all upon the degree of neuromuscular blockade, but also upon the frequency (50 or 100 Hz) and duration of stimulation is applied. A tetanic stimulation must not be applied more often than every 6 min[8,9].

When a tetanic stimulation is combined with single twitch stimulation applied both before and after the tetanic stimulation an increased post-tetanic twitch response (PTF, PTP) is oberved

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during non-depolarising blockade. This is due to a post tetantic increase in mobilisation and synthesis of acetylcholine, which remain increased for some time after the tetanic stimulation. The increased posttetanic twitch respone returns to pretetanic levels when the acetylcholine mobilisation returns to pretetanic levels. During intense neuromuscular blockade the number of posttetanic responses can be counted (see later). This is called the posttetanic count or PTC. For each non-depolarizing relaxant an inverse correlation exists between PTC and time to first reaction to train-of-four nerve stimulation[10].

Train-of-four Stimulation

Train-of-four (TOF) nerve stimulation is a short train of four supramaximal stimuli applied at intervals of 0.5 s over a period of 2 s (2 Hz)[9, 11, 12]. The TOF stimuli are normally repeated every 10-12 s (fig 2). The amplitude of the fourth response in relation to the first is called the TOF ratio and is used as an index of the degree of non-depolarizing blockade. The TOF ratio is reduced following administration of a non-depolarizing relaxant, and is inversely proportional to the degree of the neuromuscular block. TOF stimulation is less painful than a tetanic stimulation, and the neuromuscular block remains uninfluenced by the stimulation. Contrary to the response to single twitch stimulation, the response to TOF stimulation can be evaluated without a prior control response.

The Nerve Stimulator

Several different nerve stimulators with different characteristics are available for clinical use. There are, however, some important demands on a nerve stimulator. The stimulator should be handy and simple to use and it should be able to give the following patterns of stimulation: TOF, single twitch stimuli at frequencies of 0.1 and 1.0 Hz and a tetanic stimulation of 50 Hz. Ideally the nerve stimulator should have an inbuilt time-constant system to facilitate the use of the PTC method. The response to tetanic and posttetanic stimulation depends on the frequency and duration of the tetanic stimulus and the time lapse between the conclusion of that stimulus and the first posttetanic single stimulus. It is therefore essential to keep these variables constant. The duration of the tetanic stimulus should be 5 s and the first posttetanic twitch stimulation should follow 3 s later.

The nerve stimulator should be a constant current stimulator. This means that the current to the stimulated nerve will be unchanged irrespective of changes in impedance between the electrodes[5]. In our department, a Myotest nerve stimulator[13] is used for routine anaesthesia (fig. 3). The Myotest is battery operated and very simple to use. It has the above mentioned patterns of stimulation and an inbuilt electronically controlled time-constant system which makes it possible to compare the neuromuscular response to tetanic and post-tetanic stimulation at different times during anaesthesia. The nerve stimulator gives a unipolar current impulse with an adjustable amplitude from 0-61 mA.

Placement of the Electrodes

Commonly the ulnar nerve is used for stimulation, but other peripheral nerves can be used as well, i.e. the facial nerve, the posterior tibialis nerve or the peroneal nerve. Stimulation of the ulnar nerve results in thumb adduction as the short adductor pollicis muscle is the only muscle innervated by the ulnar nerve acting at the thumb. For evaluation of the response, the arm is ideally placed in 90% abduction with the hand in supination. The skin should be properly cleansed before placing the electrodes. It is essential to place the electrodes so that nerve and not muscle is stimulated (fig. 3). Surface, i.e. rubber or disposable e.c.g. electrodes, or needle electrodes may be used. Needles are to be prefered in obese patient and in patients with very cold extremities. The impedance of rubber electrodes increases with time, especially if they are not properly cleaned after each use. Therefore, they should not be allowed to get too old.

Evaulation of the Response to Nerve Stimulation

The response to peripheral nerve stimulation can be evaluated visually, or by touch. In our department we prefer to evaluate the response of the thumb by touch, mainly because in this way the chance of direct muscle stimulation is less.

Following an intubation dose of a non-depolarizing relaxant three phases of levels of neuromuscular blockade can be recoginized (fig. 4): A phase of intense blockade, a phase of moderate or surgical blockade and a recovery phase. A few minutes after injection of relaxant the response to single twitch and TOF stimulation disappears for a period of time, the duration of which depends on the relaxant and the dose used. This period of intense blockade is called "period of no response". It is possible to quantify a part of this period by applying a tetanic stimulation and counting the number of twitches (the PTC) following the tetanic stimulation[10].

Tetanic and post-tetanic stimulation

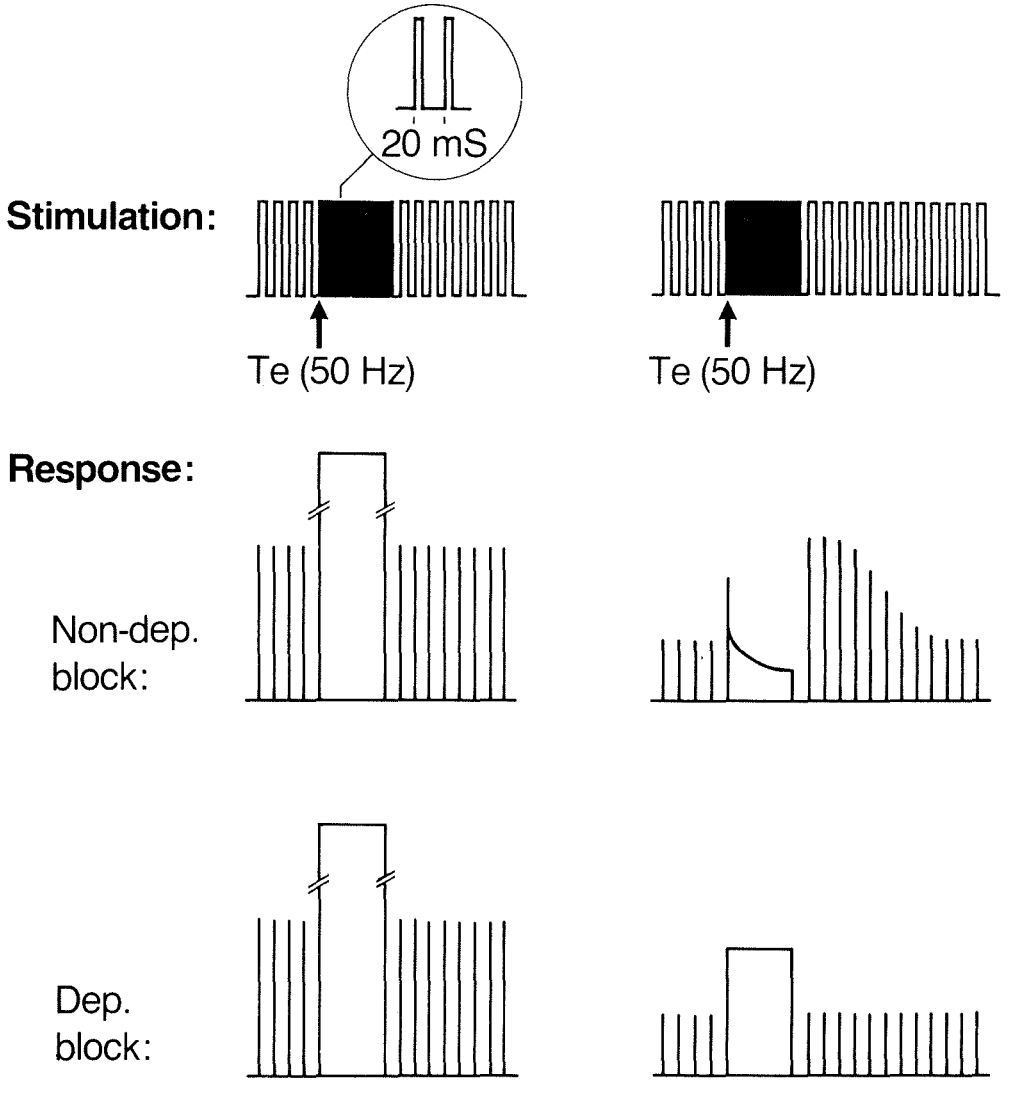


FIG. 1 illustrates a diagrammatic illustration of the evoked response to tetanic and post-tetanic twitch stimulation following injection of a non-depolarizing and a depolarizing myoneural blocking drug. From J. Viby-Mogensen 1984 with kind permission of Boerhaave Committee for Postgraduate Medical Education.

Train-of-four (TOF) stimulation

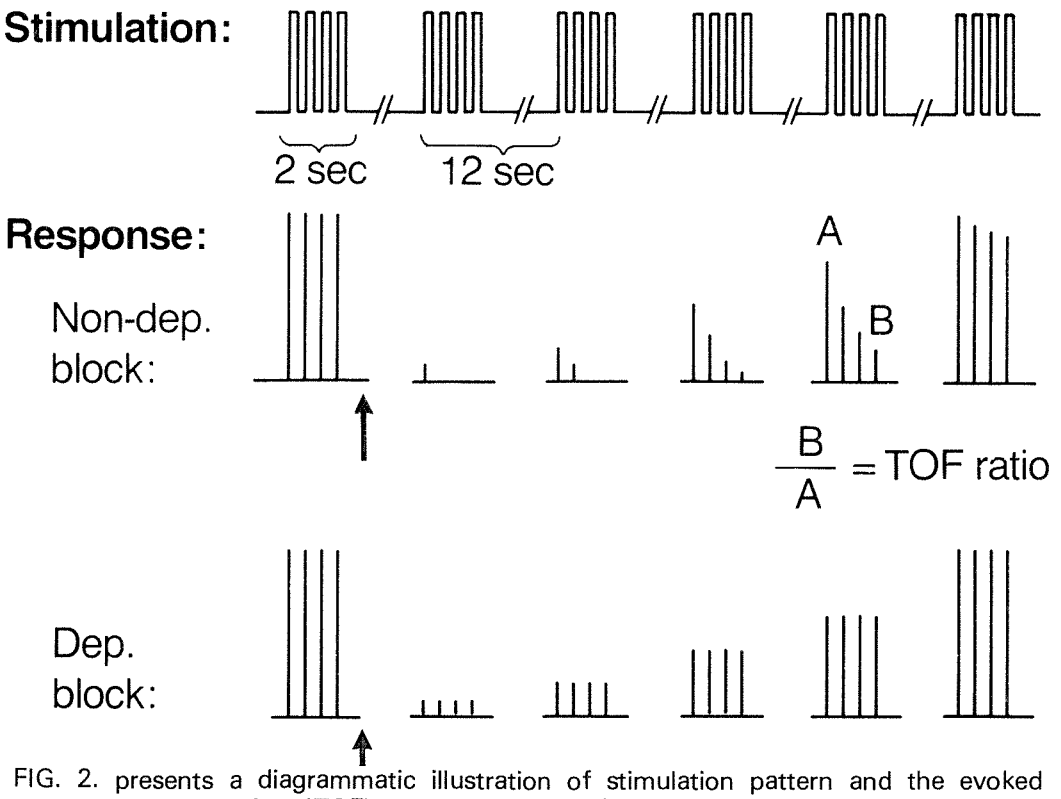


FIG. 2. presents a diagrammatic illustration of stimulation pattern and the evoked response to train-of-four (TOF) nerve stimulation. Arrows indicate injection of myoneural blocking agent. From J. Viby-Mogensen 1984 with kind permission of Boerhaave Committee for Postgraduate Medical Education.

