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An Original Contribution

Local Anesthetic "Resistance"

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The incidence of inadequate analgesia despite technically well performed injections led our clinic to prospectively test patients for response to a variety of local aesthetics. Skin testing was performed on the skin of the forearm away from the site of pathology. Patients were asked to identify "which is the most numb" of the skin wheals. Although most were equally numb to all three local anesthetics (lidocaine, bupivicaine, and mepivicaine), 7.5% of the patients consistently chose mepivicaine as the local anesthetic resulting in the most hypoesthesia. For patients who had previously undergone an unsuccessful procedure with bupivicaine (the standard local anesthetic used in our practice), the same procedure with mepivicaine provided good relief. Patients are now questioned on their initial evaluation about a history of difficulty getting numb, for instance at the dentist, and preemptively skin tested prior to any invasive procedure.

Keywords: Local anesthetics, analgesia, lidocaine, bupivacaine, mepivacaine, resistance

All interventional pain practitioners have had patients who complained that they had "no relief" from well-performed procedures. The most dramatic situation that comes to mind is that of a spinal anesthetic performed with free flow of cerebrospinal fluid but no surgical anesthesia. All of us have been taught to blame "bad" local anesthetic or a "hysterical" patient for complaints of inadequate analgesia. Several years ago we postulated that the problem might be an atypical reaction to certain local anesthetics, and we started skin testing patients with a variety of different local anesthetics. We were able to identify clear examples of patients who would exhibit hypoesthesia to one local but not to another. In fact, when several family members were tested, it appeared to be an inherited characteristic (i.e. a father and a daughter might share the same local anesthetic "resistance", but the mother would become hypoesthetic to all tested local anesthetics). Additonally, when the same injection that had previously given no relief was repeated with the "sensitive" local anesthetic, the patient would note numbness and pain relief. To evaluate the prevalence of this apparent local anesthetic "resistance", we set out to do a pilot-screening project.

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Methods

All patients presenting to The Pain Center for the month of March 2001 were interviewed specifically as to whether they had become "numb" after their last injection. All patients who reported poor or minimal temporary relief from an injection in the prior month, and all new patients who reported a history of difficulty getting numb from injections (such as for sutures or the dentist) were evaluated. Three tuberculin syringes were prepared for each patient consisting of a small amount of one of each local anesthetic: lidocaine, bupivicaine, and mepivicaine. A standard amount of liquid was drawn into each type of syringe so that the volume in the syringe would identify to the technician at a glance which local anesthetic was being injected (Fig. 1). After alcohol prep, a small aliquot from each syringe was injected subcutaneously via a 30g needle into a different but adjacent area of the forearm, forming a subcutaneous wheal, similar to a TB tine test (Fig. 2). The edge of

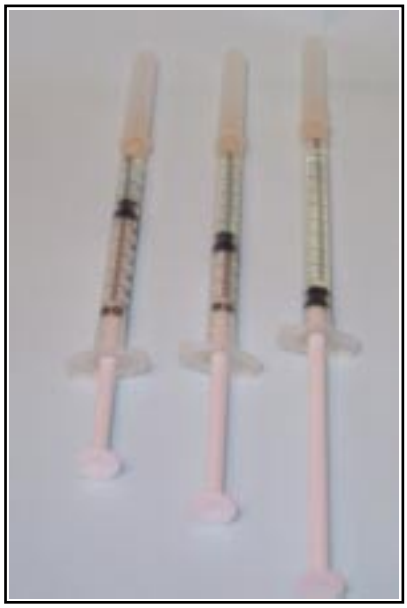

Fig. 1. *Tuberculin syringes with local anesthetic*

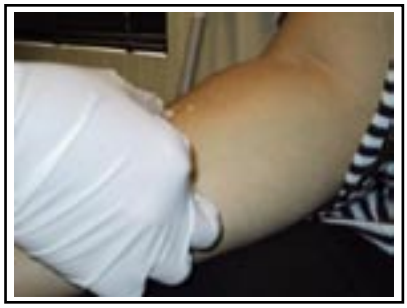

Fig. 2. *Skin wheals*

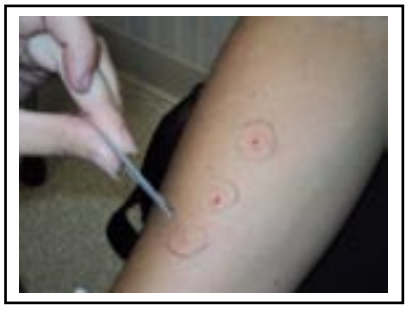

Fig. 3. *Scratch*

an un openned alcohol packet was then used to scratch first the adjacent skin and then the skin over each wheal sequentially (Fig. 3). The patients were told to compare the initial scratch ("this is scratchy") to each of the other sites ("which feels the least scratchy or the most numb- A, B, or C?"). The patient was blinded to the type of local injected.

