Current Trends and Developments in the Field of Local Anaesthetics

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Summary

Local anaesthetic agents belong to a surprisingly homogenous family of drugs that are able temporarily to interrupt impulse trnasmission along nerves in a relatively predictable and reversible manner.

During the past hundred years, more efficacious, safer, and varied types of local anaesthetic agents have been developed. Since the mechanisms by which these drugs block impulse conduction are becoming better understood, many responses to nerve block can be readily explained in physiologic terms[4]. Such basic understanding is important to the clinician, especially when complications arise or his block is only partly successful. The purpose of this paper is to summarize current knowledge regarding the areas of drug development, basic mechanism of local anaesthesia, clinical pharmacology of local anaesthetic drugs, and comparative effects of regional and general anaesthesia. It is emphasized that the bibliography is not a complete list of the vast literature but merely intends to list major reviews on the subject.

Key Words
Local anaesthetics
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Areas of Drug Development

There is no doubt that the local anaesthetic drugs currently available are highly effective for the majority of surgical and obstetrical procedures in which regional anaesthesia is indicated.

The situation in regard to postoperative pain alleviation is, however, much less satisfactory[2]. There is no drug or preparation that can provide ultra-long duration of analgesia, not for several hours but, preferably for the first 24-28 hours. Such an agent should selectively block sensory fibres with no or minimal motor blockade and sparing autonomic function. The pelvic parasympatheic control of bladder and sphincter function should be particularly retained.

So far, inspite of considerable efforts, minimal success has been achieved in developing a clinically useful, ultra-long-acting local anaesthetic preparation.

Attempts to prolong the action of procaine by the use of peanut-oil vehicle, which would provide a depot type preparation, failed because of its unacceptable neurotoxicity.

Dextran has been utilized as vehicle for local anaesthetic drugs in order to produce a depot-type, slow releasing anaesthetic preparation. It has been shown that dextran could extend the duration of conventional local anaesthetics by a few hours although conflicting data exist.[3,4]

In recent years two interesting approaches have been pursued. In early 70's the concept of cyclizing compounds was introduced.[5] The idea was that a tertiary amine compound would be injected and than taken up by the nerve membrane, where it would be converted to a quaternary-ammonium agent which could not readily diffuse out of the membrane, providing long duration of anaesthetic activity. Although preliminary results in animals were encouraging, no suitable agent was developed for human trials.

Another hope for an ultra-long-lasting local anaesthetic agent was sought in the biotoxins i.e. tetradotoxin and saxitoxin.[6] Unfortunately, the very high systemic toxicity of tetradotoxin and saxitoxin and their unreliability in terms of predictable anaesthetic duration limit their potential usefulness. The biotoxins do not penetrate neural sheaths easily, so that results of peripheral nerve blocks in animals were not satisfactory. However, spinal anaesthesia of 24 hours duration was obtained in sheep with tetradotoxin, where no neural barrier is present to obstruct the diffusion of the biotoxins to the receptor site in the nerve membrane. Currently, efforts are focused to modify the structure of tetradotoxin or

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saxitoxin in order to provide acceptable agents of ultra-long duration.

At the present time, the use of epidural and intrathecal opiates in prolonged pain relief have opened up a new area of applied neuraxial pharmacology, not only for narcotics, but for adrenergic agonists as well. The analgesic properties of intraspinal narcotics are uniquely powerful, since they appear to act mainly on primary afferent nocioceptive synapses in the dorsal horn.[7] Although intraspinaly applied narcotics offer the greatest promise for prolonged pain relief at present, they are not free of side-effects. Delayed respiratory depression and urinary retention are the main danger, but both are treatable by i.v. naloxone

Most recently Scurlock & Curtis (1981) have opened a new area of promise by using derivatives of tetraethyl-ammonium.[8] A phenomenal duration of sensory analgesia of approximately 400 hours (16 days) was observed following infraorbital nerve block when compounds with a chain length of C-12 or longer were used in rats. Studies of the mode of action suggest that the ultra-long duration of action of these agents is produced by binding to a receptor site in the potassium channel[9]. Important features include reversibility of the blocks and absence of persistent neurotoxicity.

Further studies are required to establish the ultimate efficacy of these tetraethyl-ammonium compounds.

The concept of temporarily blocking the sodium and potassium transport at the membrane channels to produce ultra-long selective sensory analgesia should provide the basis for developing new agents that might fulfill the clinical criteria for use in control of chronic pain.

Basic Mechanism of Local Anaesthesia

In terms of impulse transmitting properties, the membrane is the most important part of the nerve fibre.

Local anaesthetic drugs block a nerve without damaging it and are unique in that their action is reversible.

