The Role of pH in the Development of Tachyphylaxis to Local Anesthetic Agents

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Evidence for tachyphylaxis to the local anesthetic agents lidocaine and mepivacaine has been found in a study of continuous caudal anesthesia in obstetrical patients. Reduced response to these drugs is shown to be independent of the increasing pain of labor.

An experimental study of tachyphylaxis in the dog was undertaken, utilizing 14C-lidocaine and 14C-procaine administered by a continuous spinal technique. Repeated injections of the acid anesthetic salt were associated with continued decreases in pH of the cerebrospinal fluid and proportionate increases in the concentration of local anesthetic. Calculations of the percentages of the free base form (lipid-soluble) indicated significant shifts with minor changes in pH. It is suggested that tachyphylaxis to local anesthetic agents may be associated with changes in pH and shifts in the amounts of ionized and nonionized forms. The limited buffer reserve available in the cerebrospinal fluid (and presumably, the extradural space) makes these areas especially vulnerable.

TACHYPHYLAXIS has etymologic derivation from the Greek (tachys—swift, and phylax—guard) which implies a rapid development of protection. Marcel Gley, the French physiologist, was the first to apply this term to describe the immunization provided against the toxic effects of an extract which could be produced by prior injections of small doses of the same material.1 In present usage, tachyphylaxis describes the increasing tolerance to a drug that develops following its repeated administration.

The occurrence of tachyphylaxis to local anesthetic agents has been suggested in a number of clinical reports2-5 which describe development of tolerance to the anesthetic effects of such drugs following repeated or prolonged usage. Experimental evidence suggesting that repeated injection of a local anesthetic agent into the sciatic nerve results in a decreased effect through alteration of binding of the agent to nerve tissue also has been presented.6 On the other hand, clinical and laboratory data from these studies are limited, and a totally satisfactory explanation for the phenomenon of tachyphylaxis has not yet been presented.

The present study represents an attempt to isolate in the experimental animal factors that could be involved in development of tachyphylaxis to local anesthetic agents, and to elucidate possible mechanisms. Since it was desirable to measure the concentration of the local anesthetic agent, and also the hydrogen ion concentration of the surrounding tissue or fluid, it was decided to study tachyphylaxis as it could be produced with continuous spinal anesthesia in the experimental animal.

Procedure

Ten mongrel dogs, average weight 22.6 kg. (± 3.3), were anesthetized in the fasting state with single injections of intravenous sodium pentobarbital, 30 mg./kg. Anesthesia was supplemented as needed by incremental injections. Controlled ventilation with room air was provided through an endotracheal tube and a fixed-volume Harvard respirator. The latter was adjusted to deliver a minute volume of 300 ml./kg. body weight, which served to maintain constant arterial pH (7.43 ± 0.02) throughout the prolonged experimental period.
It proved difficult to introduce the spinal catheters into the intrathecal space with a blind-needle technique, and it was necessary to bore a small hole through the arch of the spine to expose a few millimeters of the dural sac. It was then usually possible to introduce two fine polyethylene catheters into the subdural space without further trauma. The intradural catheters were inserted at the level of the sixth lumbar spine and threaded cephalad 10–12 cm. to approximately the second lumbar vertebra. The first catheter was used for injection of the local anesthetic agent, and the second catheter (placed 2 cm. caudad) was used for collection of cerebrospinal fluid specimens.

The studies were designed to determine continuing changes in the cerebrospinal fluid pH and in the contained concentration of local anesthetic agent. The drug was administered in five separate intrathecal injections (1 ml.) at intervals of 90 minutes, and after each injection the catheter was flushed carefully with 0.05 ml. of cerebrospinal fluid. Procaine hydrochloride (25 mg./ml.) or lidocaine hydrochloride (25 mg./ml.) was injected, each volume containing a sufficient amount of 14C-labelled tracer drug to permit scintillation counting. The local anesthetic agents were administered as the acid salt in unbuffered Ringer’s lactate solution, or were adjusted to a predefined pH with THAM.)*

Samples of cerebrospinal fluid (0.2 ml.) were withdrawn at regular intervals (30, 45, 60, and 90 minutes) after intrathecal injection of the local anesthetic agent, sufficient time thus being allowed for adequate redistribution of the drug. In each instance the catheter volume was first withdrawn and later returned. Samples were obtained only following the first, third, and fifth injections of anesthetic agent, to conserve cerebrospinal fluid. In some animals (for technical reasons) it was not possible to complete the entire series of cerebrospinal fluid samplings, and only the first and third injections of the local anesthetic agent were examined. Samples of cerebrospinal fluid were placed in glass vials containing 10 ml. of scintillation-counting fluid † before introduction into the counting chamber. At the termination of each 90-minute interval, an additional 0.3 ml. of cerebrospinal fluid was withdrawn and the pH determined with an

* 2-amino-2-hydroxymethyl-1,3-propanediol. It was possible to utilize THAM buffer only for procaine, since in the drug concentrations employed lidocaine base precipitates at pH 6.7.

