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Spinal cord blood flow following subarachnoid tetracaine

Spinal cord and spinal dural blood flow in the cervical, thoracic and lumbosacral regions were measured in dogs using the radioactive microsphere technique. Measurements were taken before and 20 and 40 minutes after lumbar subarachnoid injection of one of the following: (1) physiologic saline; (2) tetracaine 20 mg or (3) tetracaine 20 mg with epinephrine 200 µg. No significant change in spinal cord or spinal dural blood flow occurred following subarachnoid physiologic saline or tetracaine with epinephrine. Dogs receiving subarachnoid tetracaine demonstrated a significant increase in lumbosacral spinal cord, and thoracic and lumbosacral dural blood flow at 20 and 40 minutes following injection. Cervical dural blood flow was significantly increased at 40 minutes after subarachnoid tetracaine. Lumbar subarachnoid tetracaine (20 mg) produces a regional spinal cord and generalized dural hyperemia which is prevented by the addition of epinephrine (200 µg).

Key words

ANAESTHETIC TECHNIQUES: subarachnoid block;
ANAESTHETICS, LOCAL: tetracaine; SYMPATHETIC
NERVOUS SYSTEM, CATECHOLAMINES: epinephrine;
SPINAL CORD: blood flow.

Prolongation of tetracaine spinal anaesthesia through the use of epinephrine as an adjunct has been well documented.¹⁻⁴ The mechanism of epinephrine induced prolongation of tetracaine spinal anaesthesia is however controversial.

Classical theory has led to the concept that prolongation of spinal anaesthesia by the use of epinephrine is through vasoconstriction of the regional circulation. Studies using intrathecal lidocaine and bupivacaine with epinephrine have shown that the duration of clinically useful spinal anaesthesia is not prolonged by the addition of epinephrine.⁴⁻⁶ These studies suggest that regional vasoconstriction may not be an important factor. Other studies suggest that epinephrine may augment spinal analgesia by a direct spinal neuronal antinociceptive mechanism.^{7,8}

We recently demonstrated that lumbar subarachnoid epinephrine (200 µg) did not affect the spinal cord circulation but did produce regional dural vasoconstriction.⁹ In view of the present uncertainty this study was undertaken to determine the effects of subarachnoid tetracaine with and without epinephrine on the spinal cord and spinal dural circulations.

Methods

Eighteen mongrel dogs of either sex weighing 15–32 kg (19.8 ± 4.4 , mean $\pm$ S.D.) were studied. The animals were anaesthetized with pentobarbitone, 30 mg·kg⁻¹ induction dose followed by a maintenance dose of 2–5 mg·kg⁻¹·hr⁻¹. After tracheal intubation, the animals were ventilated using an Ohio Model 300 ventilator with 100 per cent oxygen at a tidal volume of 15 ml·kg⁻¹. The respiratory rate was adjusted to maintain a PaCO₂ of 35–43 torr.

The University of Manitoba guidelines for the humane use of animals were followed.

The surgical preparation consisted of a right inguinal incision for insertion of polyvinyl catheters

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TABLE 1 Haemodynamic parameters in dogs prior to and following intrathecal injection

Groups	MABP (mmHg)	PCWP (mmHg)	C.I. (ml·kg ⁻¹ ·min ⁻¹)	H.R. (beats/min)
<i>Saline</i>				
Pre-injection	135 ± 2	7 ± 1	164 ± 26	178 ± 3
20 min post-injection	138 ± 9	6 ± 1	167 ± 28	195 ± 13
40 min post-injection	146 ± 7	6 ± 1	150 ± 27	175 ± 12
<i>Tetracaine</i>				
Pre-injection	143 ± 7	7 ± 1	233 ± 19	161 ± 9
20 min post-injection	108 ± 9*	10 ± 2	229 ± 25	149 ± 20
40 min post-injection	113 ± 6*	9 ± 1	211 ± 28	132 ± 6
<i>Tetracaine with epinephrine</i>				
Pre-injection	127 ± 4	5 ± 1	200 ± 21	167 ± 12
20 min post-injection	96 ± 3*	13 ± 2	334 ± 29*	161 ± 8
40 min post-injection	103 ± 3*	11 ± 2	338 ± 21*	167 ± 14

n = 6 in each group.

