ASPECTS OF THE PHARMACOLOGY OF LOCAL ANAESTHETIC AGENTS

BY

B. Löfström

The use of local anaesthetic techniques varies with the anaesthetist's working conditions, direction of interest, and hence geographically. Thus they are mainly used in certain centres in America and Canada, and in the Scandinavian countries. Interest in, and use of, local anaesthesia has increased during the last decade. There are many reasons for this. The use of these techniques enables the anaesthetist to rationalize his working day, enables him to adjust the extent of the anaesthesia to the type of operation planned, to the individual patient, and to the auxiliary personnel at his disposal. The purely technical performance of the block gives him a satisfaction, all the more apparent when he can use his skill in the performance of therapeutic blocks.

Local anaesthetic agents and techniques have been a stimulating field for research. Several new anaesthetic agents have made their appearance during this decade. New tests methods have appeared which enable the anaesthetist, who has but limited resources, to produce work of scientific merit under practical clinical conditions.

The aim of this presentation is to review the results of investigations published mainly during the last ten years. Excellent reviews of earlier work in this field have appeared regularly in this journal (Geddes, 1954, 1962; Lloyd, 1955; Stout, 1957; cf. de Jong and Wagman, 1963).

MODE OF ACTION

Transmission in the myelinated nerve takes place step by step. The myelin sheath insulates the nerve, so that the impulse is transmitted by a series of jumps, from one node of Ranvier to the other (saltatory conduction). The insulation of the axon breaks down only at the node of Ranvier, where it is separated from the surrounding tissue merely by lipid and polypeptide (as are so-called non-myelinated nerve fibres, along their whole length). These layers are penetrated by pores or sluices, through which electrolytes can pass with ease during depolarization (fig. 1). Local anaesthetics are presumed to penetrate at the nodes of Ranvier, thereby blocking these sluices and preventing depolarization (cf. de Jong and Wagman, 1963).

![Diagram](image-url)

**Fig. 1**

The nerve impulse is transmitted from one node of Ranvier to the other. Local anaesthetics prevent the process of depolarization by blocking the ion transmission through the nerve membrane. (After Ward and Benveniste, 1968.)

B. Löfström, M.D., Head of the Department of Anaesthesia and Assistant Professor at the Karolinska Institute, Stockholm, Sweden.
The effect of local anaesthetics is thus to prevent the process of depolarization during nerve transmission (cf. Watson, 1960; Ward and Benveniste, 1968). The chemical basis of this is thought to be by formation of a salt in the membrane. The local anaesthetic reaches or penetrates the membrane as a base. Ionic bonds and hydrogen bridges, Van der Waals forces and donor acceptor bonds, bind it reversibly to the membrane. Its blocking properties, as well as its general and local toxicity may be altered by changing its chemical structure (cf. af Ekenstam, 1966).

The pH of the solution is of great significance in determining its blocking properties. It has been clearly demonstrated that the local anaesthetic agent penetrates the nerve as a base (R.NH₂). The amount of free non-ionized lipid-soluble base available increases as the pH of the solution approaches the pKa of the compound in question. It is at this value that the minimum concentration required for nerve block is easiest to attain (cf. af Ekenstam, 1966). However, the salt (R.NH₂⁺) is probably the active form at receptor sites (Ritchie, Ritchie and Greengard, 1965a, b). Solutions of local anaesthetic agents at present available have a pH which, to a variable degree, is lower than the pKa of the drug. This is due to their water solubility characteristics and above all to the addition of adrenaline and stabilizing agents in preparations commercially available. Thus the solutions with the lowest pH are those with added adrenaline, and those with glucose intended for intradural anaesthesia. The local anaesthetic solution injected must be buffered in the tissues if a higher pH is to be attained, and the amount of free base required for nerve penetration released. Thus R.NCl + NaHCO₃ ⇌ R.N + NaCl + H₂CO₃. Tissues vary in their buffering ability; for example, the pH found in inflamed tissue is low.

Bromage et al. (1967) have suggested and tested a local anaesthetic salt of carbonic acid according to the following formula:

R.NCO₂ + H₂O ⇌ R.N + H₂CO₃.

A more rapid induction and more profound anaesthesia have been shown to follow the use of such solutions in epidural anaesthesia. Such solutions are not, as yet, commercially available.