† The scintillation cocktail consisted of a 10-ml. solution containing dioxane, PPO, and naphthalene.

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**Fig. 1.** Alteration in pH of cerebrospinal fluid following repeated injections of local anesthetic drugs at 90-minute intervals. All injections 25 mg. drug in 1-ml. volume. Each series represents three animals studied.
Astrup Radiometer. In another part of the study, plasma concentrations of lidocaine were determined by sampling arterial blood in three animals at prescribed intervals throughout the study.

Results

Changes in Cerebrospinal Fluid pH Following Injection of Local Anesthetic Agents

The intrathecal administration of unbuffered local anesthetic agents, e.g., procaine (pH 4.7) or lidocaine (pH 4.5), in Ringer’s lactate solution resulted in a rapid increase in hydrogen ion concentration in cerebrospinal fluid. Intrathecal drug injections repeated at 90-minute intervals were followed by a continuing decrease in cerebrospinal fluid pH (fig. 1). Prior adjustment of the pH of the procaine solution to 7.4 with THAM buffer permitted maintenance of a physiologic pH in the cerebrospinal fluid despite repeated intrathecal injections of the same drug (fig. 1).

Influence of pH on the Redistribution of Local Anesthetic Agents out of Cerebrospinal Fluid

The reduction of cerebrospinal fluid pH produced by the injection of the acid anesthetic
sodium was accompanied by a decreased loss of anesthetic agent from the cerebrospinal fluid. As the cerebrospinal fluid pH continued to fall with repeated intrathecal injections of unbuffered drug, a higher intradural concentration of anesthetic agent was sustained following each subsequent injection. This rising concentration was found with both local anesthetic agents studied (figs. 2 and 3). When the pH of the cerebrospinal fluid was maintained in the physiologic range with the aid of THAM buffer, the rate of loss of drug (procaine) from the cerebrospinal fluid remained constant with repeated intrathecal injections (fig. 4).

**RELATIONSHIP OF IONIZATION CONSTANT TO LOSS OF LOCAL ANESTHETIC AGENTS FROM CEREBROSPINAL FLUID**

The data in figures 2 and 3 show the effects of changes in pH on the rate of loss of local anesthetic agent from the cerebrospinal fluid. Calculation of the percentage of free base at a given pH (Henderson–Hasselbalch equation) indicated that, in the case of lidocaine, a significantly smaller fraction of nonionized (lipid-

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**Fig. 4.** Concentration of procaine in cerebrospinal fluid following three intrathecal injections at intervals of 90 minutes. Measurements were made following the first and third injections. Initial pH of injected procaine 7.4 (adjusted with THAM buffer). Each point represents an average of two animals. pH values of cerebrospinal fluid samples are indicated in brackets.

**Fig. 5.** Percentage of free anesthetic base (nonionized) at various pH ranges. Calculations were made using the Henderson-Hasselbalch equation.

\[ \text{pK}_a - \text{pH} = \log \frac{[\text{ionized}]}{[\text{non-ionized}]} \]
Table 1. Ionization Constants of Local Anesthetic Agents (25° C.)

