Drug Treatment of Disease

LOCAL ANALGESIC DRUGS

BY

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The properties demanded of an ideal local analgesic drug are many and varied. They include rapid onset and adequate duration of analgesia; low systemic toxicity, so that an adequate volume may be injected without exceeding the maximum safe dose; lack of irritation to surrounding structures and without damage to nervous tissues; and effectiveness by all routes of administration. In addition, certain physical properties, such as solubility in water and stability of solution during storage and sterilization are required.

To a great extent this formidable list is satisfied by most modern local analgesic drugs, though some compromise must be accepted. In efforts to attain the ideal a large series of drugs have been introduced, of which a comparatively small proportion have stood the test of time. However, the large number of names of these drugs, and the variety of proprietary names for the same chemical substance, have led to a highly confusing nomenclature. Indeed, it is often difficult to be sure which particular drug is referred to, especially when reading papers from overseas.

Chemistry

The majority of local analgesic drugs are tertiary amino-esters of an aromatic acid, and can be represented by the basic formula:

where R represents the acid radical, most commonly *p*-aminobenzoic acid, and R_1 , R_2 , and R_3 substitution points in the alcohol and amino groups. The best known member of this typical structure is procaine:

Changes in any part of the molecule will alter the properties of the substance. As a rule, lengthening of the alcohol chain (R_1) or substitution in the amino group (R_2 , R_3) produces a more powerful analgesic, but with an increase in toxicity. The presence of the tertiary amine is not essential for producing anaesthesia, and benzocaine is an example of a simple alkyl ester of *p*-aminobenzoic acid:

Not all local analgesics follow this general pattern, and some of the better-known agents such as lignocaine, which is an anilide derivative, and cinchocaine, which

is a quinoline derivative, must be placed in a chemical "miscellaneous" group.

Mode of Action

There is general agreement that a local analgesic drug can enter a nerve fibre or cell only in the form of free base. Since the drug is available as a water-soluble salt, usually the hydrochloride, of a basic substance, it has an acid reaction. Hydrolysis must therefore take place before the lipid-soluble base can be liberated. This is brought about by the alkaline tissue fluids and has led to suggestions that previously alkalinized solutions offered advantages, especially in greater speed of action. Unfortunately such preparations deteriorate rapidly, and, unless alkalinization is carried out most carefully, precipitation of base occurs with resulting loss of activity. Experimentally it has been shown that ionization takes place within the nerve cell, and it is the cationic form of the base which is important. In such a reaction the base changes from a tertiary amino to a quaternary ammonium compound, and many quaternary ammonium compounds have the property of blocking synaptic transmission.

A more precise interpretation of the method by which local analgesic drugs act is not possible, but certain additional facts are known. Impulses in the smaller nerve fibres are blocked before those in larger fibres, perhaps owing to the relatively greater surface area exposed to the drug. Thus in a mixed nerve autonomic and sensory fibres are anaesthetized before motor. A pattern, too, may be seen in the order in which sensory modalities are lost, but great individual variations are encountered.

Toxicity

A local analgesic drug causes toxic symptoms when the rate of administration or absorption exceeds that of elimination. These drugs are destroyed by plasma esterases and by the liver. When a patient has serious liver damage the risk of an overdose is increased. The dose which may be safely administered thus depends not only on the physical condition and age of the patient but also on the site of injection and the particular drug which has been used.

Two types of toxic reactions may be seen, affecting either the central nervous or the cardiovascular system. The most apparent is cortical stimulation characterized by convulsions, which, though impressive, are not as serious as the less obvious effects. Medullary depression may follow, as with an overdose of narcotic drugs. At the same time the myocardium is depressed and a bradycardia proclaims interference with the conduction mechanism. Convulsions, as in other circumstances, can be controlled by intravenous injection of a rapidly acting barbiturate. But this will aggravate existing cardiovascular or respiratory depression. Only a minimal dose of barbiturate should be given, and at the same time it may be necessary to give artificial respiration and restore the blood-pressure. Reactions due to a so-called sensitivity to the drug are probably so rare that they can be ignored.

Drugs

Cocaine, procaine, amethocaine, and cinchocaine are so well known that a detailed description of their properties would be superfluous; these are summarized in the Table below. Some of the more recent additions, however, should be mentioned, for they indicate the way in which chemists are attempting to satisfy clinical ideals in local analgesic drugs.

Lignocaine.—This is an anilide derivative synthesized in 1943. It is reputed to be slightly more toxic than procaine, but, being more powerful, has a higher therapeutic index. It has the advantages of stability in solution and will withstand long periods of storage and autoclaving. To these may be added a short latent period, a tendency to spread, and a pH 6.4, which approximates to that of the tissues. It is the only local analgesic drug which causes neither vasodilatation nor vasoconstriction. It is effective in all situations, and without the addition of adrenaline it may be expected to give analgesia lasting for about one and a half hours. The maximum safe dose is about 500 mg., though this can probably be exceeded in healthy young subjects. It is available not only in solution but as a jelly, ointment, and a viscous solution for topical application.

