

# Distribution of Local Anesthetic Agents in the Neuraxis of the Dog

Ellis N. Cohen, M.D.\*

Autoradiographic studies of the spinal cord in the dog indicate a specific uptake of  $^{14}\text{C}$ -labelled lidocaine and procaine by the neuraxis. The highest concentrations of the intrathecally-administered drug were found in the posterior and lateral columns, with only small concentrations noted in the anterior columns. Uptake of drug was higher in the grey matter than in the white matter of the cord, and posterior nerve roots had a higher concentration than anterior roots. Biopsies of the cord and scintillation counting of the weighed specimens provided confirmation of the autoradiographic studies. The significance of these findings is discussed, and possible explanations are considered.

IT HAS GENERALLY BEEN ASSUMED that the onset of spinal anesthesia is associated with a block of the spinal nerve roots.<sup>1</sup> Other possible sites of anesthetic action include the dorsal root ganglia,<sup>2</sup> or anesthetic block within the cord itself. The latter possibility is supported by studies which indicate a nonspecific uptake of  $^{82}\text{Br}$ -labelled procaine into the spinal cord.<sup>3</sup> Recently, Bromage has demonstrated an uptake of  $^{14}\text{C}$ -labelled lidocaine (xylocaine) in the peripheral aspects of the thoracic and lumbosacral cord.<sup>4,5</sup> The anesthetic for these studies was administered epidurally.

A recent experimental study of the mechanism of tachyphylaxis to local anesthetic agents has provided the opportunity to study further the specific uptake of labelled local anesthetic agents into the neuraxis of the dog.<sup>6</sup> In this study  $^{14}\text{C}$ -labelled lidocaine (specific activity 4.94 mc./mM) or  $^{14}\text{C}$ -labelled procaine (specific activity 2.26 mc./mM) was introduced by catheter into the intrathecal space to evaluate

the effect of changes in cerebrospinal fluid pH on uptake and distribution. Results of the present study provide autoradiographic and anatomic evidence for a localized uptake of anesthetic agents in the neuraxis of the dog.

## Procedure

Specimens of spinal cord used for the study were obtained from six dogs, average weight  $23.4 \pm 1.4$  kg. In each instance, a laminectomy was first performed under general anesthesia, and the dura exposed. In three animals, two polyethylene catheters were introduced through a thin-walled Huber-point needle inserted at the sixth lumbar vertebra and advanced cephalad to approximately the level of the second lumbar vertebra. One catheter was used for the introduction of local anesthetic drugs, and the second provided for withdrawal of small aliquots of cerebrospinal fluid. In a second series of three animals, a single catheter was introduced. Animals in the first series were also the subjects for a preliminary study of the effects of pH changes on the distribution of local anesthetic agents. Although the pH values of the cerebrospinal fluid in these animals had returned to normal, we were uncertain as to the influence of the preliminary study on the autoradiographic findings obtained later (see results). A second series of three dogs was studied under control conditions, and no preliminary experiments were performed. Similar results were obtained in both series.

In each animal lidocaine (xylocaine) or procaine (25 mg. in a 1-ml. volume of 10 per cent dextrose solution) was slowly administered through the catheter and flushed with 0.2 ml. of cerebrospinal fluid previously withdrawn. Tracer amounts (20  $\mu\text{C}$ .) of  $^{14}\text{C}$ -labelled drug had been added to each volume

\* Professor of Anesthesia.

Received from the Department of Anesthesia, Stanford University School of Medicine, Stanford, California. Accepted for publication March 26, 1968. Supported by N. I. H. Grant GM 12527.

of local anesthetic injected. The animals were sacrificed 30 minutes later by intravenous injection of potassium chloride. The carcasses were immediately transferred to a cold room ( $-10^{\circ}\text{C}.$ ) and packed in dry ice. Twenty-four hours later, a three-inch block of lumbar spinal column and contents was removed and divided into coronal sections 1 cm. in thickness (fig. 1). The thick sections, in turn, were mounted with a saturated solution of carboxymethyl-cellulose gel on a brass stage. From these blocks 30-micra sections were cut with a heavy-duty Jung sledge microtome† and mounted on a cellophane tape backing according to the technique of Ullberg.‡ After dehydrating for a minimum of 24 hours, the thin sections were placed in direct contact with Ilford G5 plates§ or with Kodak No-Screen x-ray film.¶ A sandwich made of photographic plate, dried tissue tape section, and cardboard backing was covered with heavy black paper and stored in the cold room in a light-proof box. Photographic exposure times varied from two to five days. Development of the photographic emulsion was by standard procedure. To achieve high accuracy for localization of the drug concentration, biopsies of selected tract areas within the cord were made. These cord biopsies, plus additional dissected specimens of nerve roots, ganglia, dura, fat, etc. were weighed in the wet (frozen) state, transferred to glass vials, and solubilized in 0.5-ml. NCS solution. Following the addition of PPO (2-5 diphenyloxazole) and toluene, the solubilized tissues were counted in a scintillation counter. Resultant counts per mg. of tissue established drug concentration for each specimen.