Results are Mean ± S.E.M.

*p < 0.05 when compared to pre-injection measurements.

in the femoral artery and vein. A left inguinal incision was used for the retrograde insertion of a catheter through the femoral artery into the left ventricle, using continuous pressure monitoring. The position of the left ventricular catheter was subsequently validated by post-mortem examination. A Swan-Ganz thermodilution catheter was inserted into the pulmonary arterial circulation using the left jugular vein.

Following the surgical preparation each animal was allowed to stabilize for 40 minutes.

Statham transducers were used for measuring mean arterial blood pressure (MABP) and pulmonary capillary wedge pressure (PCWP). The transducers were calibrated to zero at the mid-thoracic level. Heart rate (HR) and MABP were continuously recorded, while PCWP was determined prior to and between flow determinations. Data was recorded using a Hewlett-Packard monitor (Model 7758C) and a recorder (Model 7758A). Cardiac output was determined in duplicate prior to flow determinations. The cardiac output was measured by the thermodilution of 5 ml of room temperature physiological saline using an Edwards CO Computer (Model 9520A). A variation of five per cent or less between cardiac output measurements was accepted.

Core temperature was continuously measured using the thermistor on the thermodilution catheter.

Arterial PCO₂, PO₂ and pH were measured at 15 minute intervals and immediately preceding each flow determination. Blood was drawn from the femoral arterial catheter, analyzed on a Corning Blood Gas Machine, and temperature corrected. No flow studies were performed unless PaCO₂ was between 35 and 43 mmHg. pH was kept similar to control values by the IV infusion of NaHCO₃.

Dogs were initially fluid loaded with physiological saline solution at 38° C to a PCWP > 4 mmHg. Subsequent fluid administration was based on PCWP and MABP. If PCWP dropped below control values or if MABP decreased to < 100 mmHg, physiologic saline solution was administered.

Following the stabilization period, control spinal cord and dural arterial blood flow were measured by the radioactive microsphere technique. This method of measuring regional blood flow has been previously described as an accurate and reproducible technique¹⁰⁻¹² and has been extensively used in our laboratory. A suspension of 6-10 × 10⁶ microspheres (3M Company) 15 ± 0.5 microns in diameter, labelled with one of Cerium¹⁴¹, Chromium⁵¹ or Strontium⁸⁵ is thoroughly mixed in saline and injected over ten seconds into the left ventricle. Just prior to injection, withdrawal of blood from the femoral artery was started using a Harvard withdrawal pump (Model 940) and contin-

TABLE II Arterial blood gases, pH and temperature in dogs prior to and following intrathecal injection

Groups	PaO_2 (mmHg)	$PaCO_2$ (mmHg)	pH	Temperature (°C)
<i>Saline</i>				
Pre-injection	521 ± 23	40 ± 1	7.37 ± 0.01	37.8 ± 0.3
20 min post-injection	503 ± 29	35 ± 1	7.38 ± 0.03	38.2 ± 0.2
40 min post-injection	495 ± 4	37 ± 1	7.37 ± 0.02	38.3 ± 0.1
<i>Tetracaine</i>				
Pre-injection	482 ± 18	39 ± 1	7.38 ± 0.02	37.9 ± 0.1
20 min post-injection	481 ± 17	39 ± 1	7.34 ± 0.02	37.6 ± 0.1
40 min post-injection	456 ± 22	40 ± 1	7.35 ± 0.01	37.9 ± 0.1
<i>Tetracaine with epinephrine</i>				
Pre-injection	483 ± 9	39 ± 1	7.36 ± 0.02	38.3 ± 0.1
20 min post-injection	472 ± 12	39 ± 1	7.32 ± 0.02	38.0 ± 0.1
40 min post-injection	449 ± 19	40 ± 2	7.30 ± 0.02	37.9 ± 0.1

n = 6 in each group.