Carbocaine.—Synthesized in 1957, and, like lignocaine, is of Swedish origin. The drug is very similar to lignocaine in both its properties and chemical formula, but is said to be effective for rather more than two hours when used without a vasoconstrictor. It is also reputed to be free of undesirable systemic side-effects.

2-Chloroprocaine.—First described in 1952, 2-chloroprocaine attracted interest for the very rapid onset of analgesia it produced and its high therapeutic index. Low toxicity is due to the rapid destruction which takes place in contact with plasma. This necessarily limits the duration of effect, which without the addition of adrenaline may not exceed 20–25 minutes. It is a reasonably stable compound with a pH of 4.9.

Hexylcaine.—This drug was synthesized in 1944 and has enjoyed a considerable vogue as an agent for surface analgesia. It is moderately stable and withstands autoclaving. Toxicity is low and the duration of analgesia about two hours. Unfortunately, solutions have a low pH, and this acidity accounts for soreness and tissue irritation sufficient to limit use by injection.

Ravocaine.—This is a procaine derivative which is considered to be a better topical agent than cocaine and to have a toxicity similar to that of amethocaine (i.e., maximum safe dose about 150 mg.). It has been used

in a concentration of 0.1% for infiltration and 0.5% for nerve blocks, particularly in dentistry.

Piperocaine.—This achieved a certain fame when used as a 1.5% solution for caudal and extradural injections by virtue of the rapidity with which analgesia developed in these situations. Having a toxicity only slightly greater than that of procaine, and a duration of effect of about 45 minutes, its use led to a revival of interest in these methods of analgesia.

With the exception of lignocaine and piperocaine, these newer drugs are not freely available in the United Kingdom, but the following Table summarizes information on those which are in common use in this country.

Drug and Synonyms	Uses	Maximum Dose	Duration without Adrenaline	Concentration or Dose
Cocaine	Topical only	200 mg.	20 min.	4–10%
Procaine: Ethocaine "Novocain" "Planocaine" "Neocaine" "Sevicaine" "Novutox"	Infiltration*. Nerve blocks*. Occasionally spinal analgesia	1 g.	20 "	>0.5–2% 100–200 mg.
Amethocaine: Pantocaine Pontocaine Tetracaine "Anethaine" "Decicain"	Nerve blocks*. Infiltration*. Spinal. Topical	150 mg.	2 hr.	>1/1,000–1/2,000 5–15 mg. 2%
Cinchocaine: "Dibucaine" "Nupercaine" ("Percaïne")	Spinal. Nerve blocks*. Infiltration*. Topical	150 "	2½–3 hr.	<1/1,500 (light) 1/200 (heavy) 1/1,000
Lignocaine: Lidocaine "Xylocaine" "Xylotox"	Extradural and caudal. Nerve blocks. Infiltration. Topical. Spinal	500 "	1½–2 hr.	>1.5% >0.5–2% 4% 2–5%
Piperocaine: "Metycaine"	Extradural and caudal	1 g.	45 min.	>1.5%

* Addition of a vasoconstrictor advisable.

Local Analgesics for Prolonged Effect

Unhappily, though the demand for such agents is great, few are available which will produce long-acting analgesia without undesirable side-effects. "Depot" solutions in wax bases, mucates, and ammonium compounds have all been tried without much success. Hopes were raised by the introduction of efocaine, which was a combination of procaine base and procaine hydrochloride in a solvent. In spite of many apparent successes this drug was held responsible for a number of disastrous neurological sequelae, and on these grounds it, too, had to be abandoned. Oily solutions containing both a water-soluble salt of a local analgesic and benzyl alcohol, which causes some degree of nerve destruction, are still used, but their duration of action is somewhat variable and uncertain.

Alternatively, one must turn to alcohol and phenol, neither of which are strictly analgesic drugs. They cause analgesia of long duration only by virtue of nerve destruction. The intrathecal injection of alcohol to relieve the intractable pain of carcinoma has proved quite successful. Some disturbance of sphincters may follow but it is temporary in most instances. When injected into peripheral nerves, an efficient block may be produced, though it is sometimes followed by an unpleasant alcoholic neuritis which may persist for five to six weeks. 6% phenol solutions have been tried as an alternative, and, though the results are not so certain, they are accompanied by less disturbance and pain.

Such solutions are most effective in smaller nerve fibres and can produce a chemical sympathectomy lasting up to a year when injected into the lumbar sympathetic chain.