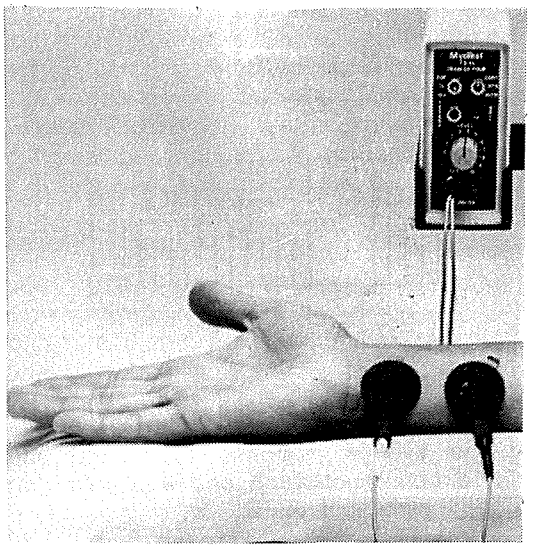
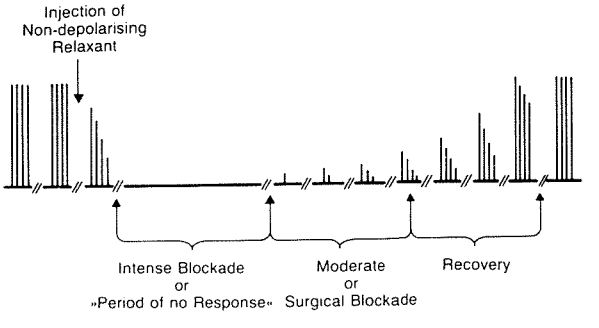


FIG. 3 represents monitoring of neuromuscular blockade without recording equipment. A myotest nerve stimulator and surface electrodes are used.

FIG. 4 presents a diagrammatic illustration of the changes in response to train-of-four (TOF) nerve stimulation during non-depolarizing neuromuscular blockade. From J. Viby-Mogensen 1985 (5) with kind permission of Clinics in Anaesthesiology.



There is a good correlation between a PTC and time to first response to TOF for any given relaxant. Following pancuronium 0.1 mg/kg, for instance, the response to post-tetanic twitch stimulation appears an average of 37 minutes before the first reaction to TOF stimulation. Fig. 5 shows the time to first reaction to TOF as a function of the number of posttetanic responses felt at the thumb at any given time[10]. Following atracurium and vecuronium the response to posttetanic twitch stimulation appears about 10 minutes before the first response to TOF stimulation[14].

Following the period of no response is the phase of surgical or moderate blockade, characterized by a gradual return of the four responses to TOF (fig.6). A relationship exists between the number of responses to the TOF stimulation and the degree of neuromuscular blockade. When only one response to TOF stimulation can be felt the degree of neuromuscular blockade is 90-95%. If all four responses are present the degree of blockade is less than 75% (15).

During recovery phase all four responses to TOF stimulation are present and the height of the fourth in relation to the first response gives the TOF ratio. A ratio of 0.7 is normally taken to reflect adequate recovery[16]. It is, however, important to realise the uncertainty in estimation of a TOF ratio without monitoring equipment. It is not possible by touch to decide whether a TOF ratio is 70, 60 or 50%. Only when the ratio is 40% or below can fade be felt with certainty[17].

Correlation Between Response to Nerve Stimulation and Clinical Parameters

When only one response to TOF stimulation can be felt – corresponding to about 10% twitch height – the degree of neuromuscular blockade is sufficient for most surgical procedures.

However, at this level of peripheral blockade respiratory movements, cough or hiccup may occur, because the respiratory muscles are less sensitive to relaxants than the peripheral muscles[18]. Therefore, when it is mandatory that the patient does not cough and no spontaneous movements take place, the block has to be more intense. In such cases, the level of blockade can be evaluated by the PTC method. To ensure that the respiratory muscles as well as the peripheral muscles are totally paralysed, the degree of peripheral block has to be so intense that no response can be elicited to post tetanic twitch stimulation (PTC = 0) (Viby-Mogensen, unpublished observation).

In the recovery phase the TOF ratio is used as an index of recovery. At a TOF ratio of 0.60 the patient is able to maintain headlift for 3 sec. A TOF ratio of 0.70 correlates well with clinical signs of adequate recovery: The patient will be able to sustain headlift for 5 sec., protrude tongue, open eyes and cough sufficiently[19].

Clinical Use

In our institution nerve stimulators are used routinely whenever relaxants are given[20]. When the patient is prepared for anaesthesia, the electrodes are placed at the wrist (fig. 3). The nerve stimulator is, however, not switched on until the patient is asleep. 1.0 Hz single twitch stimulation is used to obtain supramaximal stimulation. Hereafter, the stimulation is changed to TOF stimulation (fig. 7). Following injection of relaxant, the trachea is intubated about 30 sec. after the response to nerve stimulation has disappeared. If a non-depolarizing relaxant is used, the degree of neuromuscular blockade is evaluated by the method of PTC during the succeeding period of intense blockade. In this way, time to reappearance of the first response to TOF can be calculated, if necessary.

During the phase of surgical relaxation, TOF stimulation is used. We aim at keeping the block at a level, so that always one or two responses to the TOF stimulation are present. If a more intense level of blockade is needed for surgical reasons, the degree of blockade is again evaluated by the PTC method.

Reversal of a non-depolarizing block is normally possible when the first response in the TOF is felt. We do not therefore try to reverse the block before one and preferably two responses in TOF are felt. The reversal time is influenced by the magnitude of block at the time of injection of cholinesterase inhibitor[21]. If all responses to TOF stimulation are present, corresponding to about 25% twitch height recovery, reversal with neostigmine is always possible within 10 minutes. If no response to TOF stimulation can be felt, reversal will often be inadequate irrespective of dose of neostigmine used.

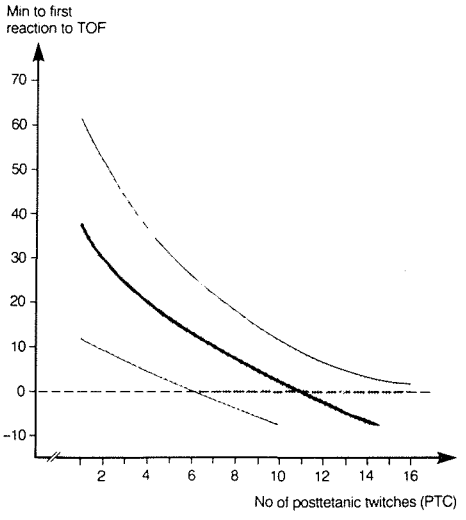


FIG. 5 illustrates the relationship between minutes to first reaction to train-of-four (TOF) and number of posttetanic twitches felt at the thumb (the posttetanic count: PTC). From J. Viby-Mogensen 1984 with kind permission of Boerhaave Committee for Postgraduate Medical Education and Excerpta Medica.

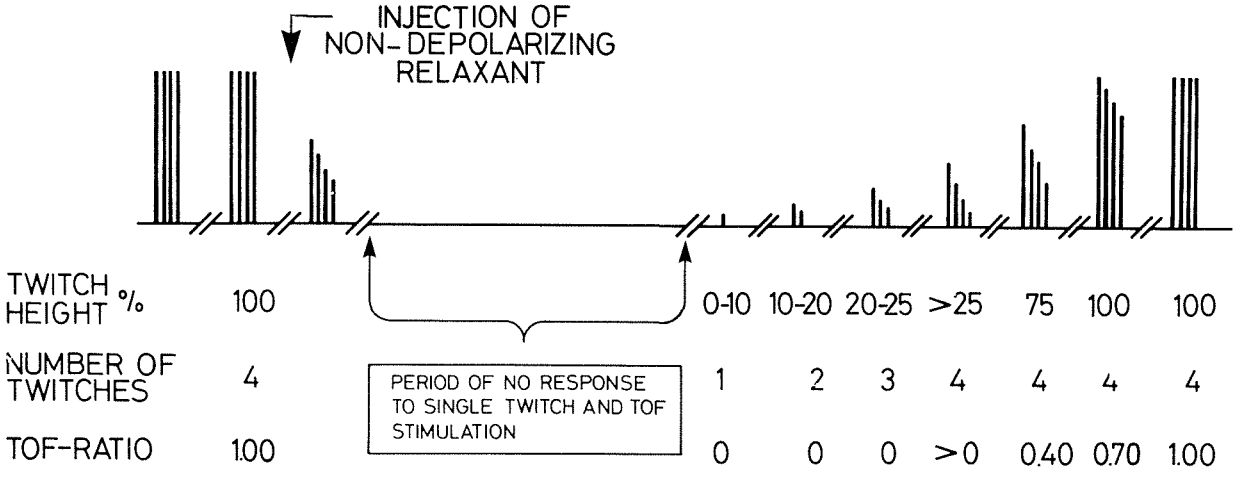


FIG. 6 presents a diagrammatic illustration of the relationship between the evoked response to single twitch (0.1 Hz) and train-of-four (TOF) nerve stimulation during non-depolarizing neuromuscular blockade, see text for further explanation. From J. Viby-Mogensen (1982) (4) with kind permission of Br J. Anaesth.

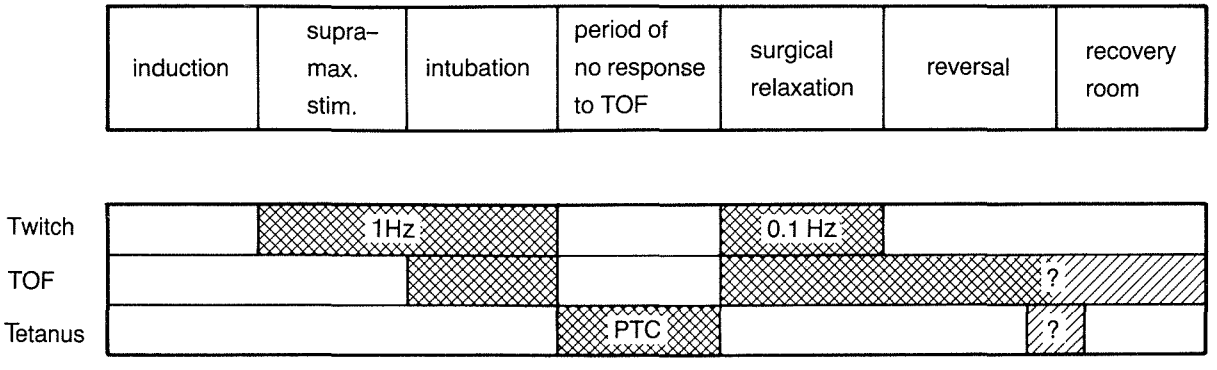


FIG. 7 represents a diagrammatic illustration of the times when different patterns of nerve stimulation are used in clinical routine at Herlev University Hospital, Copenhagen. TOF = train-of-four nerve stimulation, PTC = post-tetanic count. From J. Viby-Mogensen (1983) (18) with kind permission of Excerpta Medica.

Conclusion

Because of the difficulties in estimating a TOF ratio visually or by touch we never evaluate degree of recovery solely on the basis of the TOF response. The clinical signs of adequate recovery are always used as well.

By applying a nerve stimulator before induction and using it throughout anaesthesia overdose of relaxants can be avoided and safe reversal performed. Potentially life threatening residual curarisation can therefore be avoided.

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Curare Monitoring in the Ventilated Infant

M.J.M. GOVAERTS, V. CAPOUET

Summary

This paper reviews the indications for:
1. Neuromuscular blocade during ventilation in paediatric intensive care,
2. the expected benefits
3. the classical administration schemes.

It is the authors wish to propose a method of evaluating the depth of the block in order to ensure smooth relaxation for prolonged periods.

Introduction

Neuromuscular blockade in long term mechanical ventilation in infants and children has been advocated for some time by different authors.