Results are Mean ± S.E.M.

No significant difference.

used for 30 seconds after completion of the injection into the left ventricle. The isotope emissions from blood and tissue samples were determined using a Searle Mark III scintillation counter. Radioactive counts in the arterial blood were used as the reference to calculate blood flow to the spinal cord and dura. By comparing microsphere counts trapped in the tissue to counts in the arterial blood supplying that tissue (arterial reference sample), we were able to calculate regional tissue blood flow. Three blood flow determinations to each tissue were made using the three different radioactive microsphere labels.

Following control blood flow measurements, a lumbar dural puncture was performed at the L5-L6 or L6-L7 interspace using a 22 gauge spinal needle. Successful dura penetration was demonstrated by the free flow of one to two drops of cerebral spinal fluid from the needle hub. Animals were randomly assigned to receive one of three solutions intrathecally:

- Physiologic saline – 5 ml;
- 0.4 per cent tetracaine (20 mg) in physiologic saline – 5 ml;
- 0.4 per cent tetracaine (20 mg) with 1/25,000 epinephrine (200 µg) in physiologic saline – 5 ml.

All solutions were injected at 37° C. The rate of injection was standardized at 0.5 ml per second.

Following intrathecal injection, the needle was removed, the dogs were placed supine, and the table levelled. Blood flow measurements were performed at 20 and 40 minutes after intrathecal injection.

Following the spinal flow measurements, the animals were sacrificed by the intravenous injection of saturated KCl solution. The spinal cord and dura were removed intact, and divided into cervical, thoracic and lumbosacral regions. The dura was dissected from the spinal cord and microsphere counts performed on each cord and dural specimen. Blood flow to the spinal cord and dural areas was calculated as described.

All data were analyzed using analysis of variance and Student's paired and unpaired T-tests where appropriate. The data are presented as a mean value ± standard error of the mean. A value of $p < 0.05$ is considered to be significant.

Results

In all groups HR, and PCWP were initially similar and did not significantly change during the study period (Table I). Dogs receiving tetracaine with epinephrine had a tendency to higher PCWP's because of greater fluid infusion required to maintain MABP > 100 mmHg. Initial cardiac index (CI) in the three groups were not statistically different, however, the CI's tended to be lower in the control group than in the other two groups. No specific

TABLE III Spinal cord blood flow in dogs prior to and following intrathecal injection

Groups	Regional flow (ml·100 gm ⁻¹ ·min ⁻¹)		
	Cervical cord	Thoracic cord	Lumbo-sacral cord
<i>Saline</i>			
Pre-injection	26 ± 3	21 ± 3	32 ± 5
20 min post-injection	26 ± 5	22 ± 3	39 ± 9
40 min post-injection	20 ± 2	19 ± 2	35 ± 10
<i>Tetracaine</i>			
Pre-injection	17 ± 2	15 ± 2	21 ± 2
20 min post-injection	22 ± 9	21 ± 5	47 ± 12*
40 min post-injection	24 ± 9	25 ± 7	55 ± 13*
<i>Tetracaine with epinephrine</i>			
Pre-injection	20 ± 3	16 ± 2	24 ± 2
20 min post-injection	16 ± 1	20 ± 3	24 ± 5
40 min post-injection	15 ± 1	18 ± 3	23 ± 6

n = 6 in each group.

Results are Mean ± S.E.M.

*p < 0.05 compared to pre-injection measurements.

reason for this occurrence could be found. In dogs receiving subarachnoid tetracaine with epinephrine a significant increase in cardiac index occurred at 20 and 40 minutes following injection. The increase in CI was secondary to fluid infusion and the systemic absorption of epinephrine in this group. Mean arterial blood pressure fell significantly in dogs receiving subarachnoid tetracaine or tetracaine with epinephrine at 20 and 40 minutes following injection.

PaO₂, PaCO₂, pH and temperature were not statistically different in the three groups during the study (Table II).