Vasoconstricting Drugs

No description of local analgesic drugs can be complete without mention of the vasoconstrictors which are commonly added. The function of these drugs is twofold: to prolong the action of the analgesic drug, thus reducing the rate of absorption, and hence, at the same time, reducing the risk of toxic reactions. In fact, it is a safe rule to add a vasoconstricting agent when injecting any local analgesic which causes vasodilatation.

Adrenaline is still the commonest drug used in spite of not infrequent systemic side-effects. These reactions are usually the result of overdosage or inadvertent intravenous injection. Adrenaline is most frequently marketed in a 1/1,000 solution, and strict observance of 0.5 ml. as the maximum dose (0.5 mg.) will much reduce their incidence. For most purposes a concentration of 1:200,000 is adequate, and even 1:600,000 can produce efficient vasoconstriction if given sufficient time to act. Adrenaline is difficult to sterilize and readily decomposes. Thus its addition to a local analgesic solution, unless this is freshly prepared, requires an acid pH, which in turn leads to irritation of tissues and pain on injection. However, the alternatives such as phenylephrine, which is reputed to have little effect on the heart or cerebral cortex, and cobefrin, which produces less vasoconstriction and cannot be autoclaved, have found little favour in Great Britain.

Mucolytic Enzyme

Hyaluronidase is the mucolytic enzyme which breaks down hyaluronic acid and provides a greater area of distribution for injected drugs. When used with local analgesic solutions it provides a more extensive field of analgesia and rapid penetration of nerve fibres. But, since absorption may take place from a larger area, the duration of analgesia is shortened and the toxicity increased. While having obvious possibilities, this drug should never be used as an excuse for a poor technique and an inadequate knowledge of anatomy.

Choice of Drugs

Procaine may still be used most commonly, but lignocaine, in spite of a relatively higher cost, is more efficient and convenient for general use, quite apart from being the undoubted drug of choice for extradural analgesia.

If vasoconstriction and shrinkage of mucous membranes is required for ear, nose, and throat surgery, cocaine retains pride of place for topical application. But if vasoconstriction is unimportant, lignocaine, amethocaine, and cinchocaine all have their adherents, who base their preference on a fear of the toxic reactions from cocaine.

For spinal analgesia cinchocaine or amethocaine offers a duration of effect adequate for most surgical procedures. Lignocaine would not appear to have any particular advantages in this method of analgesia except in the conduct of a continuous spinal block maintained with serial injections. Whatever the merits or otherwise of spinal analgesia, there is little evidence that any particular drug in use to-day can be blamed for the post-spinal sequelae which have tended to bring the method into disrepute.

The limitations of the various drugs available having been accepted, the choice will probably be determined by such practical considerations as expense, convenience, and familiarity. Each drug has its own particular advantages, but an understanding of their properties and limitations will lead to more efficient analgesia and fewer undesirable side-effects.

RESIDENTIAL CARE OF MENTALLY HANDICAPPED CHILDREN*

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There are 60,000 mental defectives in institutional care in England and Wales, of whom 8,500 are children, mainly of idiot or imbecile grade. It is widely thought that because of the increased emphasis upon home care for the mentally subnormal the numbers going into institutions are likely to fall in the near future. While this may be true of adults, who for the most part present rather different problems, I do not think it is true of children. The number of severely subnormal children who survive infancy has almost certainly increased markedly in recent years: four times as many mongols, for example, survive until the age of 10 years to-day as did in 1929 (Carter, 1958). Moreover, even to-day the number of mentally subnormal children who go into mental deficiency hospitals is arbitrarily restricted by the number of beds available. The pressure to find more places is bound to grow—and is likely to prove irresistible. It is therefore a matter of public concern how we can best look after these children, and how far their potentialities can be realized.

Both in this country, which probably leads the world in this field, and in other countries, which have mostly modelled their practice upon ours, mental defectives in residential care are usually housed in large comprehensive institutions or "colonies" containing up to 2,000 beds. Some hospitals have only children and others only adults; but most contain children and adults, and both high-grade and low-grade cases. The pattern of institutional care has not changed very much over the last century. Though there is to-day much discussion about hostels, large institutions are still being built, and existing large institutions are being increased still further in size. Few attempts have been made during the past 30 years to think out the basis of our policy of institutional care and to see what changes are desirable to bring it into line with changing mental health needs and our increased understanding of these.

Present Study

In August, 1957, I had the opportunity—through the generosity of the National Society for Mentally Handicapped Children, which provided a grant for a three-year research project—to begin a study of psychological and educational problems of imbecile children. The study of residential care which is described here forms part of this research, and has been carried out in a 16-bed unit under the control of the

*Based on a paper read to the British Association for the Advancement of Science on September 7, 1959.