ANESTHESIOLOGY

The Journal of

THE AMERICAN SOCIETY OF ANESTHESIOLOGISTS, INC.

Volume 15 JANUARY, 1954 Number 1

THE CONCENTRATION OF PONTOCAINE HYDROCHLORIDE IN THE CEREBROSPINAL FLUID DURING SPINAL ANESTHESIA, AND THE INFLUENCE OF EPINEPHRINE IN PROLONGING THE SENSORY ANESTHETIC EFFECT *

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Albany, New York

Received for publication March 3, 1953

THE duration of action of various local anesthetic agents injected intrathecally to produce spinal anesthesia has been thought to depend upon the length of time these agents remain in the cerebrospinal fluid at a concentration great enough to block the spinal nerves (1, 2, 3). The concentration has been thought to be highest immediately after injection, and then to fall progressively as the drug becomes absorbed from the cerebrospinal fluid into the general circulation where it is destroyed (4). The mechanism by which various vasopressor drugs prolong spinal anesthesia when added to the intrathecal anesthetic agent has been considered to be similar to that by which they prolong local anesthesia when added to the anesthetic agent at the time of infiltration, that is, by producing vasoconstriction locally to decrease vascularity and inhibit absorption of the anesthetic agent from the site of injection (5). Reports on the effect of epinephrine and other vasopressor agents upon the duration of spinal anesthesia produced by various agents have not been in complete agreement (6, 7, 8), probably owing to differences in clinical techniques and methods used, and to lack of quantitative data. The concentration of the anesthetic agent in the cerebrospinal fluid during spinal anesthesia with procaine has

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been quantitatively determined and the influence of epinephrine and other vasopressor drugs upon procaine concentration has been studied (2). Similar studies during spinal anesthesia with pontocaine, however, have not been published. It was our purpose to determine the concentration and fate of pontocaine in cerebrospinal fluid during spinal anesthesia, and to study the influence of epinephrine upon this.

METHOD

Fifteen patients, subjected to spinal anesthesia for surgical procedures varying from vein stripping and herniorrhaphy to abdominoperineal resection and subtotal gastrectomy, were studied. Ages ranged from 20 to 72 years, and 4 of the patients were women. All patients received a barbiturate, opiate and belladonna derivative in appropriate dosage preparatory for anesthesia and surgery. In each patient, a Tuohy spinal catheter was introduced through the second lumbar interspace and up the spinal canal for a distance of 5 cm., so that the tip of it rested approximately at the level of the twelfth thoracic. Through this catheter, a control sample (2 cc.) of cerebrospinal fluid was collected. Then a 24 gauge spinal needle was introduced through the third lumbar interspace for the administration of the spinal anesthetic. Each of 9 patients received 16 mg. of 1 per cent pontocaine mixed with 2.4 cc. of 10 per cent dextrose, and each of 6 patients received 14 mg. of 1 per cent pontocaine mixed with 2.1 cc. of 10 per cent dextrose plus 0.5 cc. of 1:1,000 epinephrine. The total volume of anesthetic mixture injected intrathecally in each of the 15 patients was the same (4 cc.). Appropriate fluids were administered by intravenous infusion, but no additional anesthetic was administered. Spinal fluid samples (2 cc. each) were collected from the Tuohy catheter five, ten, fifteen, thirty, sixty, ninety and 120 minutes after the intrathecal injection of the spinal anesthetic mixture. Each sample was drawn from the catheter into a clean syringe only after the contents of the catheter (1 cc.) residual from the previous sampling had been discarded. At the time of each sampling, the level of sensory anesthesia to pinprick was tested and the blood pressure and pulse rate were determined. All spinal fluid samples were analyzed quantitatively for pontocaine by the acid-dye technique of Auerbach, Davis and Foldes, employing a Coleman Model 6A photoelectric colorimeter (9). All samples were analyzed in duplicate and each sample was identified by code numbers only. Preliminary *in vitro* tests showed that epinephrine did not interfere with the quantitative analysis for pontocaine.