# Results

The essential findings of this study are illustrated in figures 2 and 3. In each of these sections there is direct evidence for penetration of the anesthetic drug and its localization within the neuraxis. The highest concentrations of drug are present on the periphery of the cord in the posterior and lateral aspects, while only a small concentration is noted on

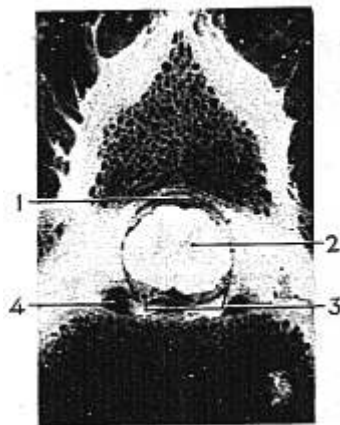


FIG. 1. Thick section of lumbar spinal column from the dog. 1, dura; 2, grey matter; 3, plastic catheters; 4, vertebral vein.

the anterior aspect. The central white matter of the cord contains less drug, but a relatively high concentration is present in the grey matter, especially in the region of the posterior horn.

Table 1 provides an analysis of drug concentrations determined in various components of the cord. This analysis confirms autoradiographic evidence that the highest concentrations of local anesthetic are found in the posterior and lateral columns, and that considerably smaller amounts are present in the anterior columns. A selectively high concentration is present in the grey matter, in contrast to the central white matter of the cord. The substantia gelatinosa of the posterior horn, in turn, contains more radioactivity than the ganglion cells of the anterior horn. A higher concentration is also present in the posterior roots, compared to the anterior roots. Large amounts of drug are also present in the dura, with smaller concentrations in the extradural fat.

# Discussion

The evidence for a selective uptake of local anesthetics by the neuraxis of the dog is quite clear. Not only is the drug highly concen-

† Model K. A. G. Jung, Heidelberg, Germany.

‡ Ilford Ltd., Ilford, Essex, England.

§ Kodak Company, Rochester, N. Y.

¶ Nuclear Chicago, Des Plaines, Illinois.

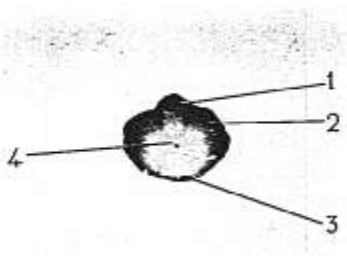


FIG. 2. Autoradiograph prepared from 30-micra section of lumbar spinal cord. Note concentrations of radioactive drug in the posterior and lateral columns and in the grey matter. 1, posterior column; 2, lateral column; 3, anterior column; 4, grey matter.

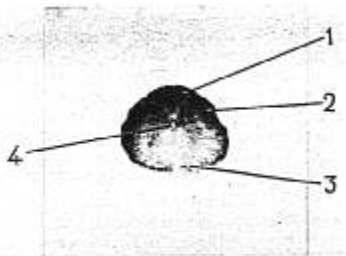


FIG. 3. Autoradiograph prepared from 30-micra section of lumbar spinal cord. Note concentrations of radioactive drug in the posterior and lateral columns and in the grey matter. 1, posterior column; 2, lateral column; 3, anterior column; 4, grey matter.

trated in the posterior and lateral aspects of the cord, but a selective uptake is also demonstrated within the cord in the grey matter. It is unlikely that gravity or the animal's position during the experiment significantly influenced the localized concentrations found in the posterior or lateral peripheral cord. Figure 1 indicates anterior placement of the polyethylene catheters (including the tip) used for the intrathecal drug injections. Since the experi-

ments were carried out with the dorsal aspect of the animal uppermost, the hyperbaric drug would tend to gravitate away from the dorsal cord.

Although little doubt as to the selective distribution observed exists, one must exercise caution in translating the above evidence directly to man. The dog is a good experimental subject, but there are a number of important species differences, including thickness of the dura, amounts of cerebrospinal fluid, etc., which must be considered carefully.

Explanations for the localized drug distribution include both circulatory and physicochemical factors. It does not appear that the drug distribution can be explained solely on the basis of regional vascular supply, since (in man) the spinal cord is supplied primarily by an arterial network originating in an anterior trunk which passes through the anterior median fissure into the cord substance. It is of interest that the posterior column has an additional arterial blood supply which perforates the cord directly and courses with the posterior root.<sup>8</sup> One also finds anatomic evidence for a threefold increase in arterial vasculature in the grey matter of the spinal cord over that of the white matter.<sup>9</sup> Although little is known concerning biochemical differences in various structures of the cord, such a possibility must also be considered. Anatomically, the posterior and lateral funiculi contain heavily-myelinated nerve fibers, while

TABLE 1. Concentration of Lidocaine or Procaine ( $\mu\text{g./mg.} \pm \text{S.E.}$ ) in the Lumbar Spinal Cords of Six Animals Following Intrathecal Injection of 25 mg. in 1-ml. volume (Concentrations of total drug calculated in terms of measured radioactivity.)