In the paediatric intensive care unit, there are indications for neuromuscular blockade in medically as well as surgically indicated ventilatory support.

Whatever the indications, when a decision is taken to paralyse a child, it must be kept in mind that such action will suppress most visible reactions from the child, including reactions to pain and discomfort.

Adequate analgesia and sedation is thus mandatory when muscle relaxants are administered[1] as well as prophylactic antacid therapy via a naso-gastric tube or intravenously.

Indications for neuromuscular blockade should be correctly delineated.

1. MEDICAL INDICATIONS

Some paediatric intensivists make use of muscle relaxants whenever ventilation becomes difficult for whatever reason: for example when the child "struggles" with the ventilator. The authors do not favour this attitude but prefer to treat the cause of the problem through correct sedation or analgesia, improving ventilation conditions or emptying the bladder. A more generally accepted reason for curarisation is when good gas exchange can only be obtained by increasing positive pressure.

In those conditions, the suppression of resistance due to muscle tone can lower the pressure needed for adequate ventilation, reducing the risks of lung dysplasia and of pneumothorax due to excessive positive pressures.[2]

Finally, certain pathologic conditions due to some degree of muscle tension demand mechanical ventilation as is the case in tetanus infection.

In these conditions, where the aims is to reduce ventilatory pressure the benefits of muscle relaxants are self explanatory.

2. SURGICAL INDICATIONS

After closure of a diaphragmatic hernia, transpulmonary pressure must be maintained as low as possible to avoid rupture of the hypoglastic lung.

Primary suture of the oesophagus in the oesophagal atresia is not uncommonly performed under tension. Any rise in the intra thoracic pressure can be damaging for the suture line.

After closure of a parietal defect of the abdominal wall, gastroschisis or exomphalos, whether complete or with a temporary silastic bag containing part of the gut, any muscle activity will counteract the relaxation of the abdominal wall and interfere with healing.

Muscle relaxants are very useful in all those conditions. When surgical conditions requires neuromuscular blockade, its depth should be strictly maintained at a near surgical level i.e. 20 to 25% of twitch height.

This level should then be as stable as possible. Sudden coughing as well as other manifestations of partial reversal should never occur.

DOSAGE AND CONTROL

In most cases, administration of muscle relaxants in the ICU follows one of two schemes: either a fixed dose, administered when ventilation of the child is difficult to achieve – the "on demand" method, or a fixed dose repeated at fixed intervals – the "by the clock method.

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More recently, with the introduction of shorter acting non depolarizing muscle relaxants, a third method has been developed: continuous infusion technique with either Vecuronium[3] or Atracurium[4].

The first two schemes have serious drawbacks.

The "on demand" administration based on sheer observation of the infant leads to irregular and somewhat erratic levels of curarisation. The numerous factors involved in the genesis of pressure rise makes it unrealistic to regulate relaxant administration by following the airway pressure. This measurement can only be used to decide on the moment of weaning from the drug. The good stability can be achieved with the "by the clock method", but the dosage is based on average needs for the age and weight. Individual sensitivity can lead to either inadequate or excessive blocakde.

The probability of excessive block is increased when very sick babies whose renal and hepatic-function are impaired. Excessive block is especially inconvenient when the patient is ready to be weaned from IPPV or when it is important to assess cerebral status.

To maintain a stable level of curarisation and obtain a rapid recovery from neuromuscular blockade, continuous infusion of the new shorter acting curares has been tested in the ICU.[3,4] Atracurium infusions would be the most suitable in severly ill patients with impaired renal or hepatic functions.

However, Laudanosine, Atracurium's main metabolite, is excreted through the kidney, and since high doses produce seizures in animals,[5], caution is still required in infants with immature kidney or children with impaired renal function, until long term studies are completed.

To avoid inadequate curarisation, a more accurate monitoring of the neuromuscular blockade is advocated during muscle relaxation for mechanical ventilation in paediatric intensive care. Two methods of monitoring the end plate are commonly used in theatre anaesthetic practice: isometric contraction measurement using the pressure transducer and the stimulated electromyographic measurements. The latter is certainly more suitable in childhood due to the difficulty of adapting the pressure transducer to a small thumb. Whatever the technique, two measurements are possible: one is the twitch height (T.H.) or ratio of the muscle responses to a supramaximal single twitch at a definite time and before curarisation or ratio of the fourth to the first responses of the muscle to a train of 4 stimulations at a frequency of 2 Hertz.

This second measurement presents the advantage to be independant of any precurarisation measurement and can thus be performed at any time, more over it will not vary with alterations of the electrodes impedance. Whatever the technique used, continuous recording is mandatory. In the case of a long or medium term ventilated infant, continuous measurement as well as pre-administration measurement can be unpractical. It shuold be remembered that after a T4 stimulation a visible response to the first twitch corresponds to about 10% of T.H. recovery, to the first 2 corresponds about 20%, to three 25% and to all four 40%. Observation of the responses is thus a way of monitoring the depth of paralysis suitable in most clinical situations. In our ICU, calculation of dosage administered with this simple monitoring in comparison with a fixed interval scheme "by the clock method" has shown an economy of about 25% in circulatory stable infants.

A T.H. of about 20% should be maintained for adequate relaxation.

PRACTICAL HINTS

Assessment of adequate curarisation can be performed with a simple and compact stimulator that can be installed after the first dose of relaxant has been given and all resuscitative measures have been taken. Two electrodes are glued to the forearm on the course of the ulnar nerve. A T4 stimulation is then performed every 15 minutes until 1 or 2 contractions are elicited in the fifth finger. Stimulations are then performed every 5 minutes and a dose of relaxant is administered when the third contraction appears. Measurements can then be suspended for half an hour. The rate of measurements and the dosage is subsequently easily adapted.

The stability of the blocade is excellent and overdosage becomes practically impossible.

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Effects of Flunitrazepam – Atracurium Administration on the Pressor Response to Laryngoscopy and Tracheal Intubation

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Introduction

The pressor response to direct laryngoscopy and endotracheal intubation was recognized by many investigators (Burstein et al.)[1], (Stoelting et al.)[2]. The transitory nature of hypertension and tachycardia are probably of no consequence in healthy individuals, but may be hazardous in those patients suffering from cardiovascular diseases (Katz and Brigger)[3]. Attempts to attenuate this pressor response were not satisfactory either because the reflex was incompletely blocked or the agent used may be too long acting and sometimes causes undesirable side effects (King et al.)[4].

The aim of the present study is to evaluate the pressor response to laryngoscopy and tracheal intubation following anaesthetic induction using Flunitrazipam Atracurium sequence and comparing the results with the commonly used Thiopentone-Suxamethonium one.

Material and Methods

After obtaining hospital authorities permission a study was performed on 23 informed and consenting ASA class I patients. The pulse rate and arterial blood pressure were measured while the patients were breathing oxygen via a face mask. Through an intracath all patients received Atropine 0.01 mg/kg b.w. just before the inducing agent.

In the first group of 10 patients (7 males and 3 females) repeated readings were performed: –

a. one minute following the injection of Thiopentone sodium 5 mg/kg b.w.
b. one minute after Suxamethonium 1 mg/kg b.w.
c. during laryngoscopy and tracheal intubation and then
d. 1, 3, 5 and ten minutes afterwards.

The second group comprising 13 patients (7 males and 7 females) had the pulse rate and arterial blood pressure measured and then anaesthesia induced. The pulse rate and arterial blood pressure were measured: –

a. one minute after Flunitrazepam 0.02 mg/kg b.w.
b. one minute after Atracurium 0.5 mg/kg b.w.
c. during laryngoscopy and tracheal intubation
d. 1, 3, 5 and ten minutes later.

Anaesthesia was maintained by N_2O : O_2 (6 : 3 L/min) and Halothane 0.5% and the respiration controlled mechanically using Manley Pulmovent Model MPT.

As a muscle relaxant both groups had Atracurium 0.5 mg/kg b.w. given at 20 minutes intervals.

Results

The demographic data of both groups of patients are shown in *table 1*. In the first group the mean basal pulse rate was insignificantly altered following Thiopentone and Suxamethonium administration while it was significantly increased during laryngoscopy and tracheal intubation (P less than 0.001). This significant increase was recorded also one and three minutes after tracheal intubation (P less than 0.001 and P less than 0.01 respectively) but it returned to the basal rate (*table 2*). The systolic arterial blood pressure was significantly increased during laryngoscopy and tracheal intubation (P less than 0.001), at one minute (P less than 0.001) and three minutes (P less than 0.01) after intubation (*table 3*).

The diastolic arterial blood pressure was significantly increased during endotracheal intubation (P less than 0.001) one minute (P less than 0.001), three minutes (P less than 0.01) and at 5 minutes (P less than 0.05) from intubation (*table 4*).

In the second group of patients there was an insignificant alteration in the pulse rate following the administration of Flunitrazepam, Atracurium or during laryngoscopy and tracheal intubation (*table 5*). An insignificant alteration in the arterial blood pressure was found during the administration of Flunitrazepam and Atracurium while a significant increase in the systolic blood pressure was measured during tracheal intubation (P less than 0.001) and one minute later (P less than 0.01). The

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diastolic blood pressure was significantly increased during laryngoscopy and tracheal intubation (P less than 0.001) and after one minute (P less than 0.05). However, both the systolic and diastolic arterial pressures returned to the basal levels (*table 6 and 7* respectively). It is to be noted that quicker return to basal levels occured in group one compared to group two.

TABLE 1:

	Thiopentone – Suxamethonium		Flunitrazepam – Atracurium	
	Age / Years	Weight / kg	Age / Years	Weight / kg
Range	18 – 60	60 – 70	16 – 63	55 – 75
Mean ±	35	63.5	27.5	65.1
S.D.	14.1	4.1	8.8	6.1

Demographic data of the patients of the Thiopentone – Suxamethonium group (10 patients) and the Flunitrazepam – Atracurium group (13 patients)

TABLE 2:

	Basal pulse rate/ min.	1 min. after Thiopen-entone Atropine	1 min. after Suxame-thonium	During Laryn-goscopy and intub.	1 min. after intuba-ation	3 min. after intuba-ation	5 min. after ibtuba-ation	10 min. after intuba-ation
Mean	94.4	101.8	100.6	129	127.8	111.8	104	97
Range	80-100	90-120	82-124	100-150	110-150	100-128	90-120	88-112
S.D. ±	7.088	11.173	14.485	15.699	12.090	11.013	11.738	7.071
t. value		1.678	1.153	6.026	7.150	3.986	2.100	0.779
P.				(0.001	(0.001	(0.005		
		Insig.	Insig.	Sig.	Sig.	Sig.	Insig.	Insig.

Showing pulse rate changes before and after Atropine 0.01 mg/kg b.w. Thiopentone (5 mg/kg b.w.), 1 minute after Suxamethonium (1 mg/kg -1 b.w.) during laryngoscopy and endotracheal intubation and then 1, 3, 5 and 10 minutes after intubation.

TABLE 3:

	Basal systolic blood press-ure	1 min. after Thiopen-entone Atropine	1 min. after Suxame-thonium	During Laryn-goscopy and intub.	1 min. after intuba-ation	3 min. after intuba-ation	5 min. after ibtuba-ation	10 min. after intuba-ation
Mean	131.5	125	130.5	188	190	158	41	131.5
Range	110-150	110-140	115-150	170-220	170-220	140-180	120-150	120-150
S.D. ±	11.559	12.019	10.069	18.737	18.708	16.193	9.944	12.030
t. value		1.169	0.196	7.699	7.981	3.996	1.869	0
P.				(0.001	(0.001	(0.01		
		Insig.	Insig.	Sig.	Sig.	Sig.	Insig.	Insig.

