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A COMPARISON OF THE HYDROCHLORIDE AND CARBON DIOXIDE SALTS OF LIDOCAINE AND PRILOCAINE IN EPIDURAL ANALGESIA

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In epidural analgesia the quality and extent of blockade varies widely with different drugs, and the technique provides a useful means of comparing the efficiency of local anaesthetics in man, since the onset and spread of analgesia is slow, allowing plenty of time for observation and comparative measurements.

TRUANT and BROMAGE (unpublished data) have shown, both *in vivo* and *in vitro,* that the carbonic salts of local anaesthetics have a more powerful blocking action than the conventional hydrochloride salts in equivalent concentration.

This paper presents the effects of the 2% and 3% hydrochloride salts of lidocaine and prilocaine (propitocaine), compared with their carbonated salts formed by combining the anaesthetic bases with carbonic acid.

THEORY OF CARBONATED LOCAL ANAESTHETIC SOLUTIONS

Hydrogen-ion concentration is one of the most important factors influencing uptake of local anaesthetic drugs (KRAHL et al. 1940, ALBERT 1952), and the choice of pH is a compromise between the two conflicting interests of water solubility on the one hand and solubility in a lipoid medium on the other, since an injectable local anaesthetic must dissolve in both media before it can reach its site of action.

Local anaesthetics penetrate the lipoid phase of cell membranes as the electrically indifferent undissociated base, but since the base is only poorly soluble in water it must be prepared as a water-soluble salt before it can be injected in an aqueous medium:

The equation:

$$R-\overset{|}{\underset{|}{NH^+}} \underset{\text{(Low pH)}}{\overset{\text{(High pH)}}{\rightleftharpoons}} R-\overset{|}{\underset{|}{N}} + H^+$$

proceeds to the left in an acid pH when ionization is almost complete, and to the right in an alkaline medium when ionization is minimal (Fig. 1). Many local anaesthetic solutions are dispensed with a low pH in the region of 4.0, for purposes of stability and prolonged storage life, and these solutions must be buffered in the tissues before sufficient free base is liberated to effect blockade. The time taken to buffer these acid salts delays analgesic action, and so potency tends to vary inversely with the initial hydrogen ion concentration (LÖFGREN 1948).

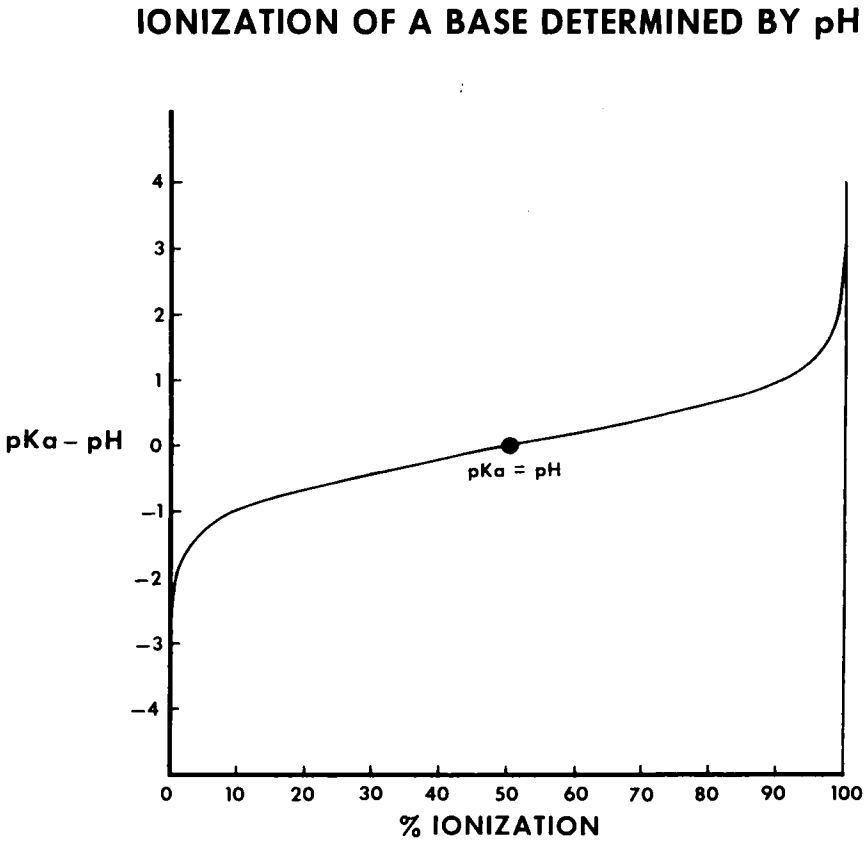

FIG. 1.—Relationship between pH and degree of ionization of local anaesthetics. When the pKa = pH of solution, the ratio $\frac{[B^+]}{[B]} = 1$.

