RELATIONSHIP BETWEEN THE PASSAGE OF LOCAL ANAESTHETICS ACROSS THE BLOOD-BRAIN BARRIER AND THEIR EFFECTS ON THE CENTRAL NERVOUS SYSTEM

BY
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SUMMARY
The transfer of procaine and lignocaine from blood to cerebrospinal fluid (c.s.f.) was studied in six patients and in twelve dogs. Local anaesthetics appeared very rapidly in the c.s.f. after intravenous administration. Within 20 minutes, a c.s.f./plasma ultrafiltrate ratio around 0.9 was reached. Para-aminobenzoic acid, a procaine metabolite, appeared in c.s.f. later than procaine. This is explained by a different rate of drug entry into the c.s.f. and by the need for previous procaine splitting by plasma cholinesterase. The rapid transfer of local anaesthetics corresponds with their high lipid-solubility and low degree of ionic dissociation at the pH of the body. The free movement of drugs to and from the brain accounts for the controllability of general anaesthesia induced by the intravenous administration of local anaesthetics.

It is well known that when increased doses of local anaesthetics, including procaine and lignocaine are given intravenously, they produce sedation, systemic analgesia and generalized convulsions. These central nervous system effects are accompanied by marked changes in the electrical activity of the brain (de Jong and Walts, 1966; Foldes et al., 1965; Usubiaga, 1966; Usubiaga et al., 1966). Because these effects can be dissociated by dose, it is possible to produce general analgesia by administering the proper amount of local anaesthetics intravenously. Combined with nitrous oxide and oxygen, these agents were used some years ago in the northern hemisphere but were rapidly abandoned (Graubard, Robertazzi and Peterson, 1947). In South America, intravenous local anaesthetics were introduced at a time when nitrous oxide was unavailable. For that reason they were combined with barbiturate and skeletal muscle relaxants (Goñi Moreno and Bluscke Castellanos, 1951) and they are still used there (Usubiaga and Wikinski, 1964). Despite the common use of local anaesthetics as central nervous system depressants, there is no fundamental knowledge on their passage from blood to the extracellular space of the brain. The present study was designed to determine the rate of entry of two commonly used local anaesthetics, procaine and lignocaine, into the cerebrospinal fluid of man and dog.

MATERIALS AND METHODS
The experiments were performed on six neurosurgical patients with brain tumours in whom a puncture of the lateral ventricle was anticipated, and on twelve dogs.

Clinical studies.
Anaesthesia was induced with intravenous thiopentone (4-6 mg/kg) and maintained with trichloroethylene-oxygen in a non-rebreathing circuit. Endotracheal intubation was performed under suxamethonium paralysis and respiration was intermittently assisted. The lateral ventricle and a brachial artery were cannulated, trichloroethylene administration was discontinued, and...
1 per cent procaine or 0.5 per cent lignocaine solution in doses ranging from 5 to 20 mg/kg (table I) was injected intravenously over a period of 5–10 minutes. These doses are within the range used in the technique of intravenous general anaesthesia (Usubiaga and Wikinski, 1964).

**Table I**

*Local anaesthetic concentrations in arterial blood and c.s.f. 5 minutes following the intravenous administration of procaine or lignocaine to six neurosurgical patients.*

<table>
<thead>
<tr>
<th>Local anaesthetic injection (mg/kg)</th>
<th>Arterial blood concentration (µg/ml)</th>
<th>Cerebrospinal fluid concentration (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procaine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>12.5</td>
<td>7.2</td>
</tr>
<tr>
<td>15</td>
<td>16.0</td>
<td>9.5</td>
</tr>
<tr>
<td>20</td>
<td>28.0</td>
<td>16.5</td>
</tr>
<tr>
<td>Lignocaine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>5.2</td>
<td>3.8</td>
</tr>
<tr>
<td>8</td>
<td>6.1</td>
<td>5.0</td>
</tr>
<tr>
<td>10</td>
<td>15.0</td>
<td>11.5</td>
</tr>
</tbody>
</table>

Samples of cerebrospinal fluid (c.s.f.) and arterial blood were taken before administration of the local anaesthetics and periodically thereafter.

**Animal experiments.**

Anaesthesia was induced by intravenous injection of pentobarbitone 40 mg/kg. After tracheal intubation, plastic catheters were placed into a femoral artery and vein for recording intravascular pressures. Lead II of the electrocardiogram was also recorded. A 20-gauge spinal needle was introduced into the cisterna magna and catheters were placed in the other femoral artery and the external jugular vein for sampling. Procaine hydrochloride, 1 per cent in saline, was injected into a podalic vein in doses ranging from 10 to 50 mg/kg (table II) over a period of 5–10 minutes. At various times after this injection, samples of arterial and venous blood (2 ml) and c.s.f. (1–2 ml) were withdrawn. Two experiments were prematurely terminated owing to bloody c.s.f.