The local anaesthetics belonging to the ester group are destroyed in the plasma by cholinesterases. Those belonging to the amide group are metabolized mainly in the liver. The local anaesthetics which are esters, like procaine, formerly so widely used, and amethocaine and dichloroprocaine, are metabolized much more rapidly than the newer agents of the amide group (cf. Foldes, 1966; Greene, 1968). Use of these latter agents carries the risk of accumulation, especially when repeated injections are performed at short intervals (cf. fig. 2).

Local anaesthetic agents are thought to migrate freely in the body, and rapidly to reach the CNS (Usubiaga et al., 1967). Studies using radioactive local anaesthetic agents demonstrate their early distribution mainly to the lungs, heart muscle and CNS. During the redistribution phase they also appear early in intestinal fluid, bile, muscles, and in the urine (Kristerson, Hoffman and Hansson, 1965; Hansson, Hoffman and Kristerston, 1965; Hansen, Ohnesorge and Palisaar, 1968; Katz, 1968; Widman, 1968; Hansen, 1969). These studies using isotopes also demonstrated that a considerable proportion of local anaesthetic agents is eliminated via the kidneys. The conditions required for rapid renal elimination have been studied by Eriksson, Granberg and Örtengren (1966) who demonstrated that the excretion of lignocaine and prilocaine, for example, in the urine is by non-ionc diffusion. It is enhanced by a low urine pH.

**THE EVALUATION OF LOCAL ANAESTHETIC AGENTS:**

**BLOCKING EFFECTS**

The evaluation and comparison of different local anaesthetic agents require data on their blocking capabilities, as well as their general and local toxicity. These three characteristics will be discussed and analyzed in turn.

The blocking effect of a local anaesthetic agent refers to the drug's ability to block pain impulses, motor impulses to striated muscle, and, to a certain extent, the ability to block both perception of touch and autonomic impulses. The time of onset, duration of action and time of regression (that is the time from when analgesia begins to wane, until pain perception has returned) (cf. Albért and Lüfström, 1965a, b) are of special interest as is the effect on the blocking ability of
the addition of adrenaline to the local anaesthetic solution.

The conditions under which the investigation is performed must fulfil certain criteria if a true assessment of the blocking effect of a drug is to be made. Bonica (1957) has indicated how such investigations should be planned. He stresses the importance of defining the aim of the study and of standardizing the methods to be used before its commencement. The planning and execution of the investigations must be valid statistically, and a double-blind technique should be used. The study must be adequately controlled, as when a standard reference drug is used.

Studies using bilateral ulnar nerve blocks in human volunteers will, in this presentation, serve as a background to a discussion of the differences in the blocking effect of various local anaesthetic agents (Albert and Löfström, 1961, 1965a, b).

Bilateral ulnar nerve blocks were performed in cross-over experiments on volunteers by the intraneural injection of exactly 1 ml of the test solution, after paraesthesia had been elicited. The test solutions were in coded ampoules, labelled according to a randomized procedure. A reference drug was used in each investigation. Thus the ulnar nerve on one side acted as a control for the opposite side. The blocking technique was strictly defined under these conditions.

The results of testing for changes in sensibility were well correlated with the results of more objective test methods, such as the blocking of sudomotor activity, Ninhydrin test (Dhuner, Edshage and Wilhelm, 1960; Widman, 1964) or the sympathogalvanic test (Löfström and Thulin, 1965). Changes in motor activity were studied by means of a defined abduction and adduction of the little finger.

The time of onset was short for all the agents investigated in this study, and no statistically significant difference between the various drugs could be demonstrated (table I). Nevertheless, a remarkably short time of onset for lignocaine with adrenaline was obtained (cf. Bromage et al., 1964). Furthermore, bupivacaine appears to have
TABLE

