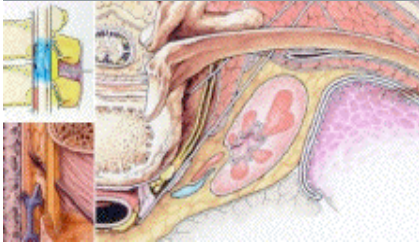


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Insights Into Clinical Practice

LIDOCAINE VS CHLOROPROCAINE

Over the years, anesthesia practitioners have become embroiled in some issues which make no sense to me. One of these issues is whether to use 3% chloroprocaine versus 2% lidocaine to establish anesthetic conditions for emergent c-sections in parturients who have been laboring with epidural analgesia. Those that contend that chloroprocaine is the best drug argue that since it is more concentrated (i.e. 3% vs 2%), it has the potential for having a faster onset of action. I say, if you consider the chemical nature of chloroprocaine, this makes no sense. What do I mean?



Let us begin by discussing some basic tenants of drug diffusion. First, textbooks always point to the fact that most drugs used in anesthetic practice are either weak acids or weak bases, both of which tend to ionize when they are placed in a physiologic solution. This is important because, in solution, it is the nonionized portion of the drug that confers pharmacologic activity since it is free to permeate the lipid bilayer of biologic membranes. The magnitude of the lipid permeability of a drug depends on both the pKa of the drug and the pH of the solution in which the drug is placed. The pKa of a drug is derived from our old friend, the Henderson-Hasselbach equation, in which Ka is the constant that describes a state in which 50% of the drug remains in an associated or nonionized form HA, and 50% is in a dissociated or ionized form [H+][A-]. The relationship of these factors is expressed in the following equation :

$$K_a = \frac{[H^+][A^-]}{[HA]}$$

Okay, that's simple enough. The brackets surrounding the factors in the equation represent the concentration of the various forms (ionized and nonionized) of the drug. Logarithms are frequently used for solving this equation, resulting in the equation taking on the following form:

$$\log K_a = \log \frac{[H^+][A^-]}{[HA]}$$

For those of you who have forgotten how to multiply logarithms the following rule applies: The logarithm of a product (i.e. $\log K_a$) is actually the summation of the logarithms of its multiplicands (Huh!?) What that means is that the above equation takes on the following appearance:

$$\log K_a = \log [H^+] + \log [A^-]/[HA]$$

If you were to actually perform the arithmetic, you would find the answer to this equation is expressed in rather unwieldy negative exponential numbers. Positive numbers are so much more easier to handle, don't you think? Thank goodness, this is easily remedied by taking the negative logarithm of the factors.

In certain scientific parlances, the negative logarithm is expressed as p . Thus, the above equation is transformed into:

$$pK_a = pH + \log [HA]/[A^-]$$

The factors $[A^-]/[HA]$ are inverted because the negative of a logarithm is actually the logarithm of the reciprocal, so that $-\log ([A^-]/[HA])$ is the same thing as $\log [HA]/[A^-]$. Read this sentence several times. If it still sounds like gobble-de-gook, ignore it! In fact, this is a good time to take a break and go to the movies especially if math was never your forte. This stuff will still be here once you return. But for you diehards...read on.

Rearranging the equation ($pK_a = pH + \log [HA]/[A^-]$) gives us an idea of the relationship between ionization and the pK_a of the drug and the pH of its solution to be expressed. Two forms of this rearrangement exist, depending on whether the drug in question is a weak base or a weak acid. For drugs that are basic in nature, the equation takes on the appearance of:

$$pK_a - pH = \log [HA]/[A^-]$$

On the other if the drug is a weak acid, then equation takes on this form:

$$pH - pK_a = \log [A^-]/[HA]$$

Using these equations, a number can be derived that gives you some idea of the degree of drug absorption. For example, oral diazepam, which is a weakly basic drug, has a pK_a of 3.3. If it is placed in a gastric medium whose pH is 2.3 (gastric pH can range from 1.5 to 7), then the ratio of nonionized-to-ionized drug can be determined, as follows:

$$3.3 - 2.3 = \log [HA]/[A^-] = 1$$

The ratio of readily absorbed (nonionized) to poorly absorbed (ionized) diazepam can be determined by the antilog of the answer (i.e the antilog of 1 = 10). Therefore, at a gastric pH of 2.3, 10 times more diazepam is in its nonionized form (HA); this amount is available for absorption. If the gastric contents were to be alkalized, an effect that would raise the pH say to 3.9, then as shown by the equation below the protonated or nonionized form of the drug would be only one fourth (0.25) of the ionized form, and hence less would be absorbed.

$$3.3 - 3.9 = \log [HA^+]/[A^-] = \log -0.6 = 0.25$$

You may have noticed that there is a simple way of appreciating the relationship between a drug's pK_a , the pH of the solution in which the drug is placed, and its degree of ionization. For a basic drug when the $pK_a - pH$ is less than zero, less nonionized drug is available. However, as the pH of the solution becomes less acidic, and the $pK_a - pH$ is greater than zero, more nonionized drug is available for absorption. The antithesis of this is true for acidic drugs. Thus when the $pH - pK_a$ is greater than zero, more of the drug is ionized. Many drugs used in anesthetic practice are prepared as salt solutions of hydrochloric acid or sodium hydroxide; this type of preparation permits solubility of these agents in water for ease of administration. Local anesthetics, for example, whose pK_a lie between 7.5 and 9.0, are manufactured on the acidic side of their pK_a (see below).