Showing systolic blood changes before and after Atropine (0.01 mg/kg b.w.) Thiopentone (5 mg/kg b.w.), 1 min after Suxamethonium (1 mg/kg -1 b.w.) during laryngoscopy and endotracheal intubation and then 1, 3, 5 and ten minutes after intubation.

TABLE 4:

	Basal systolic blood pressure	1 min. after Thiopentone Atropine	1 min. after Suxamethonium	During Laryngoscopy and intub.	1 min. after intubation	3 min. after intubation	5 min. after ibtubation	10 min. after intubation
Mean	84	79.8	86.5	122.5	122	100	93	86
Range	70-95	70-95	80-100	100-180	95-180	90-120	80-100	80-100
S.D. ±	8.756	8.727	6.687	23.482	24.290	8.165	6.749	6.992
t. value		1.019	0.681	4.609	4.415	4.009	2.442	0.535
P.				(0.001	(0.001	(0.005	(0.05	
		Insig.	Insig.	Sig.	Sig.	Sig.	Sig.	Insig.

Showing diastolic blood changes before and after Atropine (0.01 mg/kg b.w.) and after Thiopentine (5 mg/kg b.w.), 1 min after Suxamethonium (1 mg/kg) during laryngoscopy and intubation then 1, 3, 5 and ten minutes after laryngoscopy and endotracheal intubation.

TABLE 5:

	Preanaesthetic. pulse/ minute	1 min. after Flunitrazepam	1 min. after Atracurium	During Laryngoscopy and intub.	1 min. after intubation	3 min. after intubation	5 min. after ibtubation	10 min. after intubation
Mean	111.38	109.23	103.15	119.92	112.77	110	103.92	99.69
Range	86-160	90-140	80-132	100-160	98-136	94-130	94-120	80-120
S.D. ±	18.350	18.647	16.842	16.148	11.649	12.936	10.004	12.486
t. value		0.285	1.145	1.210	0.222	0.213	1.237	1.825
P.								
		Insig.	Insig.	Insig.	Insig.	Insig.	Insig.	Insig.

Showing pulse rate changes before and after Flunitrazepam (0.02 mg/kg) one minute after Atracurium (0.5 mg/kg b.w.) during laryngoscopy and endotracheal intubation then 1, 3, 5 and 10 minutes after endotracheal intubation.

TABLE 6:

	Preanaesthetic. Systolic Blood Pressure	1 min. after Flunitrazepam	1 min. after Atracurium	During Laryngoscopy and intub.	1 min. after intubation	3 min. after intubation	5 min. after ibtubation	10 min. after intubation
Mean	128.85	123.85	123.5	155.38	143.46	125.38	122.69	121.92
Range	120-140	110-150	110-160	140-170	110-160	110-150	110-140	110-140
S.D. ±	7.403	9.608	12.647	10.500	13.751	10.500	8.807	9.903
t. value		1.428	1.265	7.153	3.241	0.936	1.855	1.942
P.				(0.001	(0.01			
		Insig.	Insig.	Sig.	Sig.	Insig.	Insig.	Insig.

Showing systolic blood pressure changes before and after Flunitrazepam (0.02 mg/kg) one minute after Atracurium (0.5 mg/kg b.w.) during laryngoscopy and endotracheal intubation then 1, 3, 5 and 10 minutes after intubation.

TABLE 7:

	Preanaesthetic. Diastolic Blood Pressure	1 min. after Flunitrazepam	1 min. after Atracurium	During Laryngoscopy and intub.	1 min. after intubation	3 min. after intubation	5 min. after ibtubation	10 min. after intubation
Mean	86.15	81.92	82	102.69	93.85	83.38	83.08	81.769
Range	75-100	75-95	75-100	90-120	80-110	75-100	75-100	75-90
S.D. ±	7.946	6.262	7.937	7.804	8.454	7.292	7.511	6.379
t. value		1.414	1.280	5.145	2.299	0.247	0.973	1.489
P.				(0.001	(0.01			
		Insig.	Insig.	Sig.	Sig.	Insig.	Insig.	Insig.

Showing diastolic blood pressure changes before and after Flunitrazepam (0.02 mg/kg) one minute after Atracurium (5 mg/kg b.w.) during laryngoscopy and endotracheal intubation then 1, 3, 5 and 10 minutes after endotracheal intubation.

Discussion

The increase in the heart rate and arterial blood pressure during laryngoscopy and endotracheal intubation were probably due to reflex stimulation of the sympathoadrenal system and the consequent increase in the circulating catecholamine levels (Fox, et al., 1977) (5).

Flunitrazepam, a fluorinated benzodiazpine derivative is a new drug used for anaesthetic induction and it is less cardiovascular and respiratory depressant than Thiopentone sodium. The muscle relaxant requirement after both agents is not different.

Slowing of the heart rate is a common finding following induction of sleep with Flunitrazepam and this is probably related to its sedative and hypnotic effects together with an increase in the vagal tone (Stovner et al.)[6]. The moderate decrease in the systematic arterial blood pressure following the administration of Flunitrazepam is explained by (Haldemann et al.)[7] to be due to a decrease in the total peripheral resistance.

Most neuromuscular blocking agents cause haemodynamic changes. D-tubocurarine causes significant hypotension by stimulating histamine release or sympathetic ganglion blockade or both (Savarese)[8]. Gallamine (Thomas)[9] and Pancuronium (Stoelting)[10] may cause tachycardia and hypertension as a result of vagolytic or sympathomimetic effects. (Nigrovic et al.)[11].

Suxamethonium may interact with the nicotinic receptors releasing endogenous catecholamines which is responsible for the occasionally reported cardiovascular instability following its administration. Atracurium (Hughes and Chapple)[12] unlike many of the currently available muscle relaxants is devoid of any significant cardiovascular effects even at multiples of full neuromuscular blocking doses. However Basta et al.[13] demonstrated a transient significant decrease in the heart rate and arterial pressure, occuring 60 -90 seconds after the administration of Atracurium 0.6 mg/kg or more but these effects disappeared within 5 minutes.

In the present study a transient significant increase in the pulse rate, systolic and diastolic arterial blood pressure were recorded in the Thiopentone-Suxamethonium group of patients during laryngoscopy and tracheal intubation. These results agree with those reported by previous investigators and are associated with a significant increase in the plasma noradrenaline levels which lasted for 5 minutes before decreasing to the preanaesthetic values.

In the present study an insignificant alteration in the pulse rate was demonstrated during laryngoscopy and tracheal intubation in the Flunitrazepam Atracurium treated group of patients. In addition the systolic and diastolic arterial blood pressure although increased during laryngoscopy and tracheal intubation, returned to pre-aneasthesia levels quicker in this group.

Haigh et al[14] demonstrated a significant increase in the mean arterial pressure during laryngoscopy and intubation after Thiopentone – Suxamethonium as also after Thiopentone-atracurium sequences. It is quite possible that the use of Flunitrazepam and Atracurium through a combined enchantment of the cardiac vegal tone and the decreased total peripheral resistance modifies and attenuates the pressure response to laryngoscopy and intubation.

Conclusion

It is suggested from the present study that Flunitrazepam and Atracurium are worth using as an alternative to Thiopentone and Suxamethonium sequence in situations where these agents are contraindicated and when the pressor response to direct laryngoscopy is a real hazard.

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Pelvic Osteotomy Under General Anaesthesia Combined with Caudal Blockade in Children

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Summary

Combined anaesthesia (Local plus General) has been used at the 1st Clinic of Orthopaedics since 1986. A trial is described involving 21 children and comparing them with a control group of 14 cases having only inhalation anaesthesia. Caudal blockade with Bupivacaine is the local anaesthesia used to decrease stress during pelvic osteotomies. The use of combined anaesthesia provides smoothness and stability with absence of side effects and the doses of anaesthetic and postoperative analgesic agents used were less than in the inhalation group.

Postoperative analgesia lasts approximately 2-4 hours longer than general anaesthesia.

Introduction

The pelvis is one of the areas in the human body that when operated on triggers stress and its consequent chain reaction. This is mediated primarily via sympathetic connection between pelvis and the suprarenal glands.[1].

The medulla of the suprarenal gland originates phylogenetically from the sympathetic ganglion after the postganglionic neurons have lost their axons and turned to gland cells participating in stress reactions by secreting adrenaline and noradrenaline directly in the blood stream.

Therefore the interruption of sympathetic connection between the site of operation, the pelvis and the suprarenal gland by means of local anaesthesia has prophylactic importance in avoiding stress during and after operation.

Caudal block anaesthesia is the local method used for pelvic osteotomies at our clinic.

Material and Method

The investigated groups needing pelvic operations consisted of 21 children aged 2 - 17 years (average 11 years) and a control group of 14 children 4 - 18 years (average 14 years) see Table No. 1.

The caudal blockade was performed in a left or a right side position under general anaesthesia. Routine premedication was administered i.m. 30-45 minutes before the induction of anaesthesia. The pre-medication used was Scopolamine bromide 0.01mg per 1kg b.w. (Benarcos SPOFA) and Chlorpromazine hydrochloride 0.5 mg per 1kg b.w. Before the induction of local anaesthesia Ketamine was used in an intramuscular dose of 8-10 mg per 1 kg b.w. For local anaesthesia Bupivacaine was administered in concentration 0,3% - 0,35% according to Cvachovec[2] in the following doses.

children under 5 years of age - age in years + 1 ml
children under 10 years of age - age in years + 2 ml
children under 15 years of age - age in years + 3 ml

After the administration of the local anaesthetic the child was placed in the supine position and an i.v. line was prepared. The operations lasted 60 -130 minutes (one lasted 180 minutes) including spica cast application.

During the operations the blood loss was minimal. Physiologic saline was administered in all cases but in two patients blood transfusion had to be given.

Results

Out of 21 cases selected for local anaesthesia successful block was obtained in 19 cases. In two cases this failed. Out of these 19 cases, 12 patients did not need any other anaesthesia but in 6 cases additional Ketamine was needed in doses of 0,5-1, 0 mg per 1 kg b.w., I.V., and in 1 case inhalation of Nitrous oxide and Oxygen had to be added.

During the operation the blood pressure decreased by 10 - 15 torr (10 - 12%) after 35 - 45 minutes.

At the same time the heart rate slowed down by 10 - 20 beats per minute (10 - 20%). Both these effects were probably due to the onset of the sympatolytic influence of local anaesthesia and

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simultaneous gradual weaning of the Ketamine - effect.

The duration of analgesia was an average of 8 hours postoperatively.

The control group was operated under inhalational anaesthesia with Nitrous oxide, Oxygen and halothane but with controlled ventilation.

During these operations there were no changes in the blood pressure. But during the pelvic osteotomy the elevation of bone grafts was accompanied by tachypnoea and tachycardia heart rate (increased by 20 - 25 beats per minute).

In this group analgesia lasted 5 hours after the operation.

The children in the first group were calmer and could be sooner contacted in the early postoperative period than those in the control group.

Discussion

The combination of Caudal block with rather heavy premedication and Ketamine has the following advantages.

1. An adequate and heavy premedication reduces global preoperative doses of anaesthetic agents.
2. Ketamine dissociative anaesthesia enables the smooth administration of the caudal blockade especially in small children.
3. The interruption of sympathetic transmission and the liberation of stressors protects the patient from cardiovascular instability.
4. Caudal blockade induces satisfactory muscle relaxation in pelvic area and lower extremities while leaving a sufficient ventilatory performance.
5. Postoperative analgesics are required 2 - 4 hours later than after inhalation anaesthesia.
6. The anaesthesia is smooth and stable.
7. After caudal blockade children recover sooner, they do not suffer from pain and soon join the social life in the ward. Bupivacaine 0,3 - 0,35% can be considered the best concentration, as lower concentrations do not guarantee adequate intraoperative analgesia and higher concentrations have shorter analgesic effect.

