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BRIEF REVIEW

Local Anesthetic Update

Terrance A. MacKenzie MB, ChB, FRCP(C),* and **Earle R. Young** BSc, DDS, BScD, MSc, FADSA*†

†Department of Anaesthesia, Faculty of Dentistry, University of Toronto.
*†The Wellesley Hospital, Toronto, Canada

The development of new local anesthetics has not been an area of particularly active research for a number of years. However, as the use of regional anesthesia has expanded, additional anesthetic requirements and techniques have stimulated the search for newer drugs and ways of modifying existing ones. This article reviews some of the more recent developments in this field.

Local anesthesia first came into prominence in 1884 when Koller introduced cocaine into clinical practice after showing its effect on a toad's eye. The first injections of cocaine for blocking conduction in sensory nerves were performed by Halsted in 1884, when he blocked the supraorbital and infraorbital nerves, and the inferior alveolar, ulnar, and musculocutaneous nerves. In the winter of 1884, Halsted achieved the first brachial plexus block by injecting the roots of the plexus after exposing them under local anesthesia with cocaine.

The next real milestone in local anesthesia was the introduction of procaine in 1904 by Einhorn. There was a further advance in 1943 with the discovery of lidocaine by Lofgren. Lidocaine, an amide anesthetic, was shown to be efficacious and relatively nontoxic, lasted a reasonable length of time, could be sterilized, and was stable. Moreover, lidocaine proved to be less allergenic than the previous ester local anesthetics chemically related to para-aminobenzoic acid.

Following the introduction of cocaine, most of the early investigations in the field of local anesthesia were concerned with the development of various regional anesthetic techniques and the development of new local anesthetic agents. Most of the anesthetic techniques that are in common practice today were described within 50 yr of the first clinical use of cocaine. Little information was available concerning the mechanism of action of local anesthetics, their physiological disposition, general pharmacology, or toxicity. During the past 25 yr, the mechanisms by which local anesthetic agents cause conduction blockade have been elucidated.[1] The general pharmacology and toxicity of this class of drugs have also been studied extensively. In addition, considerable information is now available concerning the pharmacokinetic properties of local anesthetic drugs.

In recent years, the major advances that have been made in regional anesthesia include: (1) a description of several new techniques for postoperative analgesia, (2) the development of potent new local anesthetic agents, and (3) scientific studies concerning factors that influence the action of local anesthetics on peripheral nerves and on the heart. There are a number of objectives with respect to the actual development of new local anesthetic agents. These are (1) a good topical local anesthetic to penetrate intact skin, (2) an ultrashort-acting local anesthetic, (3) a long-acting local anesthetic with less cardiotoxicity than bupivacaine or etidocaine, (4) a long-acting local anesthetic with purely sensory effects, and (5) a local anesthetic with a short latency for sensory blockade.

NEW TECHNIQUES

The most significant development in terms of new regional techniques involves the placement of an epidural catheter into the pleural space in order to administer postoperative analgesic drugs.[2] This technique has been employed to provide postoperative analgesia for patients undergoing cholecystectomy with a subcostal approach, unilateral breast operations, and renal surgery. In addition, it also has been employed in postthoracotomy patients, in trauma patients with fractured ribs, and in patients following hernia repair. A more recent description of the technique for treatment of reflex sympathetic dystrophy has also been made.[3]

Bupivacaine is the local anesthetic agent most commonly used for intrapleural regional anesthesia; 20 mL of 0.5% bupivacaine with 1 : 200,000 epinephrine is the

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Address correspondence to Dr. Earle R. Young, Department of Anaesthesia, Faculty of Dentistry, University of Toronto, 124 Edward Street, Toronto, Ontario, Canada M5G 1G6.

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formulation most commonly used. Pain relief is obtained within 15 to 20 min. Analgesia varies from 4 hr when 0.25% bupivacaine is used, to approximately 8 hr in patients receiving 0.5% bupivacaine. Occasionally, analgesia has persisted for 18 hr.