<table>
<thead>
<tr>
<th></th>
<th>Time of onset in minutes</th>
<th>Duration of action in minutes</th>
<th>Regression time in minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1% procaine</td>
<td>2 ± 0.2</td>
<td>116 ± 12</td>
<td>18 ± 3</td>
</tr>
<tr>
<td>1% lidocaine</td>
<td>3 ± 0.6</td>
<td>263 ± 15</td>
<td>45 ± 11</td>
</tr>
<tr>
<td>with adrenaline</td>
<td>4 ± 0.7</td>
<td>216 ± 24</td>
<td>81 ± 14</td>
</tr>
<tr>
<td>1% prilocaine</td>
<td>4 ± 1.3</td>
<td>148 ± 16</td>
<td>37 ± 6</td>
</tr>
<tr>
<td>with adrenaline</td>
<td>9 ± 5.3</td>
<td>263 ± 16</td>
<td>51 ± 5</td>
</tr>
<tr>
<td>1% mepivacaine</td>
<td>7 ± 2.5</td>
<td>216 ± 24</td>
<td>81 ± 14</td>
</tr>
<tr>
<td>with adrenaline</td>
<td>8 ± 3.2</td>
<td>493 ± 26</td>
<td>79 ± 13</td>
</tr>
</tbody>
</table>

* From injection until complete recovery of pain perception.

TABLE II

<table>
<thead>
<tr>
<th></th>
<th>Duration of analgesia* (min)</th>
<th>Number of observations</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mepivacaine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1% plain</td>
<td>112 ± 9</td>
<td>25</td>
<td>Albért and Löfström, 1961</td>
</tr>
<tr>
<td>1960</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1964</td>
<td>111 ± 15</td>
<td>12</td>
<td>Albért and Löfström, 1965a, b</td>
</tr>
<tr>
<td>1967</td>
<td>111 ± 11</td>
<td>12</td>
<td>Löfström (unpublished data)</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.25%</td>
<td>415 ± 23</td>
<td>12</td>
<td>Albért and Löfström, 1965a, b</td>
</tr>
<tr>
<td>c. adrenaline</td>
<td>404 ± 30</td>
<td>12</td>
<td>Löfström et al., 1969</td>
</tr>
<tr>
<td>1964</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1968</td>
<td></td>
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</tbody>
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* From injection until pain perception started to appear.

A somewhat longer time of onset, especially with regard to the blocking of motor impulses (cf. Bromage, 1969a, b).

It must not be assumed that the results from ulnar nerve block will necessarily apply to other nerve blocks, when the injection is not made intraneurally, and where varying amounts of connective tissue are present in and around the nerve. Thus the onset times reported for block of the axillary plexus are approximately four or five times longer than those obtained with ulnar nerve block (Högström, 1963; cf. Åström, 1966a; Eriksson, 1966; Hollmén, 1966).

Each drug studied had a variable duration of action. The addition of adrenaline enhanced this to a greater or lesser degree (table I). The degree of reproducibility obtained in this study using bilateral ulnar nerve blocks was close (table II).

It may be stated broadly that lignocaine's duration of action, being approximately 1 hour, is double that of procaine. But it is only half as long as that of prilocaine and mepivacaine. The addition of adrenaline prolongs appreciably the duration of action of lignocaine, less so that of prilocaine and mepivacaine. A remarkably long duration of action was recorded with bupivacaine in 0.25 per cent solution, with or without the addition of adrenaline (Albért and Löfström, 1965a; Löfström et al., 1969).

There is a remarkably good correlation between the duration of action demonstrated in ulnar nerve blocks and that obtained in more clinically useful blocks, such as in finger block ( Widman, 1964), in axillary plexus block (Eriksson, 1966; Hollmén, 1966) and with sacral analgesia (Eriksson, 1966; Lind, 1965; Herbring, 1966). The results from ulnar nerve blocks may thus serve as a guide to the anaesthetist. He must be aware, however, that the duration of action will occasionally differ markedly from the statistical mean. Thus in the case of mepivacaine 1 per cent, the range was 71–131 minutes, with a mean of 112 and a
standard error of ±16. The equivalent values for bupivacaine 0.25 per cent with adrenaline 1:200,000 were 398–665 minutes, 493 ±26 respectively (Löfström, unpublished data). Furthermore, when the duration of action is being assessed, it is the time from the attainment of complete block until the commencement of regression which is of significance. Thus, an appreciable time of onset or time of regression must not be included in the duration of action. The duration of action varies also with the age of the patient, being longer in older patients than in younger (Eriksson, 1966). The presence of shock or of some disease process in the patient also influences the duration of action of a local anaesthetic agent (Quimby, 1965; Adriani, Zepernick and Hyde, 1966; Zsigmond and Elderton, 1968). In arteriosclerotic patients Bromage (1962) has found an exaggerated spread in the extradural space.