The most efficient compromise in this dilemma between aqueous and lipoid solubility will be one that promotes rapid conversion of a water-soluble acid salt to undissociated free base. Being an acid gas, carbon dioxide can be made to combine with local anaesthetic bases, under the right conditions of low

temperature and high partial pressure, and the resultant compounds are water soluble.

Solutions of local anaesthetics prepared in this way have two interesting features. First, the drug is present in a bicarbonate form, which is very rapidly converted to the undissociated base once the partial pressure of carbon dioxide falls to that of the tissue. Second, although the pH of the carbonated solution is practically the same as that of the equivalent hydrochloride solutions, the rapid diffusion of carbon dioxide across cell membranes causes a fall of intracellular pH in the immediate neighbourhood, and the resulting electrochemical gradient favours a greater uptake of local anaesthetic base by the tissues (CALDWELL 1958, HALPERN and BINAGHI 1959, KRAHL and CLOWES 1938; KRAHL et al. 1940).

Solutions of lidocaine and prilocaine base have been made available in sealed ampoules at a pCO_2 of 700 mm Hg. The concentrations of base in these solutions was 1.75% and 1.71% respectively, which is equivalent to the amount present in 2% solutions of the corresponding hydrochloride salts.

EXPERIMENTAL METHODS

Observations of the speed of onset and segmental spread of analgesia and intensity of motor blockade were made in 659 patients receiving epidural analgesia.

Solutions

1. 2% and 3% lidocaine and prilocaine hydrochloride with and without adrenaline. When adrenaline was employed it was added freshly to the solution immediately prior to injection to produce a concentration of 1:200,000. The pH of these solutions were checked in a Radiometer pH meter and varied only between 6.27 and 6.71.

2. (a) 1.75% lidocaine CO_2-base (at a pCO_2 of 700 mm Hg) with and without adrenaline 1:200,000; (b) 1.71% prilocaine CO_2-base with adrenaline 1:200,000. The pH of these solutions was 6.49–6.51, measured at 28°C before any appreciable evolution of CO_2. After equilibration with CO_2 at 35.6 mm Hg the pH rises to 7.30.

The solutions were administered in the distribution shown in Table 1.

Uncomplicated surgical patients and volunteers were chosen for the main part of the investigation. Subjects with occlusive vascular disease were excluded from this series, since they have atypical responses to epidural blockade (BROMAGE 1962a, b). A smaller series of patients receiving continuous epidural blockade for labour pains and vaginal delivery has been presented, in order to compare the total requirements of analgesic base from the hydrochloride and CO_2-base solutions over a long period.

TABLE 1.

Distribution of analgesic solutions in a series of 659 patients receiving epidural blockade for surgical and obstetrical indications.

Solution	N	Mean Age
Surgical patients		
2 % plain lidocaine HCl	35	49.1
2 % lidocaine HCl + adrenaline	56	48.6
3 % plain lidocaine HCl	25	53.0
3 % lidocaine HCl + adrenaline	25	47.0
2 % plain prilocaine HCl	35	48.9
2 % prilocaine HCl + adrenaline	35	49.2
3 % plain prilocaine HCl	45	45.4
3 % prilocaine HCl + adrenaline	40	48.8
1.75 % lidocaine base	36	48.4
1.75 % lidocaine base + adrenaline	106	50.0
1.71 % prilocaine base + adrenaline	101	48.9
Obstetrical patients		
2 % lidocaine HCl + adrenaline	20	25.9
2 % prilocaine HCl + adrenaline	20	25.0
1.75 % lidocaine base + adrenaline	40	26.7
1.71 % prilocaine base + adrenaline	40	26.8

Epidural blockade was performed in a standardised manner at the second lumbar interspace with the patient sitting up, as previously described (BROMAGE 1962a, b). In the majority of cases, a syringe filled with air was used for the loss-of-resistance test, in order to avoid possible errors of dosage from injecting an inexact amount of diluent at the moment of piercing the ligamentum flavum.