Spinal anesthesia using bupivacaine has become very popular, especially in Germany under the influence of Hans Nolte. With the introduction of a very fine needle and a microcatheter that threads through the needle, the possibility of performing continuous spinal anesthesia for very long periods of time, and with a minimal incidence of cephalgia, has been achieved. However, recent reports of cauda equina syndrome have given cause for alarm and perhaps a rethinking of the technique.[4]

NEW AGENTS

One of the objectives in local anesthetic research has been the development of a good topical local anesthetic to penetrate intact skin. The first preparation to achieve this goal is a eutectic mixture of equal parts of lidocaine and prilocaine.[5,6] Called EMLA, the acronym for eutectic mixture of local anesthetics, this preparation is available as a 5% cream. It is applied to intact skin under an occlusive dressing and is left in place for approximately 60 min. A problem with previous mixtures of local anesthetics applied topically was that to achieve the active base form, the local anesthetic had to be dissolved in alcohol, and this tended to cause skin irritation. One of the benefits of EMLA is that it is an emulsion, and there is sufficient moisture and lipid solubility to allow excellent penetration through intact skin. Further research of its use on mucous membranes (including the oral cavity) could expand its usefulness tremendously. A form for intraoral use is currently being developed at the University of Toronto.

Another objective of research is to develop an ultrashort-acting local anesthetic. None currently exists. Chloroprocaine is short acting, but not ultrashort acting, and has also been incriminated in neurotoxic reactions following inadvertent injection of large amounts into the subarachnoid space. This problem, discussed later, has now been rectified, and chloroprocaine is back on the market.

A third research objective is the development of a long-acting local anesthetic with less cardiotoxicity than bupivacaine or etidocaine. This has been partially addressed with the recent synthesis of a new amide local anesthetic, ropivacaine. This drug is a congener of bupivacaine and mepivacaine and is intermediate in lipid solubility. Early reports indicate that it has an onset and duration of action similar to that of bupivacaine but is less cardiotoxic.[7] In animal studies it was shown to have a lower potential for producing cardiac dysrhythmias than bupivacaine, and the ratio of the cardiac collapse dose to the seizure threshold dose was shown to be considerably higher than that of bupivacaine.[7,8]

A final objective in local anesthetic research has been the development of a long-acting local anesthetic with purely sensory effects. Unfortunately, we do not have one; all local anesthetics produce both sensory and motor effects. The relative proponderance of motor to sensory blockade of etidocaine versus bupivacaine, however, suggests advances in this area are a possibility.[8]

Articaine (Ultracaine) is a new intermediate-duration local anesthetic of the amide classification. It is unlike most commonly used local anesthetics in that the aromatic portion contains a thiophene nucleus, which theoretically may impart greater lipid solubility and hence nerve-penetrating properties. It is rapidly gaining popularity in dental use where, anecdotally at least, reports of improved success and quality of nerve blockade are being made. These benefits, however, have not been borne out in well-controlled scientific studies.[9,10] The fact that articaine possesses a lipid/buffer partition coefficient greater than lidocaine, prilocaine, and bupivacaine [123 versus 10, 6.9, and 83.2 respectively) provides some physicochemical evidence of better penetration.[11] The diffusion of articaine is also apparently enhanced by its more linear molecular configuration versus more spherical molecules, such as mepivacaine and bupivacaine, which contain a piperidine ring in the terminal amine portion of the molecule.[11,12]

INCREASING THE DURATION OF ACTION

Various methods have been used to prolong the duration of action of local anesthetics. One that has been used for many years is the addition of epinephrine in various concentrations, most commonly in 1 : 100,000 or 1 : 200,000 strengths. This increases the duration of action of the local anesthetic, generally by 50% to 100%. It also reduces the vascular uptake of the local anesthetic, hence possibly reducing systemic toxicity, improves the quality of block, and reduces bleeding. Epinephrine, however, when injected into patients having general anesthesia with various inhalational agents (particularly halothane), may cause cardiac dysrhythmias, the most important being ventricular fibrillation. One should also be careful using epinephrine in patients who are hypertensive or who have preexisting cardiac or thyroid disease.