The main pharmacological action of local anaesthetics is by interfering with the impulse conducting properties of the nerve membrane.[10]

Conclusive evidence indicates that local anaesthetic agents act at the sodium channel of the nerve membrane, probably by physically occluding the transmembrane sodium channels.[11] A local anaesthetic block is a nondepolarization block, resembling in some ways the action of curare at the neuromuscular junction. It is suggested that with conventional agents, such as lidocaine, binding occurs at the receptor sites located on the inner surface of the nerve membrane. In contrast, biotoxins, such as tetradotoxin and saxitoxin, act at receptor sites located on the external surface on the membrane.

Agents such as benzocaine and benzyl alcohol act by penetrating the nerve membrane, causing membrane expansion and subsequently diminish the diameter of the sodium channel[12].

The current concept of the mechanism of action of local anaesthetic drugs is based on the following sequences: binding of local anaesthetic molecules to receptor sites in the nerve membrane; inhibition of sodium permeability; reduction in the rate of depolarization; inabilty to achieve threshold potential level; lack of development of a propagated action potential; and block of nerve conductivity.

Clinical Pharmacology of Local Anaesthetic Drugs

Thorough knowledge of the clinical pharmacology of local anaesthetics enables the performance of safe and effective regional block.

Currently, the choice of agents is wide, and it is now possible to select a drug that will suit the particular regional block technique in each individual case.

Basically, all local anaesthetic agents have the following chemical structure; aromatic portion, intermediate chain and an amine portion.

There are two major groups of local anaesthetics: amides and esters. Procaine, chlorprocaine, and tetracaine represent the ester group while the amide group includes mepivacaine, bupivacaine and etidocaine. The esters are rapidly hydrolysed in the plasma, whereas the breakdown of amides depends on hepatic metabolism.

Another significant difference between the ester and amide compounds is their allergic potential. Para-aminobenzoic acid is one of the metabolites formed from the hydrolysis of ester-type agents. This substance has a potential of inducing allergic-type reactions in a small percentage of the general population.

Allergic phenomena with amide group compounds are extremely rare.

All local anaesthetics have certain common characteristics but their anaesthetic profile is determined by their: lipid solubility, protein-binding, pK_a, non-nervous tissue diffusibility, and intrinsic vasodilator activity.

The lipid solubility of a particular anaesthetic drug appears to be a primary determinant of its anaesthetic potency. Procaine has a low lupid solubility as determined by partition coefficient measurements, and this drug is least potent in supressing conduction in an isolated nerve.

The partition coefficient of bupivacaine,

tetracaine, and etidocaine vary from about 30 to 140, indicating a high degree of lipid solubility and a high potency in supressing conduction in an isolated nerve. Indeed these drugs block nerve conduction at very low concentrations.[13]

It has been shown that approximately 90% of the axolemma consists of lipids, which is in accord with the relationship to lipid solubility. The anaesthetic agents which are highly lipid-soluble penetrate the nerve membrane more easily and this is reflected biologically in increased potency.

The duration of action of a local anaesthetic agent is primarily dependent on its protein-binding slightly faster onset of anaesthesia *in vivo*. The factors tetracaine, and etidocaine are highly bound to proteins and possess a relatively long duration of action.

The relationship between protein-binding of local anaesthetic drugs and their duration of action is consistent with the basic structure of the axolemma. Proteins account for approximately 10% of the nerve membrane. Thus, local anaesthetics which penetrate the axolemma and attach more firmly to the membrane proteins will tend to possess a prolonged duration of action.

The onset of anaesthesia is directly related to the rate of epineural diffusion which, in turn, is correlated with the amount of drug in the base form.

The pK_a values of the common local anaesthetic drugs are all greater than the physiological pH value, which means that the drugs will exist in the body predominantly in the ionized form. The percentage of a specific local anaesthetic drug which is present in the base form when injected into tissue whose pH is 7.4 is inversely proportional to the pK_a of that agent. For example, lidocaine, which has pK_a of 7.74 is 65% ionized and 35% nonionized at a tissue pH of 7.4. On the other hand, tetracaine, with a pK_a of 8.6, is 95% ionized and only 5% non-ionized at a tissue pH of 7.4. Both, *in vitro* and *in vivo* studies have confirmed that local anaesthetic drugs such as lidocaine, whose pK_a is closer to tissue pH, have a more rapid onset time than agents with high pK_a, such as tetracaine. In an isolated nerve, onset time is a function of the rate of diffusion of a compound through the epineruium which, in turn, is related to percentage of drug in the base form. However, *in vivo*, a local anaesthetic must diffuse initially through non-nervous connective tissue barriers. Naturally, differences exist between the rate of non-nervous tissue diffusion for various agents. For example, procaine and chlorprocaine have similar pK_a's of 9.1 and similar onset times for conduction blockade in an isolated nerve. However, *in vivo*, the onset of anaesthesia for chloroprocaine is significantly shorter than that of procaine, which is indicative of a more rapid rate of non-nervous tissue diffusibility. Similarly, in the amide group, lidocaine and prilocaine possess the same pK_a and onset of action in isolated nerves, whereas lidocaine has a slightly faster onset of anaesthesia in vivo. The factors that determine diffusibility through non-nervous tissue are still unclear.