In two cases of failure it was impossible to penetrate the hiatus canalis sacralis probably owing to congenital abnormalities in the sacral region.

In the group with caudal blockade no side effects, e.g. blood pressure depression, retention of urine or incontinence, infection, neurologic complication or vomiting were observed.

In the control group only one boy suffered from transitory retention of urine and two girls vomited.

Cvachovec has published similar results with caudal blockade in children in urological operation.[2]

Conclusion

The advantage of the above mentioned combined anaesthesia i.e. restriction of stress, calm and painless operative and postoperative period, lower consumption of anaesthetic agents, longer analgesic postoperative interval, satisfactory muscle relaxation of lower limbs with normal function of respiratory muscles and practically no side effects support the application of this method in pelvic operations in children.

TABLE NO. 1
Group: Ketamine + caudal blockade

Operation	**Number of Patients**
Pemberton's acetabuloplasty with open reduction of the head of the hip joint	3
Salter's osteotomy with reduction of the joint/ evacuation of the acetabulum/	3
Salter's osteotomy in Elizabethtown modification with prolongation of lower limb by 3cm	8
Salter's osteotomy without reduction	7
Steel's tripple osteotomy of pelvis	1
Bosworth shelf operation	1
Total	21

Control group: anaesthesia with O_2 + N_2O + Halothane

Pemberton's acetabuloplasty without open reduction	3
Salter's osteotomy of pelvis without reduction	9
Steel's triple osteotomy of pelvis	1
Chiari osteotomy of pelvis with transposition of great trochanter	1
Total	14

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Venous Air Embolism as a Complication of the Sitting Position in Surgery

T. WITKIEWICZ

Summary

The sitting position is the patient position mostly favoured for neurosurgical exploration of the posterior cranial fossa and cervical spine. It allows excellent physical access to the operative site and reduced bleeding – due to improved venous drainage by the physical force of gravity.

Two specific position-related problems are of interest to the anaesthetist

1. Postural haemodynamic disturbance
2. Venous air embolism

Introduction

Although aspiration of air into the venous system during surgery is possible whenever the operation site is above the right atrial level and low central venous pressure exists, this complication is rather rare.[1]

Two factors may predispose to the occurence of venous air embolism during posterior fossa surgery in the sitting position.

i. the high level of the operation site above the heart
ii. the nature of dura sinuses and skull veins whose walls attached to adjacent structures prevent their collapse.

Venous air embolism has been known since the 19th century but was mentioned as a very rare complication. Because at that time only clinically evident abnormalities such as arrhythmias and hypotension were noted it was described as being a very dangerous but rare complication.

Nowadays, Doppler ultrasonic devices enable the anaesthetist to detect airbubbles in the right atrium; bubbles as small as 0.5 ml., a size that is not significant for pulmonary embolism, are detected by the Doppler. More serious embolisation can be detected by capnography – sudden drop in end tidal pCO_2 as evidence of fall in pulmonary flow and by monitoring pulmonary vascular resistancce that rises with diminished blood flow to the lungs.[2]

The sensitivity of three current methods of venous air embolism detection was compared in the prospective study of Bedford[3] on a group of 100 sitting position operative procedures on head and neck. Doppler detection of air bubble was positive in 80 cases, pulmonary artery pressure elevation in 36 patients, end tidal pCO_2 decrease in 30 cases and yet no patient had hypotension or arrhythmias.

From a catheter in the right atrium or pulmonary artery small volumes of air 2 to 20 ml were aspirated quite commonly in the monitored cases.

Now we know that in most cases air aspirated into the veins above the heart passes on and collects in the superior vena cava-right atrium junction, it floats there causing turbulent blood flow and is slowly removed from there to the pulmonary circulation partly dissolving in the blood and partly as small bubbles ending up by blocking the small pulmonary arteries. It seldom happens that large volumes of collected air pass rapidly forward causing massive pulmonary embolism, pulmonary vasoconstriction, diminishing the right heart output, followed by low left heart preload and failure of the left ventricle performance.

Despite the tachycardia, compensatory hypotension follows and influenced by pulmonary shunts a further decrease in oxygen saturation occurs.

The development of these events depends on:

1. volume and rate of air aspiration
2. increase in volume of air bubble relation to N_2O inhalation
3. rate of clearance from superior vena cava – right atrial junction.

From studies performed on animals the possibility of estimating LD 50 of the air in ml/kg of body weight may be calculated in man.[4]

In one study utilising Doppler detection of venous air embolism the LD 50 was calculated to be 30mls air per kg body weight. As clinical symptoms developed in only 69% of children and in 36% of adults from Doppler positive groups it follows that clinical detection does not correlate with physical symptoms, even though smaller volumes of air were sufficient for symptoms to develop in children.[5] The rate of aspiration is of greater value

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than the volume aspirated. Slow I.V. injections of 1000ml of the air during 50-100 minutes were well tolerated by dogs, but rapid injections of 100ml were always fatal.

Since there is the big difference in blood/gas distribution coefficient for N_2O (0.46) and for N_2 (0.013) it is much easier for nitrous oxide to pass from air-buble to blood than for Nitrogen to do the same. During anaesthesia with 50% N_2O in Oxygen we can expect 100% enlargement of air-bubble in blood and with 70% inspired N_2O even 340% enlargement.

Management

The time taken for the air bubble to clear is well correlated with the cardiac index and the anaesthetist has to maintain a good cardiac output. The treatment of detected venous air embolism consists of the elimination of N_2O from inspiratory gas and actively sucking air and foam from a right atrium through the cardiac catheter. Immediate treatment avoids haemodynamic deterioration although pulmonary artery pressure remains elevated for minutes or even hours.

Some anaesthetists used to apply PEEP in order to prevent venous air embolism. Virtually, only high PEEP that is over +15 kPa is effective, but it eliminates one of the advantages of the sitting position by causing increased oozing of blood from the operation area. PEEP can reverse right to left atrial pressure gradient and produce the most serious venous air embolism complication – paradoxical air embolism i.e. the passing of bubbles through the patent foramen ovale to the left heart and systemic circulation and to the brain or other organs.

Assuming that a patent foramen ovale occurs with an incidence of 26 - 30% of population[6] the risk of paradoxical embolism must always be considered.[7]

Conclusion

It seems reasonable to introduce echocardiographic examination of the patient before performing the sitting position surgery and in case right-left heart patency is proven to choose a modified lateral sitting position.[8]

It is essential to have an indwelling cardiac catheter (right atrial one) during the performance of surgery in the sitting position.

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Halothane Hepatitis: A Review

D. SPITERI

Introduction

The association of liver damage and Halothane, a divisive issue hotly debated in the '60's and 70's, is now an accepted finding following the accumulation of clinical and experimental evidence. However Halothane is too often blamed when a clinician is confronted with a patient with unexplained jaundice after anaesthesia. This prejudiced attitude has been inherited from the days of Chloroform anaesthesia. It is an understandable human weakness to try and find a scape goat for whatever goes wrong – in this case an idiosyncratic reaction to an otherwise safe drug.

Historical Background

Unexplained jaundice after Chloroform anaesthesia was first recorded in 1848, only one year after its clinical introduction by James Simpson – a Professor of Obstetrics from Edinburgh. This "Delayed Chloroform Toxicity" 1 - 2 days after the anaesthetic, also involved the heart, kidneys, pancreas and spleen causing "fatty degeneration". The cause and effect relationship between Chloroform and jaundice is not as clear as was once believed. Repeated short administrations were associated with an increased incidence and severity of the syndrome. Protective factors were:

a. a good nutritional state
b. good oxygenation
c. avoidance of carbon dioxide accumulation.

Another halogenated hydrocarbon anaesthetic Trichloroethylene causes hepatotoxicity in animals only. Ether and Nitrous Oxide have never been implicated in liver damage.

Since its introduction to anaesthesia in 1956, Halothane soon became the standard volatile anaesthetic – a postion which it still holds today – due to its potency, smoothness of use and its non-inflammability. Preliminary animal studies prepared during development of the drug had not shown any propensity for hepatitis but reports of unexplained jaundice started appearing in 1958[1].

Incidence

By 1963 at least 350 possible cases of Halothane hepatitis had been reported world wide.

A large scale retrospective epidiomological study – the American National Halothane study of 1969 – was inconclusive except in confirming that Halothane hepatitis was quite a rare event. In this study 850,000 patients were reviewed. Out of this cohort of patients

30% had been anaesthetised with Halothane and in 9% the exposure was repeated.

82 patients had hepatic failure at post-mortem of these 9 patients had jaundice that could not be explained either surgically or medically but 7 of these had received Halothane some time before dying. The mortality from anaesthesia with Halothane and without Halothane was not significantly different.

Mushin in 1971[2] estimated that 1.5 million patients were anaesthetised each year with Halothane in England and Wales (i.e. 80% of general Anaesthetics) 7% were re-exposed to it within a month. A yearly average of 7 - 9 cases of jaundice after Halothane was reported.

The frequency of Halothane hepatitis was estimated as 1 : 35,000 Halothane anaesthesia, a very low figure indeed.

From analysis of 313 well documented cases of jaundice following Halothane anaesthesia reported to the Committee on Safety of Medicine in the years between 1964 and 1985 the following facts can be studied:

1. 246 of the cases (78.5%) were multi-exposed
2. 169 of these cases (54%) were re-exposed within 28 days.

Out of the 313 cases described:

1. 146 patients (47%) died
2. Mortality was 32% for patients exposed only once
3. 41% for those exposed twice
4. 54% for those multi exposed

From results of experimental studies, two, probably distinct, forms of Halothane liver damage have been identified:

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TYPE 1

Minor : Ser. Aminotransferase (AST) levels become raised during the first 1 - 3 days post-operatively in 20% of patients exposed to Halothane. These changes sometimes became manifest only in the 2nd post-operative week but the patients remain well clinically.

TYPE 2

Massive fulminant hepatic necrosis – a rare event. The onset of such a reaction takes 1 - 2 weeks to develop.

Jaundice[3,4]

Jaundice appearing in the days and weeks following general anaesthesia can be classified as:

a. Transfusion reaction; incompatibility and haemolysis of old, infected or heat haemolysed blood.
b. Effects of drugs on patients with some enzyme defects eg. G6PD deficiency.
c. Crises in certain abnormal Hb disease (eg. sickle cell).
d. Operative stress on pre-existing liver disease: Hypoxia, Hypoperfusion.
e. Drug toxicity
    1. Hepatitis: non-narcotic analgesics, antibiotics, cystotoxics, anti-epileptic drugs.
    2. Cholestasis: Antibiotics, cytotoxics, steroids, oral, hypoglycaemic agents, neuroleptic agents.
f. Hepatic infective process/abscess of the liver.
g. Viral infective A, B, non A, non B, CMV, Epstein-Barr virus. It remains true that viral hepatitis cannot yet be excluded in any patient with absolute certainty, Viral hepatitis and Halothane hepatitis are virtually indistinguishable clinically and histologically. IgM antibodies for Hepatitis A prove the presence of active infection. The presence of IgG antibodies only indicate a previous infection (Up to 80% of population have a positive test). The stress of an operation may also influence the severity of a viral hepatitis.
h. Biliary tract obstruction or leakage with biliary peritonitis.
i. Septicaemia.

Animal Studies

Different rat models have been studied[5]: one necessitates the pre-treatment of male rats with Phenobarbitone and then exposure to Halothane under hypoxic conditions (i.e. the REDUCTIVE PATHWAY). Other models require pre-treatment of guinea pigs with Thriiodothyronine or Polychlorinated biphenyl without the necessity of hypoxia during Halothane exposure, (i.e. the OXIDATIVE PATHWAY).