As a general rule, however, it would appear that the duration of action recorded with ulnar nerve block applies also in clinical practice. This may well be because clinically larger doses and often higher concentrations are used than in experimental blocks. In the case of amethocaine, however, the results from ulnar nerve block appear to be at variance with clinical experience. Thus Moore and Bridenbaugh (1962) claim that freshly prepared solutions of amethocaine with the addition of adrenaline have a very long duration of action, comparable with that of bupivacaine (cf. Telivuo, 1963; Bergh et al., 1966). Again, Herbring (1966) found the duration of action of amethocaine, used to induce sacral analgesia, to be comparable with that of bupivacaine (cf. Chinn and Wirjoatmadja, 1967) in ulnar nerve block. It would appear that the duration of action of amethocaine can vary with the freshness of the preparation of its solution.

The time of regression is of considerable interest to the anaesthetist. A short regression time may be of advantage should a rapid disappearance of the blocking effect be desired, as in outpatients or after bronchoscopy. A prolonged time of regression may be of value when, for example, a continuous block is being maintained through an indwelling catheter. In such a case, the block can be re instituted before the patient has had time to experience an appreciable period of pain. It should be noted that the fibres situated peripherally in the nerve trunk are the first to be blocked, and the first to recover. Again, it seems that postoperative pain is less distressing should pain perception return slowly.

Adrenaline prolongs appreciably the duration of action of most local anaesthetic agents, by reducing their rate of resorption, thereby also reducing the risk of general toxic reactions. This latter aspect will be discussed further, under the heading of general toxicity.

The ability of adrenaline to prolong the duration of action varies with the agent studied (table I). Thus, that of lignocaine is markedly prolonged; that of prilocaine and mepivacaine a good deal less. That the addition of adrenaline to these agents has comparatively little effect may be explained by their demonstrable anti-adrenaline action (Aström, 1964). It is remarkable that the duration of action of bupivacaine has not been shown to be altered by the addition of adrenaline (Löfström et al., 1969). It would appear that lignocaine has a relatively low affinity for tissue, but adrenaline, by vasoconstriction, prolongs its action by slowing its rate of removal from the tissues. This may also explain the rather shorter time of onset observed when adrenaline is added to solutions. Mepivacaine, prilocaine and bupivacaine are thought to have a higher affinity for tissues, which would explain their longer duration of action (cf. Truant and Wiedling, 1959).

The effect of adrenaline, however, varies not only with the agent used; the site of injection is also significant. In subcutaneous, extradural and peritonsillar injections the addition of adrenaline to solutions, e.g., of lignocaine, is followed by a lower blood concentration of the local anaesthetic agent, than when plain solutions are used (Bromage and Robson, 1961; Braid and Scott, 1965, 1966; Lund and Cwik, 1965a; Matthes and Schabert, 1966; Yoshikawa, Mima and Egawa, 1968). The addition of adrenaline to solutions of mepivacaine and prilocaine has been claimed not to alter the maximal blood concentration of the local anaesthetic agent, than when plain solutions are used (Dhuner et al., 1965) or in extradurals (Braid and Scott, 1965, 1966). And it is thought not to prolong the duration of action of local anaesthetics on mucous membranes, nor does it hinder their rapid absorption therefrom (Campbell, 1957; Adriani and Zepernick, 1963).
Among other methods of prolonging the duration of action of local anaesthetic agents reported in recent years has been the addition of dextran to their solutions (Nolte et al., 1967; Chinn and Wirjoatmadja, 1967), to bring about a depot effect. Vasoconstrictors of the polypeptide group (octopressin) have also been used (Berling, 1966; Goldman, Killey and Wright, 1966; Akerman, 1966; Klingenström, Nylén and Westermark, 1967).

The notion has been advanced that certain local anaesthetic agents such as mepivacaine and prilocaine may have an inherent vasoconstrictor effect, which would explain both their long duration of action and the relatively low blood concentrations attained. This is supported by some experimental studies with mepivacaine (de Rochemont and Hensel, 1960; Pohto and Scheinin, 1960). In contrast Haas and von Braunmühl (1966) found no vasoconstrictor effect. As a rule local anaesthetics enhance blood flow (Åström, 1966b). Dhunér and Lewis (1966) using a tissue $^{133}Xe$ clearance method, found an increased regional blood flow after injections of bupivacaine, lignocaine and mepivacaine (cf. Nishimura et al., 1965).