Results

Of the 1,198 patients interviewed, 250 were tested. 90 (7.5% of the total patients) were found to be hypoesthetic only to mepivicaine, and an additional 43 (3.8%) only to lidocaine. The rest were hypoesthetic to all or bupivicaine (the standard local used in our practice).

Discussion

Cocaine, derived from the coca leaf, was the first studied local anesthetic, and was isolated in 1860 (1). Procaine (Novocaine®) was synthesized in 1901, tetracaine (Pontocaine®) in 1928, lidocaine (Xylocaine®) in 1943, mepivacaine (Carbocaine®) in 1956, and bupivacaine (Marcaine®) in 1957. These medications share several characteristics: there is a hydrophobic benzene ring connected to an aminoester or aminoamide chain, which is then connected to a quaternary amine (which is hydrophilic) (2). The ester local anesthetics such as procaine have fallen out of favor because the liver metabolizes them into para-amino benzoic acid (PABA) which is potentially antigenic and has a high incidence of anaphylactic reactions. Lidocaine, bupiviaine, and mepivicaine, on the other hand, are amide local anesthetics that are much less likely to trigger allergic reactions (Fig. 4). The exception is amides containing methylparaben as a preservative, since the methylparabin is metabolized to PABA.

Local anesthetics are weak bases, and are usually prepared in their water-soluble salt form. In an aqueous solution such as tissue fluid, the salt ionizes to form a positively charged quaternary amine and a negatively charged chloride molecule. The charged quaternary amine is in equilibrium with the uncharged tertiary amine base. The degree of ionization is important, since it is the uncharged form that is the most lipid soluble and therefore able to cross the myelin sheath and enter the nerve itself. Low pH, such as seen in hypoxic or abscessed tissue, would shift the equilibrium away from the unionized form, decreasing the amount of effective drug available and therefore slowing the onset of analgesia. There is a surgical maxim that "you can't anesthetize an abscess". Local anesthetics containing epinephrine have a lower pH to keep the epinephrine stable; unfortunately, this makes the local anesthetic less effective as well as making the medication more painful on injection. Adding sodium bicarbonate to the local aesthetic will raise the pH and shift the equilibrium to the unionized active form (3). However, raising the pH too high will cause the base to precipitate. The pH at which these two forms are in equal concentrations is known as the pKa. Lidocaine, bupivicaine, and mepivicaine have similar pKa values, which would not explain the differences in effectiveness.

Local anesthetics block the sodium channel of the nerve, which stops depolarization. We suspect that changes in the channel itself (Fig. 6) are the biochemical explanation for the differences in local anesthetic effect observed.

This pilot study was limited n many ways. Only those patients with a history of local anesthetic failures were tested. To determine a truer incidence of anesthetic differences, all the patients should have been tested. The screening was only single blinded and there was no control injection such as saline. The screening occurred over a single month period and has not been repeated. However, at least 10% of our patients that month did not get hypoesthetic to our standard anesthetic, bupivicaine. Because of the use of sedation for procedures, patients who do not get numb from an injection may not be recognized at the time of the injection, potentially losing the diagnostic advantage of the injection itself. Mepivacaine appeared to be the local anesthetic most commonly effective in the local anesthetic "resistant" patient. However, the true significance of this observation is not yet known.

Conclusion

There may be a significant number of our patients who have undergone ineffective procedures or been denied follow-on treatment because we have not recognized

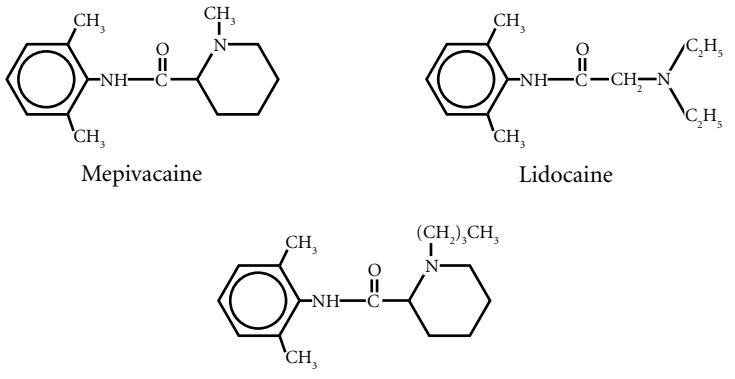

Fig. 4. ***Local anesthetics***

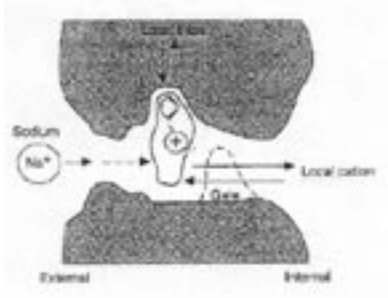

Fig. 5. ***Na Channel***

that they did not get numb from that local anesthetic. Perhaps patients should be taken more seriously when they complain of pain during a procedure despite what should be adequate local infiltration. Perhaps the patients who complain that the injections don't help might benefit from a reassessment of their response to various local anesthetics.

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