Felypressin (Octapressin), a derivative of vasopressin, is a noncatecholamine vasoconstrictor free of dysrhythmogenic side effects. It has been mixed with local anesthetics and found to be effective in reducing capillary blood flow and decreasing surgical bleeding.[13] It is, however, frequently not recommended when hemorrhage control is required due to its venular-constricting actions. Being

oxytocic, it is relatively contraindicated in pregnancy. Since felypressin also produces the other effects that epinephrine does, that is, prolonging the duration of local anesthesia and decreasing peak blood concentrations of local anesthetic, it is a useful alternative to epinephrine when the latter drug is contraindicated by disease or concomitant drug therapy.

Oxymetazoline, an α-adrenergic agonist, has been used to cause vasoconstriction, especially in nasal mucosa, where it is equally as effective as cocaine. If oxymetazoline was added to local anesthetics it would possibly be preferable to epinephrine, which has both α- and β-agonistic effects. Oxymetazoline is essentially free of direct cardiac effects.[14] Further studies are required to see whether the combination of local anesthetics with oxymetazoline will significantly prolong the duration of action of the local anesthesia.

High molecular weight dextran, such as dextran 70, mixed with local anesthetics prolongs their duration of action without producing other adverse effects. Some of the mechanisms for this increase may be that high molecular weight dextran increases the pH of the local anesthetic or that the dextran physically slows absorption of the anesthetic.[8]

A new local anesthetic dosage form is also being investigated. This involves the production of microencapsulated vesicles of the local anesthetic to produce a slow, sustained release of drug. Studies using 7% methoxyflurane in microdroplet formation, enclosed within a monolayer of lecithin, have shown that when this combination was injected into the tail of rats it produced a significant increase in pain threshold that persisted for approximately 25 hr.[15] By comparison, the administration of 1% lidocaine alleviated pain for approximately 90 min and 0.5% bupivacaine for 3 hr in the same rat model. Unfortunately, this preparation did not spread far beyond the site of injection and may therefore be limited to providing prolonged analgesia in chronic pain patients who require trigger point injections or in situations in which wound margins can be infiltrated. Similarly, the addition of small amounts of opioid, notably fentanyl, to epidural or subarachnoid injections of local anesthetics will prolong the block, enabling long periods of analgesia to be obtained without motor loss or sympathetic blockade.

A number of α_2-adrenergic agonists have been studied in animals and humans in which analgesic effects have been demonstrated. Two such agents are clonidine and guanfacine. When given epidurally in humans, both drugs also prolong the degree of postoperative analgesia. Unfortunately, they are rarely capable of producing surgical anesthesia and may cause hypotension. It has been shown that clonidine is as effective as epinephrine in prolonging motor block during spinal anesthesia with tetracaine in dogs and more effective in prolonging sensory blockade.[16] Clonidine itself has analgesic properties when injected into the epidural or subarachnoid space.[17]

SHORTENING THE ONSET TIME

The final objective in local anesthesia research has been to obtain a local anesthetic with a rapid onset time. This objective has also not yet been obtained. There have been recent developments with the use of pH-adjusted or carbonated local anesthetics to produce a more rapid onset of anesthesia. With both of these approaches, large amounts of local anesthetic penetrate the nerve membrane in their lipid-soluble, uncharged free base form and pass into the axoplasm of the nerve, where they reequilibrate and then attach to the receptors in the sodium channel. This technique has shortened the onset time by at least a factor of two when compared to the unmodified drug.[8] The carbon dioxide diffuses rapidly into the nerve cytoplasm, markedly lowering the intraneuronal pH and favoring ionization of the local anesthetic, which improves binding to the receptor in the sodium channel. Alkalinization with bicarbonate allows more of the uncharged, lipid soluble form of the molecule to be available initially, thereby enhancing diffusion across the nerve sheath and into the axolemma. The bicarbonate does not diffuse intraneuronally.

OTHER IMPORTANT CONSIDERATIONS

This last section discusses of some of the basic scientific advances that have been made concerning the effects of local anesthetics on nerves and on cardiac status.