RESULTS

(A) *Pontocaine-Glucose Mixtures.*—For each of the 9 patients who received pontocaine and dextrose *without* epinephrine, the concentrations of pontocaine in the spinal fluid and the corresponding levels of

TABLE 1

	Patient	Time from Intrathecal Injection of Anesthetic Mixture													
		5 Min.		10 Min.		15 Min.		30 Min.		60 Min.		90 Min.		120 Min.	
		Mg. %	Level	Mg. %	Level	Mg. %	Level	Mg. %	Level	Mg. %	Level	Mg. %	Level	Mg. %	Level
A. Without Epinephrine	A. J.	15.1	T5	7.2	T6	6.0	T5	2.0	T6	1.3	T7	No Sample	T9	.8	<T12
	M. S.	10.0	T6	7.9	T5	7.8	T4	3.2	T6	2.1	T8	1.0	T10	.9	<T12
	C. S.	9.1	T3	7.1	T3	6.9	T3	4.1	T4	2.6	T7	.6	T9	.9	T11
	W. D.	15.3	T4	11.7	T3	10.9	T3	4.6	T4	1.9	T9	.4	T10	No Sample	T12
	C. S.	11.2	T6	5.2	T6	4.9	T6	3.1	T6	1.3	T8	No Sample	T10	.9	<T12
	H. B.	15.1	T5	9.6	T5	8.8	T3	3.6	T3	No Sample	T5	.3	T10	.7	T11
	E. F.	12.2	T5	7.4	T4	5.8	T3	2.5	T5	1.2	T6	.3	T10	0.2	T11
	L. M.	12.1	T5	No Sample	T5	7.6	T3	No Sample	T5	1.5	T8	.4	T10	1.2	<T12
	G. D.	7.9	T6	4.3	T7	4.2	T6	.9	T6	.5	T10	No Sample	T12	No Sample	<T12
	Average	12.0	T5	7.5	T5	7.0	T4	3.0	T5	1.5	T8	0.5	T10	0.8	<T12

TABLE 1—*Continued*

	Patient	Time from Intrathecal Injection of Anesthetic Mixture													
		5 Min.		10 Min.		15 Min.		30 Min.		60 Min.		90 Min.		120 Min.	
		Mg. %	Level	Mg. %	Level	Mg. %	Level	Mg. %	Level	Mg. %	Level	Mg. %	Level	Mg. %	Level
B. With Epinephrine	P. L.	25.3	T3	13.3	T3	11.9	T4	No Sample	T3	2.0	T3	.6	T3	.3	T4
	J. K.	23.3	T5	No Sample	T3	11.9	T3	5.3	T3	No Sample	T3	.7	T4	.2	T4
	L. S.	18.0	T6	13.2	T6	12.4	T6	5.4	T6	2.6	T6	1.2	T6	No Sample	T6
	B. W.	17.8	T5	14.0	T5	12.8	T5	7.0	T5	3.8	T7	.7	T7	.1	T7
	J. S.	16.9	T5	13.3	T4	No Sample	T4	4.6	T4	2.0	T4	1.2	T4	No Sample	T4
	J. C.	18.7	T5	11.0	T4	10.9	T4	3.1	T4	2.1	T4	1.6	T4	.4	T4
	Average	20.0	T5	13.0	T4	12.0	T4	5.1	T4	2.5	T4	1.0	T5	0.25	T5

