Spinal Anesthesia: Significant Prolongation of the Pharmacologic Effect of Tetracaine with Lipid Solution of the Agent

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A novel approach for increasing the duration of anesthesia after a single subarachnoid injection of a local anesthetic is presented. Tetracaine 1% 0.5 mg/kg was administered in 10% glucose or in lipid solution (iophendylate) in two groups of rabbits via catheters chronically implanted in the subarachnoid space. The pharmacologic effect was assessed by evaluation of the intensity and duration of the motor blockade according to a three-stage scale. Significant prolongation (447 ± 13 min vs. 130 ± 7 min, P < 0.01) with a moderate decrease in the intensity of the motor blockade was observed with lipid solution as compared to the aqueous solution. This effect is attributed to the slow release of the agent from the lipid phase, which actually functions as a drug depot in the cerebrospinal fluid. The proposed method is suggested as an additional approach for the development of drug delivery system intended for prolongation of spinal anesthesia. (Key words: Anesthetic techniques, spinal prolongation. Anesthetics, local: tetracaine.)

Since the introduction of spinal anesthesia, development of appropriate drugs and the establishment of safe techniques have promoted the wide use of this method in anesthetic practice. However, relatively short duration of action limits the use of subarachnoid anesthesia to operative procedures that do not last longer than 2–3 h. Several attempts have been made to prolong the effect of spinaly administered local anesthetics. Addition of vasoconstrictors to the injected solutions prolongs the anesthetic action, but not by more than 30–60 min.2–4 Increasing the dose of the anesthetic is not recommended and may cause severe hemodynamic5,6 or respiratory7,8 effects. Prolongation of spinal anesthesia with continuous subarachnoid catheterization has been proposed since 1949.9 However, despite the recent development of small-diameter catheters, subarachnoid catheterization is still not widely used, for several reasons: the necessity for relatively large needles for this procedure may increase the possibility of postspinal headache, and the likelihood of neural injury is greater after catheterization than with the use of a needle alone. Histologic changes of spinal cord after continuous catheterization also have been reported.10,11

Therefore, the development of drug controlled-release formulations able to induce safe prolongation of action after subarachnoid administration could broaden the spectrum of surgical procedures in which spinal anesthesia is used. In the current study, a novel approach of prolonging the anesthetic action, based on the incorporation of the drug in a hyperbaric lipid solvent, is proposed. The sustained effect produced by this formulation was investigated.

Methods and Materials

Animals

Experiments described in the current study were performed in accordance with the laws and guidelines established by the regional Committee of Laboratory Animal Care. Eighteen adult male rabbits of a mixed strain, weighing 3–3.5 kg, were used. The animals were housed individually in standard cages, were given free access to food and tap water, and were kept on 12-h light–dark cycle.

Preparation of the Model

A rabbit model established in our previous report12 was used in the current study. Briefly, animals were pre-treated with cefazolin 250 mg im. Polyvinyl catheters 300 mm long and of OD 0.61 mm and ID 0.28 mm were used for the procedure. A ring from the tip of a Luer-type plastic syringe, cut 3 mm from the end, was used as a device for fixation. The distal end of the catheter was passed through the cut piece of a plastic ring and was sealed inside, 20 mm from the tip. A nylon suture was tied around the catheter 30 mm from the proximal end and fixed with epoxy glue. Catheters were disinfected in alcohol 70% and then flushed with normal saline. The proximal tip of the catheter was closed with a stainless steel plug.

Animals were premedicated with ketamine 50 mg/kg subcutaneously and placed in a restraining hammock. The surgical fields in the dorsal cervical and lumbar areas were shaved and cleaned. Three milliliters bupivacaine 0.5%
containing adrenaline 1:200,000 was injected subcutaneously over the line between the sixth lumbar and first sacral spinous processes, and 1.0 ml was injected over the base of the seventh lumbar process. The marginal ear vein was cannulated, and ketamine was continuously infused at a rate of 1–1.5 mg · kg⁻¹ · min⁻¹.

Surgical procedures were performed under aseptic conditions. The skin and subcutaneous fascia were opened by a straight midline incision, between the sixth lumbar and first sacral spinous processes. Muscles were separated by blunt dissection. The process, ligamentum flavum, and epidural fat were removed sequentially, and the underlying transparent dura with the spinal cord were exposed. A small slit was made in the dura and arachnoid membranes until leakage of cerebrospinal fluid (CSF) was detected. The distal end of the catheter was inserted beneath the arachnoid in a caudal direction. The catheter was fixed above the plastic probe to the perioseum of the posterior lamina. The external part of the catheter was stretched through a subcutaneous tunnel along the back and exteriorized via an incision on the neck. A suture previously glued 30 mm from the tip of the catheter was tied to a buttonlike polyethylene disc and then fixed to the internal surface of the skin with an additional suture. The tip of the catheter was extracted via an additional hole near the disc, and the incision was closed.

After a recovery period of 7 days, the operated rabbits were examined. Since none of the animals showed neurologic or inflammatory disorders after the operation, all of them were used in the study.