Smaller amounts of drug are required to produce an equivalent level of conduction blockade in pregnant versus nonpregnant patients. This difference was attributed initially to mechanical factors, such as the gravid uterus causing distension of vessels in the epidural space in the third trimester.[18] A study involving epidural analgesia in patients during the first trimester of pregnancy has also shown that these patients demonstrate an actual increased sensitivity to local anesthetics.[19] Studies on isolated nerves from pregnant rabbits have shown a more rapid onset of conduction block when exposed to local anesthetics.[8] In addition, the threshold for conduction block in nerves of pregnant animals is lower than those in nonpregnant animals. Local anesthetics are bound to plasma proteins in the blood, and it is the amount of free drug that determines the actual response as well as the degree of toxicity. In pregnant patients, the amount of α_1-acid glycoprotein, which is the protein that binds local anesthetics, is decreased, and this would have the effect of allowing a

greater proportion of free drug in the plasma.[8,19] This may also account for some of the cardiac problems that have been associated with the inadvertent intravenous administration of bupivacaine. The hormonal changes that occur in pregnancy may also increase neuronal sensitivity to local anesthetic blockade.[8,19] This may be related to an enhanced diffusion of local anesthetic or it may result from a basic change in the local anesthetic receptor in the nerve membrane. Decreased progesterone-induced glucuronidation of local anesthetics has also been a proposed mechanism.[8,19] Finally, it is known that pregnant patients have higher plasma concentrations of endorphins and enkephalins, which could provide additive effects with local anesthetics.

A great deal of new information has been obtained over the past few years concerning the cardiac electrophysiological properties of local anesthetics. Investigations have been initiated due in part to the concern regarding the cardiac dysrhythmic activity of bupivacaine. The major electrophysiological effect of local anesthetics appears to be a decrease in the maximum rate of depolarization.[8] There is also a decrease in the action potential amplitude and duration. Exposure to high concentrations of lidocaine and bupivacaine results in a prolongation of conduction time between Purkinje fibers and ventricular muscle cells, and in some cases conduction block supervenes. The essential difference between lidocaine and bupivacaine is the duration of the depressant effects. Lidocaine's are short lasting (seen only during tachycardia) while those of bupivacaine are very prolonged (occur at normal heart rates). Lidocaine and bupivacaine are believed to penetrate the sodium channel in the cardiac membrane rapidly. However, lidocaine diffuses out of the channel quickly, whereas bupivacaine has a slow wash out from the sodium channels. This "fast in, slow out," behavior of bupivacaine is believed responsible for initiating a unidirectional block and reentry type of dysrhythmia in animals and patients exposed to a high intravascular concentration of this agent, as may occur with an inadvertent intravenous injection. The "fast in, slow out" property of bupivacaine may be due to the bulky molecular structure of bupivacaine causing it, once within the sodium channel, to curl up, preventing it from coming out. It may also be related to the drug's high lipid solubility and protein binding. To our knowledge, however, there have not been similar cases reported with mepivacaine, which has a similar structure to that of bupivacaine. Ropivacaine, which is structurally similar to mepivacaine and bupivacaine, does cause some cardiac depression but not quite as much as bupivacaine.[8]

Recently, it has been shown that bupivacaine causes an early direct vasoconstriction rather than vasodilatation.[20] Bupivacaine has also been shown to induce skeletal muscle damage and at high concentration, mitochondrial disruption by displacing calcium from its intracellular binding sites.[21] It has been further proposed that myocardial depression is a result of a combination of the above mechanisms plus a bupivacaine-induced interference with calcium release from myocardial sarcoplasmic reticulum, thus depressing slow-channel action potentials.[22] This is in addition to the well-known blockade of sodium conductance characteristic of all conventional local anesthetics. A central mechanism for cardiac toxicity has also been suggested.[19] Etidocaine, which is more lipid soluble than bupivacaine and equally protein bound, may cause ventricular dysrhythmias and fibrillation, but the incidence appears lower than with bupivacaine.[19] A summary of findings from various bupivacaine studies can be found in a recent review by Young and MacKenzie.[23]