Measurements of Sensory Blockade

The patients were tested for analgesia to pin prick within two minutes of injection, and the upper and lower limits of segmental analgesia were charted on graph paper every minute until the spread of analgesia was complete. Thereafter, analgesia was tested every 5–10 minutes. The following information was obtained from plotting such a diagram (Fig. 2).

1. *Latency of Initial Onset*: This is the time taken for analgesia to make its first objective appearance, usually in the upper lumbar dermatomes.

2. *Latency of Complete Spread*: The time taken for analgesia to spread to its farthest limits and to become established in all segments between these upper and lower limits.

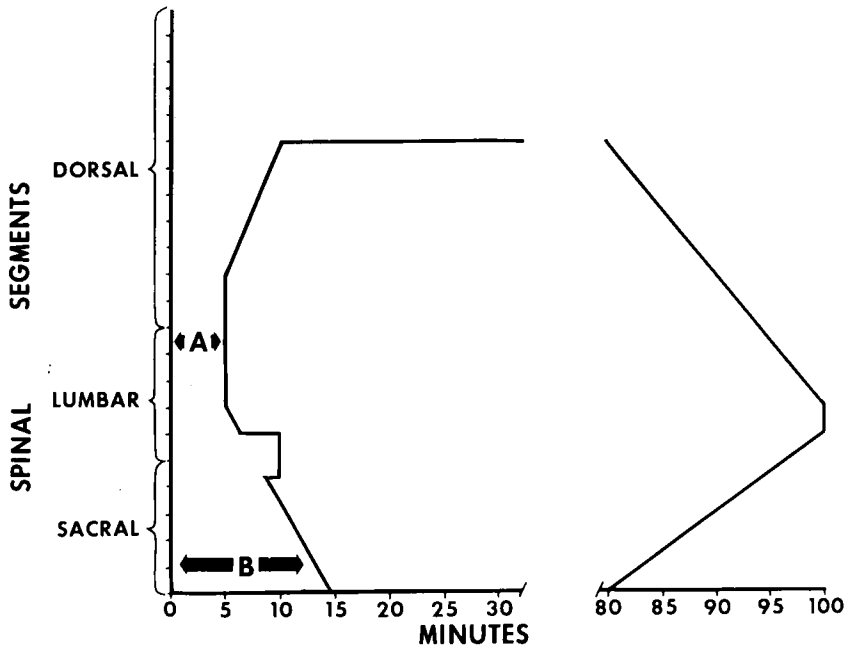

FIG. 2.—Dermatome graph of onset and decay of epidural analgesia.
A = Latency of initial onset.
B = Latency of complete spread.

3. *Extent of Segmental Spread*: In terms of the relationship between the dose of anaesthetic used and the number of dermatomes rendered analgesic. Elsewhere, it has been shown that the spread of epidural analgesia is dependent on (a) age, and (b) the mass of anaesthetic solute injected, rather than on volume or concentration alone (BROMAGE 1962a, b, 1963), and so in this paper, spread will be expressed as the mass of base required to block one spinal segment. For example, supposing an epidural injection of 20 ml of 2% lidocaine hydrochloride produced analgesia of all segments up to T_2. If we count the spinal segments up from S_5, this makes a total of 20 segments (5 sacral, 5 lumbar, and 10 thoracic). 20 ml of 2% lidocaine hydrochloride contains:

$$20 \times 17.5 \text{ mg of lidocaine base.}$$

$$\text{Thus, } \frac{\text{Dose}}{\text{Segments}} = \frac{350}{20} = 17.5 \text{ mg base per segment.}$$

By plotting the dose requirements of many individual cases against age we can obtain a mean regression line for any particular solution, and so compare the spreading effects of different solutions.

4. *Duration of Action*: Figures for duration of action are apt to be misleading unless the observer states precisely what is meant by "duration". Sometimes,

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