Concentrations of procaine and para-aminobenzoic acid (p.a.b.a.) in plasma and c.s.f. were determined by the Banfi-Wikinski method (1964). Lignocaine was analyzed by a modification of the Sung and Truant method (1954). Arterial pH was measured by the micromethod of Astrup. Rate of drug penetration into c.s.f. was calculated according to Brodie, Kurz and Schanker (1960).

**RESULTS**

**Clinical studies.**

The intravenous infusion of lignocaine 5–10 mg/kg was accompanied by a fall in systolic and diastolic blood pressure of 30–50 mm Hg and a marked depression in respiratory rate and volume; apnoea and muscle twitching developed in one patient. Procaine produced fewer systemic effects; respiration was not grossly affected and the most consistent cardiovascular change was a long-lasting tachycardia.

As shown in table I, procaine and lignocaine appeared in the c.s.f. of all patients' samples shortly after the intravenous injection. The concentrations of both drugs increased over the next 10 minutes and declined thereafter. The concentration of the local anaesthetics in the c.s.f. was always lower than in the arterial blood. Following the injection of identical doses, concentrations of lignocaine in c.s.f. were higher than those of procaine. In the patients receiving procaine, para-aminobenzoic acid was also present in blood and c.s.f. samples. Concentrations of p.a.b.a. in blood and c.s.f. increased, whereas those of procaine decreased during the sampling time.

**Table II**

*Peak concentrations of procaine and p.a.b.a. in arterial blood (a.b.) venous blood (v.b.) and cerebrospinal fluid (c.s.f.) after intravenous injection of procaine in dogs.*

<table>
<thead>
<tr>
<th>Dose of procaine injected (mg/kg)</th>
<th>Procaine (µg/ml)</th>
<th>Para-aminobenzoic acid (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>a.b. v.b. c.s.f.</td>
<td>a.b. v.b. c.s.f.</td>
</tr>
<tr>
<td>10</td>
<td>15 12 8</td>
<td>12 10 5</td>
</tr>
<tr>
<td>20</td>
<td>30 21 20</td>
<td>25 20 8</td>
</tr>
<tr>
<td>40</td>
<td>85 53 45</td>
<td>34 30 19</td>
</tr>
<tr>
<td>50</td>
<td>90 64 60</td>
<td>40 38 20</td>
</tr>
</tbody>
</table>

**Animal experiments.**

The intravenous injection of procaine produced sinus tachycardia, arterial hypotension, deepening of the S wave of the electrocardiogram and, with the larger doses, respiratory depression. Generalized convulsions were never seen.

Procaine and p.a.b.a. concentrations in arterial and venous blood and c.s.f. are presented in table II. As a general rule, the drug concentrations were dose-dependent, that is, the larger
dose injected the greater the blood and c.s.f. concentrations. Although c.s.f. procaine levels were always lower than the arterial concentrations, occasionally they were indistinguishable from those found in the venous blood. A typical plot of blood and c.s.f. procaine and p.a.b.a. concentrations against time is shown in figure 1.

![Graph showing blood and c.s.f. concentrations](image)

**FIG. 1**

Procaine and para-aminobenzoic acid (p.a.b.a.) concentrations in arterial blood and cisternal cerebrospinal fluid of a dog following intravenous injection of 50 mg/kg procaine. Blood concentrations are plotted as drug concentration in the plasma ultrafiltrate (total concentration minus amount bound to plasma proteins). Procaine concentration in blood reaches a peak immediately following its intravenous injection. Procaine appears very rapidly in c.s.f. and reaches a state of equilibrium with the blood concentrations within 20 minutes; p.a.b.a., on the other hand, appears in the c.s.f. much later than procaine, and does not reach equilibrium until 60 minutes later.

The procaine concentration in blood declined rapidly. Procaine concentration in the cisternal fluid reached a peak within 10 minutes and then rapidly achieved equilibrium with that in the blood. Para-aminobenzoic acid appeared in the c.s.f. much later than procaine; its concentration reached a peak within 25 minutes and a long time was required for it to achieve equilibrium with the blood concentration.

**DISCUSSION**

These data indicate that local anaesthetics reach the cerebrospinal fluid very rapidly. Furthermore, since c.s.f. and blood concentrations decline in parallel manner, it seems plausible that there is no barrier to inward or outward movement of the drugs. The blood brain barrier can be changed by pathological processes (Dobbing, 1961) and, since all patients in this study had brain tumours, it might be argued that the results were influenced by this factor. In a yet unpublished study, however, we found that procaine and lignocaine appeared just as rapidly in the lumbar c.s.f. of neurosurgical patients without tumours.

In general, the concentration of drugs in c.s.f. depends upon the rates of entry and removal (Brodie, Kurz and Schanker, 1960; Helrich et al., 1950). As shown in figure 2, drugs enter the c.s.f.

