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EDITORIAL VIEWS

Ultralong-acting Local Anesthetic Agents

A VARIETY of local anesthetic agents with varying durations of action are available in the United States. These drugs are probably adequate for the majority of surgical and obstetrical procedures in which regional anesthesia is indicated. The local anesthetic drugs that are currently available can be divided conveniently into three categories, based essentially on their relative durations of anesthetic action. Procaine and 2-chloroprocaine have a relatively short duration of action (30–60 min). Mepivacaine, lidocaine and prilocaine represent agents of intermediate anesthetic duration (90–240 min). Tetracaine, bupivacaine and etidocaine are agents with long durations of anesthesia (180–600 min). The wide variation in duration of anesthesia, particularly with the agents of long anesthetic activity, is basically dependent on the type of regional anesthetic procedure performed. In general, major peripheral nerve blocks, such as brachial plexus blockade, result in the longest durations of anesthesia, whereas central neural blocks, such as epidural or spinal blockade, produce shorter durations of anesthesia. Despite the availability of these various local anesthetic agents, a need for a drug or preparation that can provide ultralong duration of analgesia not just for several hours but, preferably, for several days still exists for postoperative analgesia and chronic pain. Ideally, such an agent should affect sensory fibers with minimal or no effect on motor function. It should be free of local irritation and possess an adequate therapeutic ratio with regard to systemic toxicity. Efforts have been expended to develop such an agent or to modify existing agents by means of alterations in pharmaceutical formulations. However, minimal success has been achieved in developing a clinically useful, ultralong-acting local anesthetic preparation. Originally, attempts were made to prolong the action of procaine by the use of a peanut oil vehicle which would provide a depot-type preparation, allowing for the slow release of procaine and a prolonged duration of anesthesia. These preparations failed because of unacceptable neurotoxicity. Local-anesthetic, impregnated silastoseal cuffs have been studied, but appear to be of minimal practical value since they must be implanted surgically.[1] Substances of varying molecular weight, such as dextran, have also been utilized as vehicles for local anesthetic drugs to produce a slow release depot-type, injectable anesthetic preparation. The results of prolongation of anesthesia of a local anesthetic dextran formulation are conflicting and, at best, only extend the duration of conventional local anesthetic drugs by several hours.[2,3]

With regard to new agents, two interesting areas have been pursued in recent years. The concept of cyclizing compounds was introduced by Ross and Akerman in 1972.[4] The hypothesis was pharmacologically intriguing in that a tertiary amine compound would be injected, absorbed into the nerve membrane, where it would then be converted to a quaternary-ammonium agent which could not readily diffuse out through the membrane. Thus, the agent would be trapped in the nerve membrane and provide long duration of anesthetic activity. Although preliminary animal results were encouraging, no successful agent was brought to human trials. The biotoxins, *i.e.*, tetradotoxin and saxotoxin, afforded another hope for an ultralong-acting local analgesic agent.[5] These compounds penetrated neural sheaths with difficulty, therefore, results of peripheral nerve blocks in animals were disappointing. However, it was possible to improve the frequency of sciatic blocks in rats and epidural blocks in cats by combining tetradotoxin with a conventional local anesthetic agent. Spinal anesthesia for 24-hour duration was obtained in sheep with tetradotoxin, where no neural barrier is present to obstruct the diffusion of the biotoxins to the receptor site nerve membrane. Unfortunately, these compounds proved unreliable in terms of predictable anesthetic duration. In addition, tetradotoxin and saxotoxin are extremely toxic systemically, which limit their potential usefulness. Efforts continue in some

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laboratories to modify the structure of tetradotoxin or saxotoxin to provide acceptable agents of ultralong duration.

The most recent area of promise is the use of epidural or intrathecal opiates for prolonged pain relief.[6] Numerous reports have appeared in the literature during the past two years concerning the epidural or intrathecal administration of opiates, particularly morphine. Durations of postoperative pain relief up to 72 hours have been reported following a single epidural injection of 2–10 mg of morphine. The prolonged analgesic activity following the administration of opiates into the epidural space or into cerebrospinal fluid is believed related to the activation of opiate receptors which exist in the spinal cord. The recent advances in the physiology of endorphins and the opiate receptor system in the brain and spinal cord provide a rational scientific basis for the epidural or intrathecal use of opiates. Although this mode of administration of opiates appears to offer the greatest promise for prolonged pain relief at present, it is not exempt from side effects. Delayed respiratory depression, particularly following intrathecal morphine, itching, and urinary retention have been reported. In addition, conflicting results concerning the efficacy of epidural opiates have recently appeared, particularly with regard to their use during labor.[7]

Two articles in this issue of ANESTHESIOLOGY offer another approach to the development of ultralong analgesic agents. Scurlock and Curtis synthesized and carefully studied a number of derivatives of tetraethylammonium and have shown a phenomenal duration of analgesia when compounds with a chain length of C-12 or longer were used.[8] Average durations of sensory analgesia of approximately 400 hours (16 days) were observed following infraorbital nerve blocks in rats. The blocks were reversible and no persistent neurotoxicity was observed. Studies of the mechanism of block suggest that these agents may act at the potassium channels in nerve membranes, in addition to an initial action at the sodium channel, where the conventional local anesthetic agents exert their membrane blocking effect.[9] The authors postulate that the ultralong duration of action is mediated by binding to a receptor site in the potassium channel.

Clearly, these studies are exciting, both to membrane physiologists interested in nerve condition and to clinicians who seek improved methods of prolonged pain relief. Many additional studies are required to determine the ultimate efficacy of these tetraethylammonium derivatives. A variety of other types of nerve blocks in animals must be carried out. For example, what duration of analgesia is obtained following epidural or intrathecal administration in animals? Can these agents penetrate peripheral nerve barriers to provide anesthesia with acceptable onset times? Is the blockade produced by the tetraethylammonium derivatives sensory selective in nature or does motor block also occur? Additional data on potential neurotoxicity following prolonged inhibition of nerve conduction and the potential systemic toxicity, particularly with regard to the brain and cardiovascular system, are indeed required.

Finally, even if the particular agents described in these reports do not ultimately prove of value in humans, the concept of blocking both sodium and potassium channels to produce ultralong durations of sensory analgesia should provide the basis for developing new agents or combinations of drugs that might fulfill the criteria of a safe, ultralong, sensory selective analgesic preparation for use in chronic pain control.

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