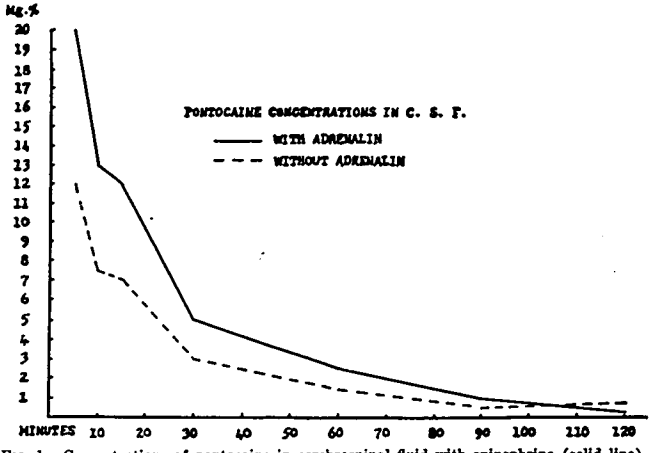

FIG. 1. Concentrations of pontocaine in cerebrospinal fluid with epinephrine (solid line) and without epinephrine (dotted line).

sensory anesthesia to pinprick are listed in table 1A, and the averages are shown graphically in figures 1 and 2 (dotted lines). Blood pressures and pulse rates remained relatively stable and within the range of preoperative values.

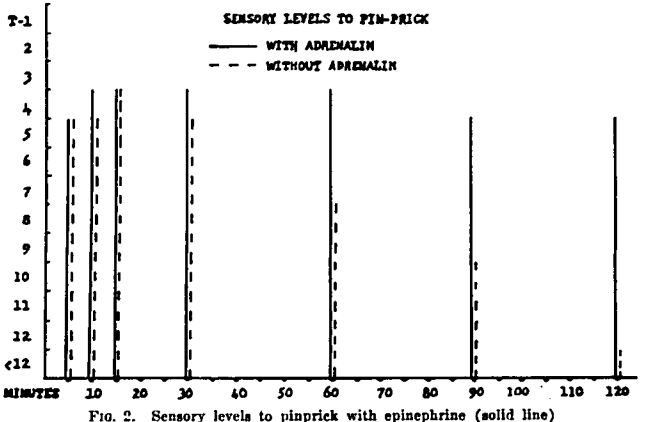

FIG. 2. Sensory levels to pinprick with epinephrine (solid line) and without epinephrine (dotted line).

(B) *Pontocaine-Glucose-Epinephrine Mixtures.*—For each of the 6 patients who received pontocaine and dextrose *with* epinephrine, the concentrations of pontocaine in the spinal fluid and the corresponding levels of sensory anesthesia to pinprick are listed in table 1B, and the averages are shown graphically in figures 1 and 2 (solid lines). Blood pressures and pulse rates remained relatively stable and within the range of preoperative levels.

COMMENT

The explanation of the mechanism by which epinephrine prolongs the duration of spinal anesthesia with procaine (3) does not adequately define the mechanism of action of epinephrine in prolonging the duration of spinal anesthesia with pontocaine, as observed under the conditions of our investigation. The following observations on the influence of epinephrine make this statement clear.

A. *Influence of Epinephrine on Initial Concentration.*—In the patients who received the pontocaine-dextrose mixture *with epinephrine,* the pontocaine concentration in the cerebrospinal fluid was substantially greater after the first five minutes than in those who received the pontocaine-dextrose mixture *without epinephrine,* this despite the fact that the dose of pontocaine originally injected was less in the former than in the latter group of patients. Although this is in considerable variance to the concentration-action curves noted by Helrich *et al.* (2) for procaine, it does conform to the commonly accepted concept that vasopressor agents delay the absorption of local anesthetics from the cerebrospinal fluid into the systemic circulation (4)—at least during the initial phase of spinal anesthesia.

B. *Influence of Epinephrine On Ultimate Concentration.*—Although epinephrine added to the anesthetic mixture injected intrathecally delayed the disappearance of pontocaine from the cerebrospinal fluid during the initial phase of spinal anesthesia, it did not prevent the pontocaine concentration in the cerebrospinal fluid from falling subsequently to the same level during anesthesia as when the pontocaine-dextrose mixture was given *without epinephrine.* At the end of ninety minutes, values for pontocaine concentrations in the cerebrospinal fluid were almost the same whether or not the anesthetic mixture initially injected contained epinephrine (fig. 1). This would appear to conflict with the concept that the existence of a "critical level" of local anesthetic concentration in cerebrospinal fluid (10) is essential for insuring the continuance of sensory anesthesia. Further confirmation of this becomes apparent when the concentrations of pontocaine and the corresponding sensory anesthetic levels, as determined 120 minutes after the administration of spinal anesthesia, are compared for the two groups studied. Although in the group receiving pontocaine and dextrose *without epinephrine* no sensory anesthesia remained when the average pontocaine concentration was still 0.8 mg. per 100 cc., in the group receiving