![Graph showing relative rate of entry](image)

**FIG. 2**

Relative rate of entry of procaine into c.s.f. in comparison with other drugs (other drugs data taken from Brodie). CPL indicates drug concentration in plasma ultrafiltrate and c.s.f. refers to drug concentration in c.s.f. Thiopentone is the fastest and sulphaguanidine the slowest drug in entering the c.s.f. Procaine approaches the rate of passage of pentobarbitone on account of its high lipid-solubility.
at widely different rates. Thiopentone and procaine enter so rapidly that a c.s.f./plasma water concentration ratio of 0.9 is reached within 20 minutes; barbitone needs 80 minutes and salicylic acid and sulphaguanidine do not approximate this ratio even in 3 hours. The characteristic which principally determines the rate at which drugs pass from blood to c.s.f. is the lipidsolubility (Brodie, Kurz and Schanker, 1960). Local anaesthetics and thiopentone are highly lipid-soluble molecules in their undissociated form. Because their dissociation constants (thiopentone pKa 7.6, lignocaine pKa 7.8, procaine pKa 8.4) approach the pH of the blood, a large percentage of the circulating drug is always undissociated. Hence, it is not surprising that they enter and leave the c.s.f. freely. Para-aminobenzoic acid enters the c.s.f. later than procaine; this tardy appearance is more evident in dogs than in man. Differences between procaine and p.a.b.a. could be due largely to dissimilar rate of drugs transfer between blood and c.s.f., for p.a.b.a. has a lower lipid-solubility than procaine. Species differences in the appearance of p.a.b.a. in the c.s.f. could result from the slower breakdown of procaine by the dog's plasmacholinesterase.

Rate of transfer across biological membranes is limited not only by lipid solubility, but also by the degree of protein binding. Local anaesthetics in the blood exist in protein-bound and free forms, and it is only the latter which can diffuse into the c.s.f. Since protein binding varies from drug to drug, its influence on local anaesthetic transfer to c.s.f. should be studied.

**Clinical implications.**

It has customarily been assumed that with equipotent doses of local anaesthetics, the probability of an untoward reaction depends upon the rate of biotransformation, that is, the more rapidly a compound is destroyed, the less dangerous it is. Following single injections, however, the most important factor appears to be the rate of entry into the central nervous system. Because the rate at which a local anaesthetic breaks down cannot match the rate of passage through the blood-brain barrier, the neurotoxicity of the easily hydrolyzed procaine is indistinguishable from that of the non-hydrolyzed lignocaine (Usubiaga et al., 1966). Nevertheless, during continuous infusion of a local anaesthetic solution, biotransformation appears to be the more significant factor (Foldes et al., 1965). The metabolism of the local anaesthetic molecules, however, introduces a new complication caused by the specific effects of their breakdown products. As an example, the procaine metabolite, p.a.b.a., can prevent convulsions induced by local anaesthetics (Richards, 1963). For this reason, the presence of p.a.b.a. in the brain might explain the surprisingly low incidence of generalized convulsions reported during the continuous infusion of intravenous procaine.

**ACKNOWLEDGEMENTS**

The authors acknowledge the co-operation of Drs. Ernesto Dowling (jr.) and Salvador Viale of the Department of Neurosurgery, Rivadavia Hospital, Buenos Aires. They are also grateful to Dr. Frank Standaert and Mr. Milton Zisowits (Cornell University, N.Y.) and to Mrs. Betty Vestal and Mr. Ted Nichols (University of Miami) for their generous assistance in different phases of the work.

**REFERENCES**


LE PASSAGE DES ANESTHESIQUES LOCAUX A TRAVERS LA BARRIERE SANG-CERVEAU ET SES RAPPORTS AVEC L’ACTION SUR LE SYSTEME NERVEUX CENTRAL

SOMMAIRE
Le passage de la procaine et de la lignocaine du sang vers le liquide céphalo-rachidien a été étudié chez 6 patients et chez 12 chiens. Les anesthésiques locaux apparaissent très vite dans le liquide céphalo-rachidien après injection intra-veineuse. En 20 minutes un rapport d’ultra filtration entre le liquide céphalo-rachidien et le plasma de 0,9 a été atteint. L’acide para-aminobenzoique, un métabolite de la procaine, apparut plus tardivement que la procaine dans le liquide céphalo-rachidien. Ceci s’explique par une vitesse d’entrée différente de cette drogue dans le liquide céphalo-rachidien et au clivage préalable de la procaine par la cholinestérase plasmatique. Le passage rapide des anesthésiques locaux correspond avec leur haute solubilité dans les lipides et au faible degré de dissociation ionique à la température normale de l’organisme. Le libre passage de médicaments vers le cerveau explique la dirigeabilité de l’anesthésie générale induite par injection intra-veineuse d’anesthésiques locaux.

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