A further attempt to elucidate the effect of local anaesthetics on the peripheral circulation in man has been made by Jorfeldt and associates (1970). Lignocaine and mepivacaine were infused into the brachial artery, and their effects on forearm blood flow, forearm vascular resistance and venous tone were studied. Both agents produced a marked increase in venous tone unaffected by sympathetic blockade. An increased vascular resistance was observed with intact sympathetic activity but not following a sympathetic blockade. Thus it would appear that the effect of mepivacaine on the peripheral circulation is a potentiation of the action of noradrenaline on nerve-endings, similar to the effect described for cocaine. Cocaine has, in fact, been demonstrated to block the reabsorption of noradrenaline after its release in receptor organs (Fröhlich and Loewi, 1910; Furchgott, 1967).

Obstetric analgesia may be induced readily, using a technique such as epidural, pudendal or paracervical block (cf. Bonica, 1967; cf. Moir and Willocks, 1968; Gunther and Bauman, 1969). The danger of general toxic side effects to the mother are present mainly when an indwelling catheter technique is used, through which repeated doses of a slowly detoxified local anaesthetic are administered (cf. Moore et al., 1968a) (fig. 2).

The foetus may be affected by the local anaesthetic agent reaching it through the placenta (Morishima et al., 1966; Epstein, Banerjee and Cockley, 1968; Poppers and Finster, 1968; Shnider and Way, 1968a, b; Thomas, Clime and Mather, 1968; Usubiaga et al., 1968; Fox and Houle, 1969; Holmén, Ojala and Korhonen, 1969; Taylor et al., 1969). Demonstrable placental transmission occurs with such local anaesthetic agents as lignocaine, mepivacaine, prilocaine and bupivacaine. This is, however, less efficient than ultrafiltration, suggesting that a certain barrier to placental transmission exists presumably related to physicochemical binding of the drug to proteins in the mother's blood and to the high haemoglobin content of the infant's blood. This would explain why the blood level of local anaesthetic agent in the infant attains only 80–25 per cent of that of the mother. The placenta, although rich in enzymes, does not, apparently, play a part in the breaking down of local anaesthetic agents.

Factors other than the concentration of the anaesthetic agent in the infant's blood may well be the cause of the depression observed in the neonate (cf. Bonica, 1967).

A variable but appreciable incidence of bradycardia and a few cases of foetal death have been reported in association with paracervical block (Bonica, 1967; cf. Rosefsky and Petersiel, 1968). Complications of a technical nature resulting in the injection of the drug directly into the foetus have occurred (Sinclair et al., 1965). The increased incidence of bradycardia and foetal depression may possibly be due to direct injection of the drug into vessels in communication with the placenta.

Epidural anaesthesia is the technique whose value in the assessment of the effect of local anaesthetics has perhaps been most studied and exploited in recent years. The factors which influence its depth and extent have been thoroughly investigated and reviewed by Bromage (1967). The extent of the epidural analgesia has been shown to depend on the volume and concentration of the solution injected, and also on the patient's
It is also greater if the solution is injected with the patient in the sitting position. This is a consequence of hydrostatic bulging of the dural sac encroaching on the caudal part of the epidural space (Erdemir, Soper and Sweet, 1965; cf. Usubiaga, Moya and Usubiaga, 1967; Usubiaga, Wikinski and Usubiaga, 1968).

It has also been stated that the local anaesthetic agent injected extradurally exerts its effect only after reaching the subarachnoid space, and thus results in intradural block. Thus nerve blocking may actually not take place in the extradural space. Lund and Covino (1967) claim to have demonstrated that this transport takes place by the blood stream, and not by direct penetration of the dura. Animal studies of the extradural administration of tagged lignocaine have demonstrated an appreciable uptake of the local anaesthetic agent by the spinal cord, the highest concentration being in the posterior and lateral columns (Cohen, 1968; cf. Bromage, Joyal and Binney, 1963).

In epidural anaesthesia, it is possible to state and compare the duration of action of various anaesthetic agents in man since Bromage's principles for testing have been followed in several investigations (Bonica et al., 1960; Ziegler et al., 1961; Bromage, 1965; Crawford, 1964; Ekblom and Widman, 1966a; Korkella, 1966; Lund, 1966; Duthie, Wyman and Lewis, 1968; Rubin and Lawson, 1968; Steel and Massey Dawkins, 1968; van Steenberge, 1968; Watt, Ross and Atkinson, 1968; Bromage, 1969a, b; Downing, 1969). The duration of action is approximately 50-75 per cent of that for the respective agent as determined by nerve block or caudal anaesthesia. The use of a large dose of local anaesthetic with production of a high block, prolongs effective surgical analgesia far beyond what the test figures would suggest. This is because regression takes place from the peripheral segments, in a central direction.