pontocaine and dextrose *with epinephrine,* sensory anesthesia persisted to the level of fifth thoracic segment even when the average pontocaine concentration had fallen to 0.25 mg. per 100 cc.

C. *Influence of Epinephrine on the Duration of Clinical Anesthesia.* —Despite similar values for pontocaine concentration in cerebrospinal fluid noted in both groups after ninety minutes, as shown in figure 1, sensory anesthesia to pinprick persisted at higher levels for longer durations in the group receiving pontocaine and dextrose *with epinephrine* (fig. 2). This is in complete agreement with most of the clinical reports which have been published regarding the effects of sympathomimetic amines upon the duration of spinal anesthesia.

DISCUSSION

Regarding local anesthetic agents, Harris (11) stated that "the duration of anesthesia depends on (1) the mass injected, (2) the nature

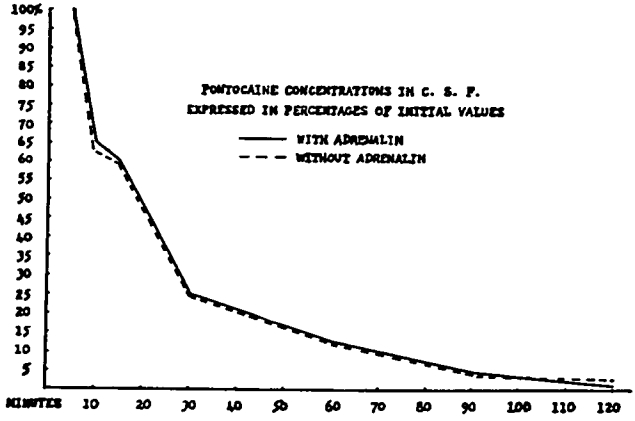

FIG. 3. Concentrations of pontocaine in cerebrospinal fluid, expressed in percentages of initial values, with epinephrine (solid line) and without epinephrine (dotted line).

of the site of injection, and (3) the physical properties of the particular local anesthetic." When the results of our investigation are considered in accordance with these precepts, the following facts are evident: (1) Although the mass of pontocaine injected was less when epinephrine was added than when it was not, the initial concentrations of pontocaine in the cerebrospinal fluid were higher in the former than in the latter instances. The mass of pontocaine injected was not the factor which determined the differences in the initial concentrations. (2)

Preliminary *in vitro* studies indicated that in pontocaine-epinephrine mixtures, the presence of epinephrine did not alter the physical properties of pontocaine, thus eliminating the possibility that epinephrine might interfere with the precipitation of free anesthetic base and thus delay the tissue uptake of this local anesthetic. The possibility that epinephrine might in some way either inhibit or enhance the dilution of pontocaine in the cerebrospinal fluid, and thereby influence the duration of spinal anesthesia, can be ruled out by observing that the absolute values (fig. 1) and percentage reductions (fig. 3) in pontocaine concentrations are relatively similar both with and without epinephrine (3). Since under the conditions of this investigation, neither the dose of pontocaine nor its physical properties appear to be the factors responsible for the differences in duration of spinal anesthesia in the two groups studied, it is apparent that the increased duration of sensory spinal anesthesia which occurred in the group receiving pontocaine and dextrose *with epinephrine* must have been due to an alteration in the nature of the site of injection, that is, the vascularity of the dura or nerve tissue, or both.‡ By producing vasoconstriction in these areas, epinephrine would delay absorption of pontocaine into the systemic circulation—but only for as long as the constrictor effect persisted.