<table>
<thead>
<tr>
<th>Anesthetic</th>
<th>pKₐ</th>
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</thead>
<tbody>
<tr>
<td>Mepivacaine</td>
<td>7.05²</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>7.86¹³</td>
</tr>
<tr>
<td>Tetracaine</td>
<td>8.49¹¹</td>
</tr>
<tr>
<td>Dibucaine</td>
<td>8.54¹³</td>
</tr>
<tr>
<td>Cocaine</td>
<td>8.80¹³</td>
</tr>
<tr>
<td>Procaine</td>
<td>8.92¹⁰</td>
</tr>
<tr>
<td>Hexylecaine</td>
<td>9.08²²</td>
</tr>
</tbody>
</table>

The hydrogen ion concentration of the bathing fluid is thus an important factor in determining the rate at which the anesthetic base may penetrate cell membranes. The relationships of ionization, pH, and pKₐ are well known, and the local anesthetic solution to be injected should possess a pH reasonably close to its pKₐ in order to ensure a favorable proportion of the lipid-soluble moiety.¹ Most local anesthetic agents possess pKₐ values close to the physiologic pH range (table 1). It follows that minor alterations in pH of the surrounding tissue or fluid may produce large shifts in concentration of the nonionized lipid-soluble base (fig. 5). Recent experiments, however, suggest that whereas it is the free-base form of the local anesthetic agent that allows penetration of cell barriers from the site of application to the site of drug action, the active anesthetic at the receptor site may be the cationic rather than the uncharged form of the drug. Thus, in these studies the bathing alkaline anesthetic solutions (largely nonionized) were more effective in sheathed preparations, and the neutral anesthetic solutions (largely ionized) were more effective in desheathed preparations.¹⁴

The following statements may be pertinent to the phenomenon of tachyphylaxis with local anesthetic agents.

1. Local anesthetic agents are marketed as acid salts to provide a convenient vehicle for entrance into the body. It is generally assumed that upon contact with the slightly alkaline extracellular fluid, release of the lipid-soluble anesthetic base occurs, and penetration of the cell membrane is thereby possible.

2. Tachyphylaxis to local anesthetic agents is most likely to occur in areas of the body where a limited buffer reserve is available to neutralize repeatedly or continuously introduced acid anesthetic salts. Theoretically, the intrathecal space is an area with limited buffer reserve. It has been shown that bicarbonate cannot readily shift into or out of the spinal fluid.¹⁵ In addition, the low protein content of the cerebrospinal fluid, combined with slow flow through the cord, further limits rapid availability of buffer. Although precise evidence is lacking, the...
assumption that limited buffer reserve is likewise available for the epidural space may also be made. This space is relatively poorly perfused, and large volumes of drug are customarily introduced to fill the space completely, to attain the desired level of anesthesia.

3. Since the body is unable to buffer adequately against repeated injections of the acidic local anesthetic salt, the pH of the surrounding milieu falls. This drop in pH results in a decreased amount of nonionized free base. It is in this form only that the anesthetic agent is lipid-soluble and able to cross cell membranes to reach its presumed site of action upon or within the nerve cell.

Present experimental results tend to support such an explanation for the development of tachyphylaxis. The introduction of the anesthetic salt has been shown to reduce the pH of the cerebrospinal fluid rapidly. By the fourth injection of 25 mg. lidocaine hydrochloride, or the fifth injection of 25 mg. procaine hydrochloride, the pH of the cerebrospinal fluid has fallen to 6.80 or less (figure 1).

Figures 2 and 3 show the effects of these changes in pH on the concentrations of local anesthetic agent remaining in the cerebrospinal fluid. As the pH drops, higher concentrations of local anesthetic agent remain. This can be demonstrated for both procaine and lidocaine. Reference to figure 5 also indicates that lidocaine (pKₐ 7.86) present as the free base is more sensitive to small changes in pH than procaine present as the free base (pKₐ 8.92).

The drop in cerebrospinal fluid pH which follows repeated intrathecal injections can be prevented experimentally by the prior adjustment of procaine solution to pH 7.4 with THAM buffer. The latter drug has been shown to diffuse very slowly into (and presumably out of) the cerebrospinal fluid over an extended period of time. As noted earlier, lidocaine base at the concentration used precipitates at pH 6.7. A similar experiment, therefore, is not feasible for this drug. In experiments with procaine hydrochloride which has been buffered with THAM, the cerebrospinal fluid pH remains constant following repeated intrathecal injections. Unlike the studies with unbuffered drug, there is no increase in the cerebrospinal fluid concentration of the pH-adjusted drug upon its repeated injection (figure 4). At a higher pH more of the procaine is found as the free base (non-ionized) form, which is lipid-soluble. In this form the drug readily crosses surrounding membrane barriers, and does not remain within the cerebrospinal fluid.
Table 2. Duration of Anesthesia Following Repeated Injection of Local Anesthetic Agents*