Another drug that has received considerable attention is 2-chloroprocaine. The reason for this was the frequency of permanent paresis in patients, notably pregnant patients, when epidural injections were inadvertently given intrathecally. The pH of the normal solution of 2-chlorprocaine was about 3, and the solution contained the antioxidant sodium metabisulfite. When tests were performed using chloroprocaine instilled into the intrathecal space at higher pH levels, chlorprocaine was found to be essentially nontoxic. Sodium metabisulfite at a pH of 7 was also nontoxic but at a pH of 3 was found to cause neuronal damage. At the pH of 3, sodium metabisulfite forms sulphur dioxide, which diffuses into neural tissue and then forms sulphurous acid intraneuronally.[19] In small amounts or where the nerves are protected with a dural sleeve, such as in the epidural space, this is probably of little significance. However, when large volumes are injected, such as the inadvertent injection of 10 to 20 mL into the intrathecal space, the tissue ability to buffer this solution is markedly diminished.

There have been a number of investigations regarding drugs affecting other conduction channels in nerve membranes. Potassium-channel block using tetraethyl ammonium and related compounds has been shown to be very effective, especially with nonmyelinated nerves. Calcium-channel blockers have also been tested. It has been shown that verapamil in a concentration of 0.25% will produce a conduction block, and in the same concentration will potentiate the action of bupivacaine markedly.[24] These are interesting avenues of research and may result in a new type of local anesthetic for the future.

As mentioned, the inadvertent intravenous injection of local anesthetics, especially bupivacaine, has plagued anesthetics for years. Patients taking propranolol, for example, may show an increased sensitivity to bupivacaine because propranolol reduces the lungs' uptake of local anesthetics, as well as reducing liver blood flow, and hence slowing the rate of metabolism. One of the many functions of the lung is the uptake and short-term storage of many

chemicals. Local anesthetics during their first pass through the lung are sequestrated in the lung to some extent.[1] Similarly, local anesthetic-induced myocardial depression may be enhanced in patients taking β-blockers and/or calcium channel blockers, as these classes of drugs have been shown to possess inherent myocardial depressant as well as local anesthetic properties. The two isomers of propranolol are equally effective as actual membrane stabilizers, although there is considerable debate how important this action is in normal therapeutic doses.[25]

Many physicians and dentists premedicate patients having a local anesthetic with one of the benzodiazepines. These drugs have been shown to raise the threshold for convulsions. Unfortunately, they do not offer any protection from the cardiac effects of local anesthetics, especially bupivacaine. If patients are premedicated with high doses of diazepam, this drug theoretically could potentiate the cardiac effects of bupivacaine due to its displacing bupivacaine from protein binding, thus increasing the amount of free bupivacaine available for attachment to the myocardium.

Finally, cooling has been known for years to cause analgesia on its own and to increase the potency and duration of lidocaine by a factor of four with a temperature drop of 10° C. The binding of local anesthetics to sodium channels increases as the temperature drops. Of course, this is not going to be clinically useful unless regional techniques are performed on hypothermic patients.

CONCLUSIONS

In summary, it would appear that some of the objectives of local anesthetic research have been met. Medicine has a new and effective method of pain control in the intrapleural technique. In the development of new local anesthetics, we have EMLA and ropivacaine, the latter which will probably partially displace bupivacaine by virtue of its less cardiodepressant properties. Although there is as yet no long-acting local anesthetic with purely sensory effects, α-adrenergic agonists and the addition of opioids to dilute solutions of local anesthetic in the subarachnoid or epidural space are able to prolong the purely sensory block. The local anesthetic with a very short latency is also not yet available, but onset can be hastened with the addition of bicarbonate or by carbonation of the local anesthetic solution.

Basic scientific studies have provided insight into the mechanism of the cardiac depression caused by bupivacaine and have led to a modified solution of 2-chloroprocaine without neurotoxicity. There is ongoing research into the application of drugs affecting nerve channels, notably the potassium and calcium channels, instead of the sodium channels that are normally targeted by local anesthetics. Unfortunately to date, no agent exists that will reverse local anesthetic action, and we think this would be a worthwhile project for future research. It should be noted however, that electronic dental anesthesia has been used to hasten recovery from local anesthesia.[26]

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