Section	Concentration of local anesthetic ( $\mu\text{g./mg.}$ of tissue)
Lateral column	$1.38 \pm 0.12$
Posterior column	$1.36 \pm 0.18$
Dura	$0.98 \pm 0.30$
Dorsal root	$0.87 \pm 0.20$
Anterior column	$0.73 \pm 0.24$
Grey matter (posterior horn)	$0.53 \pm 0.09$
Whole grey matter	$0.34 \pm 0.13$
Ventral root	$0.32 \pm 0.10$
Whole cord	$0.27 \pm 0.10$
Extradural fat	$0.25 \pm 0.10$
Grey matter (anterior horn)	$0.21 \pm 0.08$
Dorsal root ganglion*	0.16
Cerebrospinal fluid	$0.83 \pm 0.15$

\* Mean of two specimens.

the anterior funiculus (with the exception of the anterior corticospinal tract) is generally composed of less dense fibers.<sup>10</sup> It has also been shown that the posterior nerve root is more heavily myelinated than the anterior root.<sup>11</sup> In this connection the rate of uptake of certain foreign materials introduced intrathecally tended to follow the state of myelination of the nerve fibres in developing animals.<sup>12</sup> The local anesthetic agents are also known to possess high lipid solubility characteristics at physiologic pH ranges and should readily enter the myelin. A third remaining possibility (less likely) for the drug localization observed is the transfer of drug by physical passage from cerebrospinal fluid into the neuraxis via the ensheathing membrane of the posterior nerve rootlet. Such a means of transfer from the periphery into the cord may also proceed perivascularly, and has been suggested as the route of transverse myelitis following paravertebral injection of a local anesthetic agent.<sup>13</sup>

Localization of the anesthetic drug in specific anatomic sites within the cord does not, of course, prove a site of action. On the other hand, it would appear to be more than coincidence that the posterior columns, the posterior roots, and the substantia gelatinosa are each concerned with sensory modalities and contain higher concentrations of drug. This selective distribution of drug may explain the experimental and clinical observation that sensation is blocked before motor function with intrathecally-injected local anesthetic agents, and at a lower concentration of injected drug.<sup>2, 14, 15</sup> Thus it would appear that the anatomic localization demonstrated for the local anesthetic agents may well coincide with a site of action of these drugs within the neuraxis.

The author wishes to express his appreciation to Miss Nancy Hood for preparation of the autoradiographs, and to Mr. Robert Golling for assistance in the radioisotope measurements.

## References

1. Maxon, L. H.: *Spinal Anesthesia*. Philadelphia, J. B. Lippincott Co., 1938.
2. Frumin, M. J., Schwartz, H., Burns, J. J., Brodie, B. B., and Papper, E. M.: Sites of sensory blockade during segmented spinal and segmented peridural anesthesia in man, *ANESTHESIOLOGY* 14: 576, 1953.
3. Horwath, F.: Studies with a radioactive spinal anesthetic, *Brit. J. Pharmacol.* 4: 333, 1949.
4. Bromage, P. R., and Burfoot, M. F.: Further studies in the distribution and site of action of extradural local anesthetic drugs using C<sup>14</sup> labelled lidocaine in dogs, 3rd Cong. Mund. Anesth. Tom 1, Sao Paulo, 1964, p. 371.
5. Bromage, P. R., Joyal, A. C., and Binney, J. C.: Local anesthetic drugs: Penetration from the spinal extradural space into the neuraxis, *Science* 140: 392, 1963.
6. Cohen, E. N., Levine, D. A., Colliss, J., and Gunther, R.: The role of pH in the development of tachyphylaxis to local anesthetic agents, *ANESTHESIOLOGY* 29: 994, 1968.
7. Ullberg, S.: Autoradiographic studies on the distribution of labelled drugs in the body, *Proc. Second U.N. Internat. Conf. on Peaceful Uses of Atomic Energy* 24: 248, 1958.
8. Gillian, L. A.: The arterial blood supply of the human spinal cord, *J. Comp. Neurol.* 110: 75, 1958.
9. Ranson, S. W.: *The Anatomy of the Nervous System*. Philadelphia, W. B. Saunders Co., 1953.
10. Fox, M. W., Inman, O. R., and Himwich, W. A.: The postnatal development of the spinal cord of the dog, *J. Comp. Neurol.* 130: 233, 1967.
11. Truex, R. C., and Carpenter, M. B.: *Strong and Elwyn's Human Neuroanatomy*. Baltimore, Williams and Wilkins Co., 1964.
12. Dobbing, J.: The entry of cholesterol into rat brain during development, *J. Neurochem.* 10: 739, 1963.
13. Shapiro, S. K., and Norman, D. D.: Neurological complications following use of Elocaine, *J.A.M.A.* 152: 608, 1953.
14. Sarnoff, S. J., and Arrowood, J. C.: Differential spinal block, *Surgery* 20: 150, 1946.
15. Helrich, M., Papper, E. M., Brodie, B. B., Fink, M., and Rovenstine, E. A.: Fate of intrathecal procaine and spinal fluid required for surgical anesthesia, *J. Pharmacol. Exp. Ther.* 100: 78, 1950.