Intrinsic vasodilator activity of different local anaesthetic drugs could significantly influence their potency and duration of action *in vivo*. The degree and duration of nerve block is related to the amount of local anaesthetic drug which diffuses to the receptor site at the nerve membrane. Following injection of a local anaesthetic drug, some of the drug will be taken up by the nerve and some will be absorbed by the vascular system. The latter is related to the degree of blood flow through the area in which the drug is depositied. All local anaesthetic drugs, except cocaine, possess vasodilator properties. However, the degree of vasodilation produced by the various drugs differs. Studies *in vitro* have shown that the intrinsic anaesthetic potency of lidocaine is significantly greater than that of mepivacaine, while their durations of action are similar. On the other hand, *in vivo*, mepivacaine is similar in potency and produces a longer duration of anaesthesia than lidocaine. These differences between *in vitro* and *in vivo* results are probably related to the greater vascular absorption of lidocaine such that less is available for nerve blockade.

In summary, on the basis of differences in anaesthetic potency and duration of action, it is possible to classify the local anaesthetic agents into three groups: 1. Local anaesthetic drugs of high anaesthetic potency and long duration of action, i.e. tetracaine, bupivacaine and etidocaine; 2. Local anaesthetic drugs of intermediate potency and duration of action, i.e. lidocaine, mepivacaine, and prilocaine; 3. Local anaesthetic drugs of low potency and short duration of action, i.e. procaine and chloroprocaine.

Comparative Effects of Regional and General Anaesthesia

Our main task, as practising anaesthetists, is the safety of our patients.

The metabolic consequence of the neuro-endocrine response to surgical trauma are characterized by the following triad: increased resting energy expenditure, negative nitrogen balance, and altered glucose homeostasis.

Recent interest has been focused on the influence of different anaesthetic techniques in modifying the endocrine-metabolic response to surgery.

Considerable number of studies have been published in an attempt to determine the relative

advantages of general and regional anaesthesia in suppressing the surgical stress.

These studies generally fall into four categories: 1. haemodynamic effects; 2. metabolic effects of general vs. regional anaesthesia; 3. postoperative convalescence; and 4. morbidity and mortality studies.

Haemodynamic effects

The initial differences observed in the haemodynamic changes are those of a significantly greater fall in systolic, diastolic and mean arterial pressure in subjects receiving epidural anaesthesia as compared to those undergoing general anaesthesia.[15] The fall in blood pressure during epidural blockade is due almost entirely to decrease in systemic vascular resistance.

However, a significantly greater decrease in cardiac output and stroke volume is observed in those patients receiving general anaesthesia with halothane.

Supplementing epidural anaesthesia with light general anaesthesia usually results in a somewhat greater fall in systolic, diastolic, and mean arterial pressure. However, cardiac output and stroke volume remain basically unchanged, so that the fall in blood pressure is due mainly to the fall in systemic vascular resistance.

Metabolic effects of general vs regional anaesthesia

Surgical trauma evokes a neuro-endocrine response which results in substrate mobilization, a change in metabolism towards catabolism with a negative nitrogen balance and retention of salt and water[16]. A number of studies indicate that the metabolic response to surgery seems to be obtuned to a greater degree by regional anaesthesia as compared to general anaesthesia.

Postoperative convalescence

There are several studies pointing at the benefits of regional anaesthesia on postoperative organ function, especially pulmonary and cardiac. The use of regional anaesthesia is associated with decreased requirements for postoperative opiate analgesia, imporved pulmonary function, earlier ambulation, and earlier hospital discharge than the patients receiving general anaesthesia plus postoperative opiates.[17]

Morbidity and mortality studies

There are only few reports concerning the relative morbidity and mortality of regional vs general anaesthesia on surgical patients. It appears that incidence of thrombo embolism is lower following surgery under epidural anaesthesia as compared to general anaesthesia. It has been also shown that blood loss following total hip replacements in patients under epidural anaesthesia is significantly reduced as compared to those patients under general anaesthesia.[18]

However, further investigations should be undertaken to determine the relative advantages of regional vs general anaesthesia.

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