Since the action of epinephrine even in the fairly strong concentrations employed in this study is apparently a fleeting one, its influence on the uptake of local anesthetics by nerve tissue probably occurs within the first minutes of its intrathecal injection, and bears little if any relationship to the so-called "critical levels" observed at the end of one or two hours. It would appear that the effectiveness of sympathomimetic amines in prolonging the duration of spinal anesthesia results from their ability to limit vascular absorption of the anesthetic agent in the first few minutes subsequent to injection, and from the consequent immediate high concentration of local anesthetic bathing the spinal nerve roots as they cross the subarachnoid space. It would seem reasonable to assume, therefore, that the duration of spinal anesthesia is a function of the *initial* cerebral spinal level of local anesthetics rather than a function of so-called "critical level" demonstrable after thirty to sixty minutes.

In an attempt to substantiate this hypothesis, 3 additional patients were subjected to further investigation. The same technique was used for obtaining cerebrospinal fluid samples as was described for the principal study. After the intrathecal injection of 14 mg. of pontocaine mixed with 2.1 cc. of 10 per cent dextrose plus 0.5 cc. of 1:1,000 epineph-

‡ Direct visualization of dural capillaries during lumbar laminectomy, failed to show any gross change in vessel caliber following the direct application, by pledget, of solution of epinephrine in concentrations of 1:30,000. When applied in concentrations of 1:80,000, however, which concentration probably more nearly approximates that which exists intrathecally after injection of pontocaine-dextrose-epinephrine mixtures used for spinal anesthesia, we were able to visualize definite "blanching" of the dura, demonstrating the local vasoconstrictor effect of epinephrine known to exist in other body tissues.

rine, these patients had sensory anesthesia to pinprick established to the level of the third thoracic segment. Thirty minutes after the initial intrathecal injection, the intrathecal space of each patient was flushed with 40 cc. of normal saline solution,§ and subsequent samples of cerebrospinal fluid were withdrawn from the Tuohy catheter and sent to the laboratory for pontocaine determinations. Pontocaine concentrations in cerebrospinal fluid following dilution and flushing at the end of thirty minutes, as described, were of the same magnitude as those observed at the end of ninety minutes in the "unflushed" patients (fig. 1). Despite this extremely low pontocaine concentration, sensory anesthesia to the third thoracic segment persisted for at least an additional 105 minutes, the period of observation.

SUMMARY

(1) Pontocaine concentrations in cerebrospinal fluid after intrathecal injection of pontocaine in dextrose, with and without epinephrine, were studied.

(2) An hypothesis based on early competition between spinal nerve roots and intrathecal vascular supply for the injected drug is presented to explain the influence of epinephrine on the duration of spinal anesthesia. The concept that "critical levels" of local anesthetic agent in cerebrospinal fluid are necessary for the continuation of sensory anesthesia is questioned.

(3) Substantiation of this hypothesis by a clinical test in 3 patients is presented.

ACKNOWLEDGMENT

Grateful acknowledgment is made to the Department of Chemistry of the Albany Medical College, which, under the direction of Dr. Donald Remp, performed the determinations.

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§ Twenty cubic centimeters of cerebrospinal fluid was withdrawn via the Tuohy catheter and an equal volume of saline solution was injected. This procedure was repeated and the residual contents of the catheter were discarded.

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AMERICAN BOARD OF ANESTHESIOLOGY

At the meeting of the American Board of Anesthesiology in St. Paul, Minnesota on September 30, 1953, the following Directors were elected:

Dr. Milton C. Peterson of Kansas City, Missouri was elected as a Director to a six year term which expires October, 1959. Dr. Peterson will replace Dr. Charles F. McCuskey whose term has expired.

Dr. Meyer Saklad was re-elected as a Director to a six year term which will expire October, 1959.

Dr. Curtiss B. Hickcox was re-elected as a Director to a six year term which will expire October, 1959.