**Protocol**

The 18 operated rabbits were divided into three equal groups. Solutions of tetracaine HCl 1% (Sigma, St. Louis, MO) in glucose 10% and an equimolar amount of tetracaine free-base dissolved in iophendylate (Pantopaque®, Alcon Surgical) were administered to groups 1 and 2 respectively, and group 3 served as a control. Manufactured solution of pantopaque is a mixture of ethyl esters of isomeric iodophenylundecylic acids containing 30.5% of firmly bound organic iodine with a specific gravity of 1.26 at 20°C. The tetracaine-containing solutions were freshly prepared without preservatives shortly before the administration. Each injection, containing an appropriate volume of the preparation, corresponding to a dose of 0.50 mg/kg, was administered over a period of 15 s. Injections were followed by irrigation of the catheter with 50 µl water for injection (the dead space of the catheters was previously evaluated and never exceeded 18 µl). The rabbits of group 3 were divided into three equal subgroups, each of which was treated with a different dose of iophendylate (50, 75 and 100 µl/kg, respectively). Since in the current model, it was not possible to evaluate sensory blockade accurately, we used the record of motor blockade proposed by Feldman and Covino13 to evaluate the pharmacologic effect of the drug. The intensity of the motor block was assessed in 5-min intervals with the use of the Bromage scale14 modified for a rabbit model and displayed on a graph as proposed by Van Zundert15:

- **0** = free movements with hind limbs without limitation or loss of balance
- **1** = limited or asymmetrical movements of the hind limbs in order to support the body and walk
- **2** = inability to support the back of the body on hind limbs with detectable ability to move the limbs and respond to pain stimulus
- **3** = total paralysis of the hind limbs

Comparison of the durations of motor blockade between the two groups was analyzed by unpaired Student's t test. The value of \( P < 0.05 \) was chosen as the limit for significance. Comparison of the maximum magnitude of the motor blockade between groups and frequency of block reaching maximum values was assessed by the chi-squared test.

**Results**

No signs of anxiety or systemic adverse effects in the animals were recorded during the period of investigation. All animals were awake within 1 h after catheter implantation, and the injection procedures were easily tolerated. Intrathecal administration of tetracaine HCl 500 µg/kg produced third-stage motor blockade within 5 min in all the animals of group 1. The mean duration of block from stage 3 to 0 lasted 130 ± 7 min. Injection of an equimolar dose of free-base drug produced stage-2 motor blockade in all the animals of group 2. All six animals exhibited stage-1 block 5 min after injection of the anesthetic. Four of six animals reached stage-2 block 10 min after injection, and the remaining two animals reached stage-2 block 15 min after administration of the drug.

Significant prolongation of the motor block, 447 ± 13 min, was achieved by the use of the drug lipid preparation. The degrees of motor blockade produced by the two drug formulations are compared in figure 1. The two groups differed significantly in the magnitude of the motor blockade (\( P < 0.02 \)), in the frequency of reaching the maximum values (\( P < 0.02 \)), and in the duration of pharmacologic effect (\( P < 0.01 \)). Animals of group 3, treated by intrathecal injections of iophendylate, did not show any signs of motor blockade.

**Discussion**

The comparative evaluation of the pharmacologic effect after subarachnoid injection of the local anesthetic in two different solvents, aqueous versus lipid, was investigated. A significant prolongation and a moderate decrease in the peak intensity of the effect of tetracaine was recorded when the drug was administered in a lipid solvent. This effect may be attributed to the slow release of the anesthetic from the injected lipid solution.
Prolongation of Spinal Anesthesia

The prolonged release rate of the agent displayed by this drug–lipid formulation is based on the different partition profile of the two drug forms, ionized (salt) or non-ionized (free-base) in aqueous versus lipid solutions, respectively. Tetracaine HCl, which is ionized, is soluble in water and practically insoluble in lipid. In contrast, tetracaine free-base is soluble in lipid and practically insoluble in water. Hence, when the aqueous solution of tetracaine is injected intrathecally, the drug that freely and rapidly diffuses in the CSF is almost totally available to the nervous target and produces a fast and intensive pharmacologic effect.

When the hyperbaric lipid solution of tetracaine free-base is administered, the injected solution settles and accumulates in the lower part of the dural sac, where it acts as a drug depot. The release rate of the drug from the lipid solution is governed by a complex overall kinetic process, which should be affected by the partition coefficient of the agent, by the pKa, and by the pH of the CSF. Diffusion of the drug is preceded by its conversion from the nonionized, lipid-soluble form to the ionized, water-soluble form. A fraction of the agent dissolved in the spinal fluid is then redistributed between the aqueous and lipid milieu of the CSF and the membranes of the spinal space. A small amount of the base form that is present in the CSF, corresponding to the equilibrium between ionized and nonionized fractions, is available for penetration into the nervous tissue. Since tetracaine is highly lipid-soluble, only a small fraction of the injected drug is available to the CSF and to the spinal cord at any given time.

The lipid agent iopencydylate was chosen as the solvent in the current study because of its high density and relative safety for intrathecal use. In contrast to most lipid compounds, which are hypobaric relative to the CSF, iopencydylate is synthesized as an iodized fatty acid with high specific gravity due to the iodine included in its molecular structure. Higher specific gravity than that of CSF is one of the most important requirements that the solvent should meet. If it is not of higher specific gravity, migration of the injected solution cephalad and probable release of the drug in upper segments of spinal cord (or above) may produce severe complications caused by the direct action on the respiratory and cardiovascular centers.

Apparently, head-up position of the body is required in order to prevent cephalad spread of the injected solution.

It is clearly understood that extensive physiologic, pharmacologic, and toxicologic studies are required before the approach proposed in this study reaches the stage of clinical application. However, the significant prolongation of drug effect offered by this method makes it worthy of further investigation.

References

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