Although these models helped considerably in the understanding of Halothane hepatitis; they may not be totally relevant in man;

1. Halothane hepatitis in animal models is a temporary and relatively mild disorder.
2. Patients taking inducing drugs e.g. epileptics have not been shown to have a greater risk of Halothane hepatitis.
3. Mice, dogs, female rates, non-adult rats and a certain strains of rats are resistant to liver injury by Halothane but not to hypoxic liver damage. This highlights the considerable species, sex, age and even strain differences that exist in susceplibility to Halothane hepatitis.

Human Studies

Several features of Halothane hepatitis gave rise to the concept that allergy or hypersensitivity were implicated.

1. Multiple administrations increased both the incidence and the severity of the hepatitis; massive necrosis has happened. Rarely after a single exposure. There have been instances where patients had jaundice attributed to a 2nd Halothane anaesthetic who received a third exposure without mishap.
2. Serological abnormalities indicative of hypersensitivity reaction are often found in patients having Halothane jaundice. These are peripheral eosinophilia, circulating immune complexes, serum antibodies (notably liver-kidney microsomal antibody and antibody to thyroglobulin) could be demonstrated in 44% of cases during the liver failure.
3. Liver damage following occupational exposure to Halothane has been reported in operating theatre personnel. These exhibit raised AST's, evidence of hepatitis on liver biopsy, demonstration of specific antibodies to halothane, altered hepotocytes and in some cases positive 'challenge tests'. With avoidance of exposure the AST levels returned to normal values in four weeks.
4. Induction of liver enzymes, often occurs with chronic exposure, to trace concentrations.

Anaesthetics are known to alter cell membranes – this fact is the basis of one theory for their mode of action – but they do this reversibly. It is unlikely that the appearance of the antigen is due to a haptene

effect of Halothane on the membrane. The antigen is not present on the membrane immediately following exposure[6].

Enhanced metabolism of the drug cause the development of reactive metabolites which bind covalently to the endoplasmic reticulum. These potential antigenic complexes will later be incorporated in the cell surface membrane and thus become exposed to immune attack, an antigen – antibody reaction.

The biotransformation of Halothane was not known to exist before it had been in use for at least 6 years! But by 1967 it was established that about 18% of inhaled Halothane is in fact metabolised. Halothane may undergo metabolism through 2 pathways. Both can give rise to reactive intermediates.

a. OXIDATIVE METABOLISM is the major metabolic pathway for Halothane, and is stimulated by high oxygen tensions. Several compounds produced in this way but mainly it is Trifluoroacetic acid that dominates the picture.
b. REDUCTIVE METABOLISM of Halothane was first described in 1973 and noted to be stimulated by hypoxic conditions and pretreatment with enzyme inducers (eg. Phenobarbitone), Fluoride and bromide ions are released freely during this type of degradation.

The association with hypoxia led some investigators to implicate hypoxia as a necessary factor in all cases of hepatotoxicity in man. However it is rare that liver necrosis is the primary and sole untoward event seen with hypoxic episodes in man. Hypoxia and splanchnic hypoperfusion are much more common during anaesthesia than we would like to remember and yet massive liver necrosis is rare. Furthermore the timing and type of lesion occuring with hypoxia is quite different from that with Halothane hepatitis.

Features Associated with Halothane Hepatitis

Brown et al.[7] and Travel et al. [8] when describing the adverse effect to volatile anaesthetics could classify the following:

1. Female to male ratio 1:8:1
2. More than 2/3 of the patients were obese.
3. The age range of 21 to 76 years (mean 57) is somewhat older than the general age distribution of patients undergoing anaesthesia. It also contrasts appreciably with the much younger age distribution for viral hepatitis – (10 - 60 years (mean 25).
4. There is no association with type or length of surgery.
5. Repeated exposure to Halothane within a 'relatively' short time. However cases are known where the interval was 6 and 7 years.
6. 60% may show retrospective evidence of an adverse reaction to Halothane.
7. In one third a history of allergy to some other drug was obtained.
8. In 75% of cases, unaccountable post-operative high pyrexia is seen.
9. Deep jaundice appearing in about 5 days (2 - 26 days) post-op. The shorter the period of re-exposure the quicker the onset of jaundice. The presence of other signs of severe liver damage: Prothrombin time, 18 raised to 150 secs, Serum Aspartate 386 raised to 10,272 units and hepatic encephalopathy.
10. Exclusion of viral hepatitis with the generally available serological tests.
11. Demonstration of antibody which reacts with Halothane-altered liver-cell preparation – a positive means of diagnosis – but not generally available except in certain research centres.

Halothane Hepatitis in Malta

In St Luke's Hospital, Malta over 18,000 General Anaesthetics are administered yearly and Halothane is the agent used in 80% of these cases. The incidence of Halothane hepatitis is rare but I could find confirmation of two cases of this happening.

In the first case Mrs G.P. 54 years, 80Kg body weight, married with three children had been operated in 1950 for uterine fibroids. She was allergic to Penicillin and Tetanus Toxoid. She suffered from hypertension and was on Methyldopa 50mg and Frusemide 40mg daily. As she was also suffering from an anxiety neurosis she was having Lorazepam 3mg and Maprotilene 50mg daily. She smoked 40 cigarettes a day.

In September 1986 she was admitted with a lump in the breast and after frozen section biopsy, mastectomy and axillary lymph node clearance was performed. She was given Midazolam 0.005mg per kg b.w. and Atropine 0.01mg per kg b.w. as premedication and then Fentanyl 0.001mg per kg b.w., Pentothal 5mg per kg b.w. and Suxamethonium 1mg per kg b.w.

After recovery from the intubating dose of Suxamethonium, breathing was spontaneous and the patient had Halothane 2% in N_2O and Oxygen, 4 litres each. Pentazocine 0.5mg per kg b.w. was given for pain post-operatively on a pro re neta basis (3 doses in all).

Three days post-operatively she had a temperature (39°C) and was started on Erythromycin Stearate 5mg per kg b.w. peros. Her BP was controlled by Pindolol 10mg and Clopamide 5mg, daily, and for sedation Diazepam 10mg and Lorazepam 4mg given.

The histology result was reported as infiltrating ductal carinoma with metastasis in the axillary lymph nodes present. She still had a swinging temperature and the antibiotic was changed to Gentamicin 3mg per kg b.w. Both a skeletal survey and an ultra-sound done some days later showed absence of liver metastasis.

As there was partial wound breakdown secondary suturing was necessary in 4 weeks time. It was a short procedure done under Pethidine 1mg per 1 kg b.w. Scoline 1mg per kg b.w. for intubation, Nitrous Oxide, Oxygen and Halothane 2% were used for maintenance of the 15 minutes procedure. Breathing was spontaneous. Post-operatively she was put on Gentamicin, 3mg per kg b.w. and for pain relief had Pethidine 1mg per kg b.w. for two doses at 6 hour intervals.

On the day following she had a temperature 39°C and on the 3rd post-operative day jaundice was first noticed. Murphy's sign was negative. Stools were normal in colour. Urinalysis showed urobilin and absence of urobilinogen. All current drugs were stopped. Coombs' test was negative. Serum testing for Hepatitis A, Australia antigen and Paul Bunnel were negative. She was started on IV 5% Dextrose and KCL, 1gm given in the bottle to correct a low pressure and a multi vitamin preparation and oral luctose were started. By 10 days she was afebrile, but lethargic showed a slight flap of the outstreched hands, the liver was palpable for 1 - 2 fingers. The spleen was not felt and no ascites could be demonstrated. The abdomen was not tender anywhere. Urine output was good. (See Table 1).

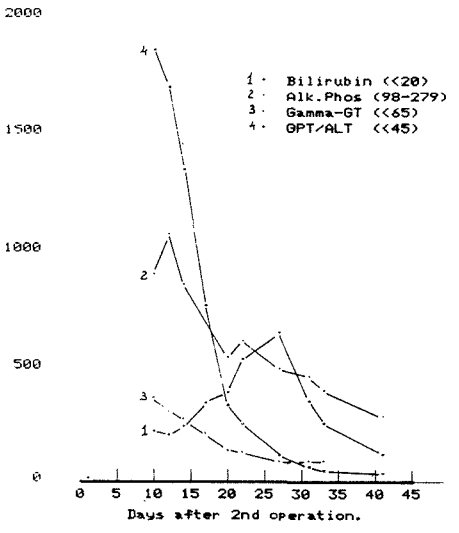
On the 12th day she fainted while straining at stools, her condition deteriorated and the jaundice became deeper, she started vomiting and became drowsy, and the next day the BP was 95/60 and she had a decreased urine output. Plasma and Mannitol 10% were given in adequate amounts.

A liver biopsy performed on the third day of jaundice showed an inflammatory infiltrate arranged in septal patterns, composed of mononuclears and some eosinophils with necrotic foci and areas of bile stasis. This was said to be compatible with Halothane induced hepatitis.

The wound was infected but the temperature was now normal. A swab from the wound gave Staph, aureus on culture. An ultra-sound showed no intra/extrahepatic biliary-duct dilation. CT-Scan confirmed generalised liver enlargement but no biliary tree dilatation. She was much better by the 15th day although the wound showed delayed healing, and a swab now yielded Pseudonomas aureginosa on culture. Some days after she was discharged from hospital without further problems.

TABLE 1

Liver function tests



In the second case of Halothane hepatitis Miss JGS. 15 years, with no past medical complaints, or allergies was admitted on the 20th of February 1986 with a fracture of shaft left tibia and fibula following a sports injury. Closed reduction under Thiopentone 5mg per 1kg b.w. I.V. and Nitrous oxide in Oxygen 4 litres in each and Halothane 2% carried out the same day. After 15 days she was readmitted as the fracture was displaced and re-manipulation was again carried out under the same kind of anaesthesia. She was discharged home later in the day. Next day she came back with a pyrexia of 40 degrees C and vomiting. Jaundice was noted on the third post op date. LFT's showed:

ALT 46, Alk.phos 650 u/l, Bilirubin 166 u/l and Gt 140 u/l. Her parents took her to a London Hospital and repeat LFT's showed:

AST 46, Alk.phos 112, Bilirubin 29 and Gt 95. Prothrombin time 0.9.

Serum testing for Hepatitis A, B, CMV and Epstein Barr virus were negative. Halothane antibody testing by ELIZA technique was not confirmed.

After 6 weeks she underwent internal fixation under spinal anaesthesia and Midazolam sedation. Recovery was uneventful and repeat LFT's were normal.

Discussion

Halothane hepatitis is widely held to be almost non-existent in children. Wark (9) reviewed 23 years of Grt. Ormond Street paediatric operation performed under general anaesthesia, from 1957 - 1979 (165,400 patients) and only found two unexplained cases of hepatitis, 267 patients underwent multiple exposure within 28 days with impunity. He concluded that the chances of a child developing Halothane hepatitis are 1:82,000. The reportage of major adverse drug reactions is similar in children and adults: 1:2,000 - 1:10,000 but no explanations can be given why the condition of Halothane hepatitis is rare in children.

Enflurane hepatotoxicity occurs – since its introduction in 1973 15 cases have been assessed by Eger and colleages from 88 reported cases as being probable Ethrane Hepatitis (1 in 800,000). This is far below the spontaneous viral hepatitis attack rate. Mortality following Enflurane hepatitis is 21% so far.