It would appear, furthermore, that the duration of action of solutions of bupivacaine injected into the extradural space is little altered by the addition of adrenaline (Nishimura, 1966; Nishioka, 1967; Yasuda et al., 1967; Löfström et al., 1969).

The addition of adrenaline to the anaesthetic solution not merely prolongs the duration of action and reduces absorption, it also reduces the incidence of low blood pressure. The circulatory depression resulting from a preganglionic sympathetic block, an invariable consequence of widespread epidural anaesthesia, is significantly reduced by the adrenaline absorbed from the epidural space. Circulatory disturbances are the most frequent complication of epidural anaesthesia, since respiratory function is usually retained, even with extensive block (Kennedy et al., 1966; McLean et al., 1967).

Spinal analgesia is a well-established method of inducing analgesia which has, in general, retained its popularity in the centres where it is in routine use (cf. Moore, et al., 1968b). Neurological complications are exceedingly rare, if a modern technique is practised (absolute sterility of the instruments, anaesthetist's gloved hands, autoclaved local anaesthetic ampoules, and the use of fine-gauge needles). The newer local anaesthetic agents such as bupivacaine have no demonstrable advantages over amethocaine or mepivacaine in this field (Poe, Dornette and Johnsson, 1962; Ekblom and Widman, 1966b; Lipton, Sennott and Batt, 1966).

Several local anaesthetic solutions intended for intradural administration have a pH far below 7.00. This may be a disadvantage since the buffering properties of the CSF are significantly inferior to those of blood.

**GENERAL TOXICITY**

That local anaesthetic agents are toxic is clear from clinical experience. Thus fatal cases have been reported from every country where local anaesthetic techniques are practised.

Significant cardiovascular and respiratory depression has been observed in animal experiments (Henn, 1960; Stewart et al., 1963; Gordh, 1964; Austin and Moran, 1965; Henn and Brattsand, 1966), although only after doses appreciably higher than those used in clinical practice. However, experience gained from the unexpected appearance of serious complications would suggest that the whole concept of toxicity of local anaesthetics should be re-examined. Such complications have appeared following the administration of very small doses, as in dental surgery and following skin infiltration prior to the puncture of a blood-vessel. It would thus appear that the incidence of complications is not always directly related to the dose administered (cf. Gjessing and Harley, 1969). Nevertheless the fatal outcome of
During the infusion of mepivacaine (5 mg/kg/20 minutes) no depressive effect on the central circulation was observed. (By courtesy of Jorfeldt et al., 1968, and Acta anaesth. scand.)

several cases may be explained by the gross overdose administered, often in combination with the indiscriminate use of central depressant or stimulant drugs for the treatment of convulsions and hypotension (Moore, 1966; Richards, Smith and Katz, 1968; Adriani, 1968). It has been clearly demonstrated, in both animal experiments and in man that local anaesthetic agents administered in doses sufficient to attain convulsant blood or plasma levels, or approaching thereto, do not have a deleterious effect on the circulation (fig. 3) (cf. Bromage and Robson, 1961; Kao and Jalar, 1959; Foldes et al., 1960; Foldes et al., 1965; Eriksson et al., 1966; Binnion, 1968). The increase in blood pressure observed by us (Jorfeldt et al., 1968, 1970) seems to be due to the redistribution of blood to the central circulation, a consequence of the increased peripheral venous tone. The reduction in the peripheral resistance observed simultaneously may be due to changes in baroreceptor tone following an increased cardiac output, and thus counteracting a further rise in blood pressure. The reduction in forearm blood flow resulting from the intravenous infusion of local anaesthetic agent is not observed in a limb in which the sympathetic nerve supply has been blocked.

In animal experiments (Jorfeldt et al., 1968) respiratory function is so well preserved that it can compensate for the metabolic acidosis induced by the intense muscular activity which accompanies seizures.