Drug	pKa	pH of Commercial preparation	Protein binding	% ionized fraction at pH 7.4
Chloroprocaine	8.7	2.7 - 4.0	95	95
Tetracaine	8.5	3.2- 6.0	76	93
Procaine	8.92	6	97	97
Mepivacaine	7.65	4.5 - 6.8	77	61
Lidocaine	7.87	6.0-7.0	70	75
Bupivacaine	8.05	3.3-5.5	95	85
Etidocaine	7.74	4.0-5.0	94	67

Consequently, only about 3% of the local anesthetics are present in their nonionized lipid soluble form. Once injected, the acid salt must be neutralized in the tissues, and the free base must be liberated, before the drug can penetrate the tissues. Notice that when chloroprocaine is injected into a physiological system, 95 % of the drug becomes ionized leaving only 5% in its lipophilic active form. This is in contrast to lidocaine whose pKa of 7.87 is closer to physiologic pH, resulting in an ionized fraction of 75% and a 25% active form.

You don't have to be a rocket scientist to appreciate that for all intents and purposes, lidocaine should establish anesthetic conditions faster than chloroprocaine. And pushing up the mass of the drug from 2% to 3% chloroprocaine really doesn't make much of a difference as to onset. In fact a prospective, randomized, double-blind study actually examined this issue(1). The speed of onset and anesthetic quality of 2-chloroprocaine versus a solution of lidocaine with epinephrine was determined in a group of 40 parturients scheduled for elective cesarean delivery. The 2-chloroprocaine group received 2-chloroprocaine 30 mg/mL (I guess that's why they called it the chloroprocaine group) and the lidocaine group received lidocaine 20 mg/mL with 5 mcg/mL epinephrine. The end of injection was defined as time zero and the start of anesthesia and the speed of onset was defined as the time taken to loss of cold sensation from 70% ethanol application at T5. In these demographically similar groups, the time to achieve loss of cold sensation at T5 was 8 min in the chloroprocaine group and 5 min in the lidocaine group, which, according to the authors, is not significantly different. Moreover, the time to reach the highest level of anesthesia was 12.4±1.1 min and 13.3±1.3 min in the two groups, respectively (also not statistically different). The time from the start of anesthesia to the start of operation was 27.0±1.6 min and 28.0±1.2 min in the chloroprocaine and lidocaine groups, respectively. You guessed it...not statistically different! Furthermore, there were no statistically significant differences in the degree of motor block, the need for opioids, and the pain scores on VAS. Apgar scores at 1 and 5 min did not differ in the infants in the two groups, and no serious complications occurred in the neonates. And surprisingly, the regress of motor block was equal in the two groups. The authors concluded (and you can see why) that 2-chloroprocaine and lidocaine with epinephrine have a rapid onset and are suitable local anesthetics for cesarean section.

For those of you who are still not convinced that lidocaine is a better drug than or at least just as good as chloroprocaine in rapidly establishing anesthesia for cesarean section (you are probably one of those few who still think George Bush is a good president), then consider that 2 chloroprocaine given via epidurally dramatically reduces the analgesic efficacy of epidurally administered morphine. A study by Karambelkar et al found that the mean cumulative 24-h i.v. PCA morphine requirement in the 2-chloroprocaine, 2-chloroprocaine +epi and Lidocaine+epi groups respectively was 20.5 +/- 24, 33.1.5 +/- 27 and 4.07 +/- (mean +/- SD) (2). The reason for this antagonism is not entirely clear, but Camann and colleagues suggest that chloroprocaine may competitively interfere with an opioids ability to bind with mu receptors(3)

Still not convinced? Well too bad. We don't carry chloroprocaine at our institution.

References:

1. Bjornestad E, Iversen OL, Raeder J. Similar Onset time of 2-Chloroprocaine and Lidocaine + Epinephrine for Epidural Anesthesia for Elective Cesarean Section. *Acta Anaesthesiologica Scandinavica* 2006 Mar; 50(3): 358-63
2. Karambelkar DJ, Ramanathan S. 2-Chloroprocaine antagonism of epidural morphine analgesia. *Acta Anaesthesiol Scand*. 1997 Jun;41(6):774-8.
3. Camann WR, Hartigan PM, Gilbertson LI, Johnson MD, Datta S. Chloroprocaine antagonism of epidural opioid analgesia: a receptor-specific phenomenon? *Anesthesiology*. 1990 Nov;73(5):860-3.