Only one unconvincing report of jaundice with Isoflurane (introduced in 1984) has been reported. One may note that whereas Halothane is 20% metabolised, Enflurane is only 2% and Isoflurane less than 0.2% metabolised. One cannot forget the expense of these more recent introduced agents:

Halothane which used to be called 'Liquid Gold' costs 7.50 pounds sterling, Enflurane 29 pounds and Isoflurane 72 pounds per 250ml.

The modern anaesthetist may be fortunate in having alternative techniques at his disposal but they have by no means been shown to be safer for the patients[10]. In children the position is even more vague. Should an incidence of 1:82,00 influence the usage of Halothane which has been proved to be of great value with regards to overall safety?

Conclusion

It seems prudent in the light of present knowledge to recommend that:

1. In the pre-operative evaluation previous exposure to halothane and any possible reaction to it are looked for.
2. Unless any overiding consideration exists re-exposure to Halothane within 3 months should be avoided in adults.
3. A patient with a history of unexplained jaundice or pyrexia following exposure to Halothane should not be re-exposed to Halothane. This fact should be clearly marked on the case-history.
4. In those patients who are likely to require multiple anaesthetics (eg. burns patients) and those associated with a higher risk (eg. females, obesity, familial history) (allergy ?); Halothane is best avoided.

Since Halothane hepatitis has been reported appearing after the first exposure while many patients undergo repeat re-exposure with impunity, and still others develop Halothane hepatitis after an exposure many years after a series of operations, it is quite clear that no firm 'safe period' between repeat Halothane exposure can be scientifically agreed upon, however avoiding re-exposure within a 3 month period has been recommended for medico-legal purpose.

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The Intensive Care of Chest Injuries

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Summary

This is a survey and assessment of all patients with chest injuries admitted to the Intensive Therapy Unit at St Luke's Hospital during a period of thirty months from January 1984 to June 1986. Cases of simple uncomplicated rib fractures admitted to ITU for observation are excluded. Out of the total of 21 patients, 12 suffered other major trauma besides the chest injury. The management of chest injuries and their complications are discussed.

Introduction

The Intensive Therapy Unit at St Luke's Hospital is a 10 bed unit catering for all critically ill patients on the islands of Malta and Gozo. Out of 1300 patients admitted to the ITU for intensive resuscitation, monitoring and treatment during the study period, these 21 patients represent 1.6%.

Results

Of the 21 patients, 19 (90%) were male and 2 (10%) were female. The ages ranged from 5 to 75 years, but 57% were under 40 years with the highest incidence in the twenties age group (6 cases) Fig. 1.

18 patients (86%) had a blunt chest injury. 3 patients were suffering from penetrating chest wounds Fig. 2.

i) **Blunt injuries**: 18 patients

Seventeen patients had rib fractures (8 bilateral) and two patients had a fractured sternum. They have been subdivided into two main groups.

a) chest wall alone: 3 patients.

Two of these needed long term ventilation while the other required antibiotics and physiotherapy for pulmonary atelectasis. No deaths were recorded.

b) chest wall and thoracic visceral involvement: 15 patients.

Most patients fell into this group and the visceral injuries are shown in Table 1.

left pleural collection which resolved spontaneously while the two patients with firearm injuries required thoracotomy for persistant intra-thoracic bleeding. At operation one patient had a torn azygos vein and pulmonary lacerations. The other patient was bleeding from intercostal and subscapular vessels and lacerations of the left upper lobe. All three patients survived their injury.

Mortality

Of the three patients who died, two suffered multiple injuries following falls from a height. A 24 year old female psychiatric patient sustained a cervical spine fracture, head injury and fractures of the pelvis, ankle and wrist after falling a height of 16 meters. Initial resuscitative measures failed to correct hypovolaemic shock and she was submitted to emergency laparatomy as intra-abdominal bleeding was suspected. At operation there was no major bleeding site but the patient died soon after. A post mortem declared the cause of death as being due to hypovolaemia from multiple injuries incompatible with life.

A 71 year old alcoholic patient fell backwards a height of 3 metres. He had an occipito-temporal fracture with severe contusion of the cerebellum and both frontal lobes, multiple fractured ribs with a flail segment, and intra-abdominal haemorrhage from a lacerated spleen. He required splenectomy and needed ventilation. He died within 17 days post-op., having developed pancreatitis with paralytic ileus, bilateral bronchopneumonia and renal failure.

A 40 year old female driver was involved in a car crash and on admission was semi-conscious with extensive subcutaeneous emphysema on both sides of the chest extending into the neck, right arm and abdomen. She had a fractured mandible with intra-oral haemorrhage. A chest X-ray revealed fractures of the right 4th to 8th ribs and left 2nd rib. A large right pneumothorax was also present. Apical and basal right intercostal drains were inserted. Emergency tracheostomy was done in view of the fractured mandible and compromised airway. Twenty-four hours later, the patient became dyspnoeic and required ventilation with a high concentration of Oxygen (less than 60%) to maintain adequate PaO_2 The right pneumothorax persisted, and she developed adult respiratory distress syndrome (ARDS or shock lung), bilateral bronchopneumonia with septicaemia and a small left pneumothorax. In spite of intensive treatment with antibiotics, methy-

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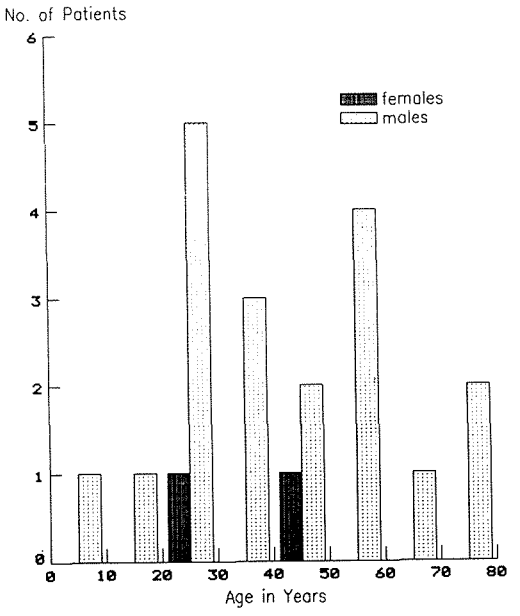

Fig. 1 Age and sex distribution of patients with chest trauma.

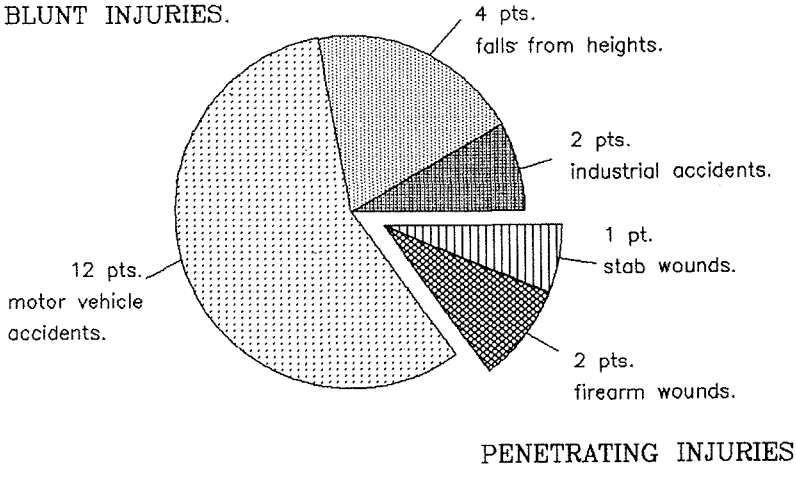

Fig. 2 Category of injury; Blunt and Penetrating (exploded sector).

Table 1

INJURY	Number of Patients
HAEMOTHORAX	12 (2 bilateral)
PULMONARY CONTUSION	5
PNEUMOTHORAX	3 (2 bilateral)
HAEMOPNEUMOTHORAX	2
MAJOR VESSEL TEAR	2
PNEUMOMEDIASTINUM	1
RUPTURED DIAPHRAGM	1

Different types of thoracic visceral involvement. Some patients sustained more than one type.

prednisolone and ventilation with 100% oxygen and positive end-expiratory pressure (PEEP) of up to 10 cm H_2O, her PaO_2 deteriorated to levels below 35mm Hg. She died of respiratory failure 25 days after admission. At post mortem the lungs were described as heavy, firm and rubbery. There were lacerations of the upper and middle lobes of the right lung with no evidence of a major bronchopleural fistula.

Discussion

Patients with a possible chest injury should be seen and assessed by a senior member of the surgical admitting team. Particular attention should be given to chest pain on inspiration and the presence of central cyanosis or dyspnoea. Crepitus over the rib cage denotes fractured ribs, while surgical emphysema is a sure sign of injury to lung or respiratory tract. If the patient is in severe shock, haemothorax with possible large vessel injury and cardiac tamponade from haemopericardium should be considered. An immediate chest X-ray may show the extent of the damage to the thoracic cage and confirm the presence of air or blood in the plerual cavity Fig. 3. Widening of the mediasti-

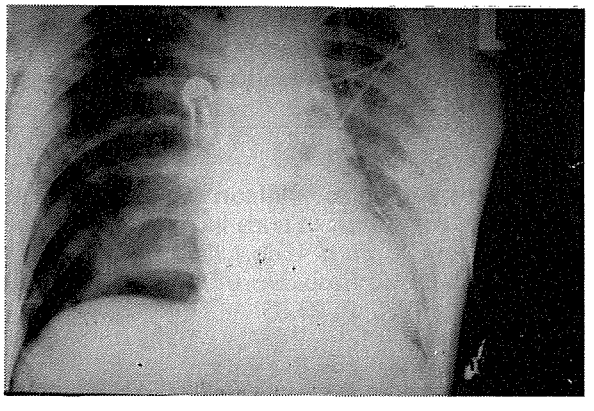

Fig. 3 Chest X-Ray of 26 year old man with (R) pneumothorax, (L) haemothorax, pneumomediastinum and surgical emphysema with pectoral muscle fibers showing in contrast.

Widening of the mediastinum could be an early sign of pericardial effusion or injury to the thoracic aorta. Mediastinal emphysema and a ruptured diaphragm result in typical chest X-ray appearances and should not be missed[1, 2]. In our experience this initial assessment has been extremely important in detecting patients who needed active surgical management of their chest injury. Fourteen patients required the insertion of intercostal drains with under-water seal. The more compact Heimlich flutter valves were used only to facilitate patient transport.

Besides the two patients with penetrating wounds, two others required emergency surgery for their thoracic injury. A 25 year old male involved in a motor cycle accident was admitted in hypovolaemic shock, with subcutaneous emphysema over the left upper chest and a pulseless left upper limb. Chest X-ray showed a fracture dislocation of the left sternoclavicular joint, fractures of the first rib and a left haemothorax. As more than three litres of blood were drained within minutes of the insertion of a left intercostal tube, major vessel trauma was diagnosed and the patient submitted to urgent thoracotomy. Lacerations of the left subclavian vein were repaired and an actively bleeding left internal thoracic artery ligated. The flail segment of the chest was stabilised with several nylon sutures.

A 5 year old boy whose abdomen was crushed under the wheel of a heavy vehicle was admitted with tenderness in the left hypochondrium. He had decreased breath sounds over the left chest with shift of the apex beat to the right. A chest X-ray revealed a ruptured left hemidiaphragm with herniation of the stomach into the chest Fig. 4

At laparotomy a lacerated spleen was removed; the stomach was reduced into the abdomen and the diaphragm repaired. The child also had a right pleural effusion and a transient paraplegia of uncertain origin.