<table>
<thead>
<tr>
<th>Injection Number</th>
<th>Total Patients in Series</th>
<th>Duration of Anesthesia (minutes)</th>
<th>S.E. of Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>29</td>
<td>104.1</td>
<td>5.2</td>
</tr>
<tr>
<td>2</td>
<td>29</td>
<td>96.9</td>
<td>5.2</td>
</tr>
<tr>
<td>3</td>
<td>29</td>
<td>78.4</td>
<td>3.5</td>
</tr>
<tr>
<td>4</td>
<td>16</td>
<td>61.9</td>
<td>4.8</td>
</tr>
<tr>
<td>Mepivacaine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>10</td>
<td>148.2</td>
<td>8.0</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>99.5</td>
<td>7.0</td>
</tr>
<tr>
<td>3</td>
<td>14</td>
<td>70.9</td>
<td>7.1</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>65.6</td>
<td>25.7</td>
</tr>
</tbody>
</table>

* Concentrations of both drugs 1 per cent with added epinephrine 1:200,000. Injection volume constant (18.3 ml. ± 2.6 ml.). Succeeding injections were repeated according to the patient's requirements for pain relief.

Of great importance is the possible application of these observations to the clinical situation. One must be cautious with any attempt to translate animal data to man, of course. In addition, the proportionately smaller volume of cerebrospinal fluid present in the dog would tend to exaggerate any hydrogen-ion shift related to introduction of the local anesthetic drug. On the other hand, a pH-dependent mechanism attending the development of tachyphylaxis would appear reasonable on the basis of the above experimental results. A recent study by Gunther et al. of the effects of continuous caudal anesthesia in obstetrical patients provides conclusive clinical evidence for the development of tachyphylaxis to two local anesthetic agents, lidocaine and mepivacaine. Full details of this study will be presented elsewhere. Certain pertinent aspects, however, are included here. In figure 7, we note a linear reduction in the duration of anesthetic effect following the repeated caudal injection of equal volumes of lidocaine and mepivacaine. Although the duration of action of each drug varies slightly, in both instances only a fraction of the original duration of effect can be produced by the fourth injection (table 2). Of further interest would be the prediction of a more rapid development of tachyphylaxis to mepivacaine on the basis of its $pK_a$ of 7.65, very close to the physiologic pH range. The more rapid development of tachyphylaxis to this drug is shown in figure 7, where the equation of the slope for mepivacaine is $a = 174.74$, $b = -33.29$, compared with the equation $a = 121.00$, $b = -14.16$ for lidocaine.

Since the intensity of pain associated with labor gradually increases with time, one might question the influence of increasing pain on the observed reduced duration of effect of anesthetic agents. Two arguments tend to negate this possibility. First, there is a steady decrease in pain relief from both drugs, despite a plateau in pain intensity associated with the transition from the pain of cervical dilatation to that of perineal pressure. Second, an analysis of the duration of pain relief in three groups of women, divided on the basis of degree of cervical dilatation, indicated the same duration of pain relief from equivalent single doses, despite presumed different level of pain intensity at the time of drug administration (table 3).

Table 3. Relationship between Cervical Dilatation and Duration of Pain Relief Following the First Injection of Lidocaine

<table>
<thead>
<tr>
<th>Cervical Dilatation</th>
<th>Number of Patients</th>
<th>Lidocaine Mean Dose ± S.E. (ml)</th>
<th>Anesthesia Mean Duration ± S.E. (minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3–5 cm.</td>
<td>59</td>
<td>19.4 ± 0.4</td>
<td>97.8 ± 4.0</td>
</tr>
<tr>
<td>6 cm.</td>
<td>61</td>
<td>19.5 ± 0.3</td>
<td>93.7 ± 4.1</td>
</tr>
<tr>
<td>7–9 cm.</td>
<td>39</td>
<td>20.4 ± 0.5</td>
<td>97.5 ± 6.3</td>
</tr>
</tbody>
</table>

Finally, the relationship of tachyphylaxis to the $pK_a$ of the anesthetic agent suggests that drugs with $pK_a$ values further from the physiologic pH range would have a possible advantage over drugs with $pK_a$ values closer to body pH, since the former would be less influenced by significant changes in cerebrospinal fluid
pH. Of special value would be the ability to buffer effectively the anesthetic salt prior to its injection. Little or no clinical data regarding the safety of long-acting buffer preparations such as THAM used for intrathecal injection are available. This would be a fruitful field for further investigation.

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References