The main toxic effect on the CNS is the appearance of epileptiform convulsions (Foldes et al., 1960; Usubiaga et al., 1966; Mark, Brand and Goldensonn, 1964; Foldes et al., 1965) initiated by the rapid passage of local anaesthetic agents from the blood to the brain, which seems to be enhanced markedly by a low blood pH (Wagman and de Jong, 1964; Englesson, Paymaster and Hill, 1965).

Thus a substance which acts as an anticonvulsant in moderate doses (Bernhard and Bohm, 1965) can give rise to convulsions in large doses. The explanation of this anomalous effect is apparently that inhibitory neurones in the CNS are blocked first, and that it is only in much higher doses of the local anaesthetic agent that excitatory neurones are blocked (Tonaka and Yamasaki, 1966; de Jong, Robles and Corbin, 1969; cf. reviews by de Jong, 1969, and Munson and Wagman, 1969). It may be presumed that activity originating in epileptogenic foci is depressed by local anaesthetic agents in low concentrations. This differential blocking action might also explain why "unexpected convulsions" may occur in anxious patients after comparatively small doses of local anaesthetic, administered under conditions of stress.
The relation between the observed mean peak values of the methaemoglobinaemia induced by different amounts of prilocaine. (By courtesy of Hjelm and Holmdahl, 1965, and Acta anaesth. scand.)

Prilocaine has a low general toxicity, to a large extent due to a more rapid uptake of the drug by body tissues (Eriksson, 1966). However, metabolites are taken up by the red blood cells and induce methaemoglobin formation (Scott, Owen and Richmond, 1964; Daly, Davenport and Newland, 1964; Hjelm and Holmdahl, 1965; Lund and Cwik, 1965b; Harris et al., 1968), in this way decreasing the oxygen-carrying capacity of the blood (fig. 4). The relationship between dose and methaemoglobin formation, and the antidotic effect of methylene blue have been elucidated by, among others, Hjelm and Holmdahl (1965).

Certain local anaesthetic agents in low or moderate concentrations selectively inhibit the activity of ventricular ectopic foci in the heart. This property has been used therapeutically, to an ever-increasing extent in intensive care and cardiac care units. The infusion of even large doses of lignocaine does not impair either the respiration or the circulation of patients suffering from heart disease. The main risk with such infusions is that of accumulation, as previously discussed. A drug such as lignocaine is but slowly eliminated; thus an increasing level of the drug manifests itself in the appearance of convulsions, or varying degrees of heart block.

**LOCAL TOXICITY**

The preliminary screening of all potentially useful local anaesthetic agents includes the assessment of local toxicity. The macroscopic or microscopic demonstration of tissue damage by the drug, in concentrations required for nerve block, automatically results in its disqualification. However, even with drugs at present clinically acceptable concentrations tissue damage may result from their use in too high a concentration.

The effect of local anaesthetic agents on the healing of wounds has been of special interest. The results of animal experiments suggest that the infiltration with local anaesthetics of an area to be operated upon has an unfavourable effect on subsequent healing (Nilsson and Wendeberg, 1957; Bodvall and Rais, 1962). This effect is even more marked with solutions containing adrenaline.

Intraneural injection is thought to carry the risk of nerve damage especially when local anaesthetics with a long duration of action are used. However, no nerve damage was demonstrable by means of electroneurography following the intraneural injection, in volunteers, of solutions of conventional anaesthetic agents whose pH lay between 3 and 4, even with the addition of adrenaline (Löfström, Wennberg and Widén, 1966). Repeated nerve puncture, the use of wide-bore needles, and the rapid injection of fluid into a nerve all gave changes in conduction velocity, the effect being maximal three weeks after the nerve had been injected. Such pathological changes demonstrable by electroneurography persist for a period of several months after the insult, even in the absence of subjective or objectively demonstrated neurological symptoms. The comparatively long period elapsing before pathological changes are maximal corresponds with the late appearance of painful neuritis after a nerve block (cf. Wolley and Vandam, 1959). These changes were thought to be due to the appearance of traumatically induced scar tissue.
SUMMARY

The local anaesthetic agents which have become available in recent years can be seen to represent a considerable advance on their predecessors. Even they, however, have undesirable side effects and it would seem that in spite of the great progress in this field the ideal local anaesthetic is yet to be found.

REFERENCES


ASPECTS OF THE PHARMACOLOGY OF LOCAL ANAESTHETIC AGENTS