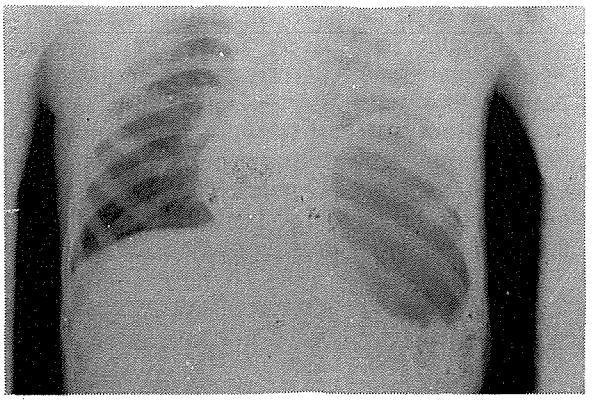

Fig. 4 Chest X-Ray of young boy with a ruptured (L) hemidiaphragm and herniation of the stomach into the chest cavity.

Management of Flail Chest

Of the seven patients admitted with a flail segment, four required mechanical ventilation; one patient had the flail chest stabilised at thoracotomy for major vessel injury, whilst the other two were treated by intercostal nerve blockade, physiotherapy and appropriate antibiotics. Patients were ventilated if tachypnoeic, dyspnoeic and blood gas analysis showed a PaO_2 less than 60mm Hg or a

$PaCO_2$ more than 60mm Hg. There is no apparent correlation between the size of the flail chest and the need to ventilate. Patients with flail chests do not usally have impaired ventilation, the $PaCO_2$ being in the range of 23-42mm Hg. Respiratory distress is due to a falling PaO_2 occuring as a result of ventilation/perfusion abnormalities brought about by pulmonary contusion, decreased cough and accumulation of secretions causing atelectasis. Mechanical ventilation is therefore indicated in cases of pulmonary tissue damage rather than chest wall instability and should be discontinued when normal gas exchange has been restored[3].

Long term ventilation is often complicated by severe infection and should not be undertaken lightly[4]. Chest infection ranging from mild basal atelectasis to a fulminant bilateral bronchopneumonia with septicaemia was the commonest complication (15 cases). The more severely affected were the patients on long term ventilation all of whom had positive sputum cultures. By far the commonest pathogen cultured was Pseudomonas aeruginosa; others included Klebsiella, Proteus, Serratia, Strep. faecalis, Haemophilus influenzae and ß-haemolytic Streptococci. The principal antibiotics used were Cefotaxime and Gentamicin. Azlocillin, Mezlocillin and Netilmycin were used as second line drugs. Virtually all organisms cultured from ventilated patients were resistant to Ampicillin. Intensive chest physiotherapy, with postural drainage, bagging, percussion and cough stimulation, was the cornerstone of management in these cases, both before and after infection. Daily replacement of the ventilator tubings and humidifier was lately introduced to further delay the onset of infection. One patient, a 19 year old male, involved in a car accident developed pyothorax following splenectomy, right nephrectomy and partial hepatectomy for traumatic rupture of these organs. He also had multiple fractured ribs with pulmonary contusion. He recovered after surgical drainage of the pyothorax.

ARDS developed and was diagnosed in one case who suffered from multiple lacerations of the lungs. Management included IPPV with PEEP and methylprednisolone (30mg/kg IV six hourly). Applying PEEP in these cases can help gas exchange and correct hypoxaemia allowing the use of a lower FiO_2, preferably less than 0.5, as early as possible. However, the use of high dose steroids is still controversial. Since complement activation is thought to play a key role in the pathophysiology of ARDS, it has been accepted that steroids might interrupt the chain of events leading to the clinical picture. On the other hand, it is possible that they may encourage infection. Most authors would agree to using steroids in one or two large doses, considering the severity of the disease and the absence of any detrimental effects[5].

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Benzodiazepine Blockers

N. AZZOPARDI

Summary

Cytostatics are known to adversly effect the dosage scheme of many drugs.[1]

A case is described where the dosage of a benzodiazepine had to be multiplied six times to obtain a reliable sedative effect in a child on cytostatic treatment.

Introduction

C.P. a four year old girl weighing 14 kilogrammes (S.L.H. No. 243896) presented with anaemia and on full investigation on acute form of lymphoblastic leukaemia was diagnosed. She was started on Vincristine 1mg IV weekly. Prednisone 80mg and Ampicillin 500mg daily by mouth. The child did not respond but developed epileptiform convulsions and an EEG showed generalised showery periodic high amplitude waves that could not be traced to a particular focus even though a CAT scan was performed. Accordingly Asparginase 3000 units IV weekly was added to the above therapy. Advice was sought from the consultant staff of the Royal Marsden Hospital and Methotrexate 6.5 mg intra thecally weekly was added to the above drug regimen.

For sedation prior to lumbar puncture Trimeperazine Tartarate (Vallergan) syrup in 60mg dosage was used with good effect every week. Still the child failed to improve and cranial irradiation was recommended by the London consultant at 1800c range each every week for three doses at weekly intervals.

To enable good alignment for radiotherapy it was demanded that the child's head be fixed and immobile during the few minutes of irradiation. Anaesthetic advice was sought for the heavy sedation required for the procedure of radiotherapy. Diazepan (Valium) 2mg and Trimeperazine Tartarate (Vallergan) syrup 10mg by mouth were given but the child could hardly be controlled and objected to head fixing and even after Pethidine 50mg was given slowly IV the child moved. The first attempt at radiotherapy was postponed. After a week a benzodiazepine Fluonitrazepam (Rohypnol) (0.1 mg per kg body weight) was chosen and 2mg by IV route given – the dosage calculated to be enough for the 14kg child. The effect was negligible and so additional doses were given IV to a total dose of 8mg until some degree of drowsiness was arrived at and adequate head fixation for the child could be effectively organised.

There was no loss of muscle power or any tidal volume deficit during the 15 minute period the child was asleep and when she woke up she was fully active and playful. Investigations carried out at the time showed a Hb of 11.5gm./Wbc 3000/1 cmm. PCV 35%. Platlets 17,000/1 cmm. The uric acid was 8.5 mg per 100 ml and the ESR 110 mm in 1 hour. Differential blood smear showed 56% lymphoblast count and the bone marrow contained 95% immature lymphoblasts. The liver function test showed a raised alkaline phosphatase 571 ITU and the plasma protein 5.7 mg per 100 ml with high globulin ratio.

Discussion

It is not fully appreciated that many cancer patients on high doses of cytostatic agents may react adversly to drugs given in the usually recommended doses.

This case illustrate an abnormal reaction to the benzodiazepine. No other side effect to this drug was encountered despite the high dosage used.

Respiration was not embarassed, the blood parameters remained normal and the child had no hangover. It is interesting to note that when another anaesthetist was called to sedate the child for radiotherapy in the following week he decided to try Ketamine (Ketalar) and gave 14 mg IV the usual dose of the drug at 1 mg per 1 kg IV and obtained sufficient sedation to enable radiotherapy to be carried out.

According to the dose response curve in man higher doses of benzodiazepine do not increase the immediate hypnotic effect but probably the period of sedation or drowsiness. This case was exceptional in that after the short sleep the child awoke refreshed and playful.[2]

Conclusion

Benzodiazepines are known to increase the sedative effect of GABA in the brain but the use of cytotoxic agents appear to reverse this effect.

The problem of plasma protein changes due to

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the leukaemic process disturbing drug ionisation cannot be supported, as the other non-benzodiazepine drugs worked satisfactorily.

A lacuna of knowledge on the effect of cytostatic agent on brain enzymes exists and further experiments are needed to elucidate the site of block.

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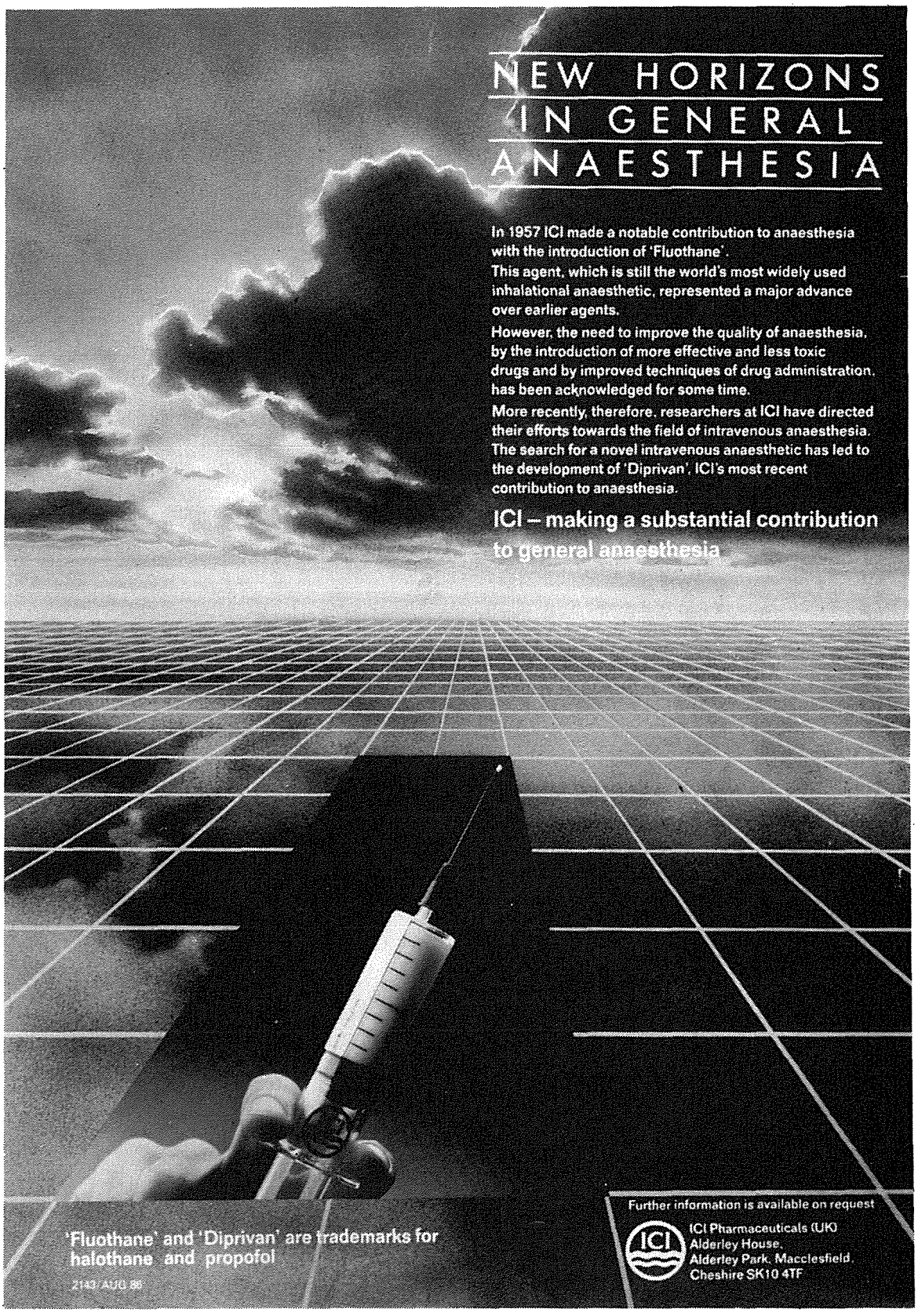

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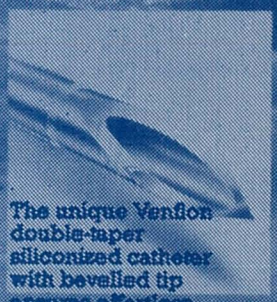

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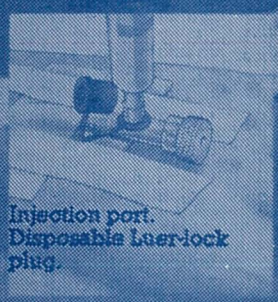

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