Pre-injection measurements of spinal cord and spinal dural blood flow were not significantly different in any given region in the three groups. Animals receiving subarachnoid physiologic saline did not demonstrate a statistically significant change in spinal cord (Table III) or dural (Table IV) blood flow in any region when compared to the pre-injection period. Dogs given intrathecal tetracaine demonstrated a significant lumbosacral spinal cord hyperemia (123 and 162 per cent respectively), at 20 and 40 minutes post-injection. Lumbosacral spinal cord blood flow increased in all dogs receiving subarachnoid tetracaine. The magnitude of

individual increases at 40 minutes following subarachnoid tetracaine ranged from 13 to 315 per cent. The variable increases in flows following subarachnoid tetracaine are reflected in the standard errors of the means. Blood flow to the cervical and thoracic spinal cord tended to increase following tetracaine but did not reach statistical significance. In dogs receiving subarachnoid tetracaine with epinephrine no change in spinal cord blood flow occurred over time in any region when compared to the pre-injection values.

A significant increase in thoracic and lumbosacral dural blood flow of 108 and 292 per cent respectively, occurred at 20 minutes following subarachnoid tetracaine. At 40 minutes the increases were 152 and 315 per cent respectively. Cervical dural blood flow was increased 91 per cent at 40 minutes following tetracaine injection. Dogs receiving subarachnoid tetracaine with epinephrine did not demonstrate any significant change in dural blood flow following injection.

Discussion

PaCO₂¹³ and temperature,¹⁴ important variables known to effect spinal cord blood flow were closely controlled in the present study. PaO₂ was kept above 100 mmHg by ventilating the animals with 100 per cent O₂.

The induction of spinal anaesthesia produced a significant decrease in mean arterial blood pressure in dogs receiving subarachnoid tetracaine and tetracaine with epinephrine. The mean arterial blood pressure, however, remained above 90 mmHg in both groups. Since spinal cord blood flow remains constant with blood pressures between 60 and 160 mmHg in dogs, the decrease seen in MABP should, in itself, not effect spinal cord blood flow.¹⁵

Spinal cord blood flow in the cervical, thoracic and lumbosacral regions in our dogs prior to intrathecal injections were similar to previously published results.¹⁶ Similarly spinal dural blood flow was comparable to previously published results from our laboratory.⁹

The dose of tetracaine (i.e., 20 mg) chosen in the present study is the maximum dose used clinically for spinal anaesthesia in man. We elected to start with this high dose to see if an effect was present in dogs. The dose of adjunctive epinephrine used (i.e., 200 µg) is the commonly recommended clinical dose for spinal anaesthesia. When mixed with

TABLE IV Spinal dural blood flow in dogs prior to and following intrathecal injection

Groups	Regional flow (ml·100 gm ⁻¹ ·min ⁻¹)		
	Cervical dura	Thoracic dura	Lumbo-sacral dura
<i>Saline</i>			
Pre-injection	3.9 ± 0.8	3.7 ± 0.5	4.3 ± 0.5
20 min post-injection	5.2 ± 1.6	5.1 ± 1.2	5.1 ± 1.1
40 min post-injection	4.5 ± 1.3	4.6 ± 1.1	5.1 ± 0.8
<i>Tetracaine</i>			
Pre-injection	5.7 ± 1.6	4.8 ± 1.2	4.9 ± 1.1
20 min post-injection	9.4 ± 2.0	10.0 ± 2.2*	19.2 ± 5.1*
40 min post-injection	10.9 ± 2.0*	12.1 ± 2.8*	20.4 ± 5.1*
<i>Tetracaine with epinephrine</i>			
Pre-injection	6.2 ± 1.2	4.2 ± 0.8	4.3 ± 0.6
20 min post-injection	6.0 ± 0.9	3.6 ± 0.8	4.7 ± 1.1
40 min post-injection	4.7 ± 0.7	3.0 ± 0.4	3.7 ± 0.8

n = 6 in each group.

Results are Mean ± S.E.M.

*p < 0.05 compared to pre-injection measurements.

saline the final concentration of tetracaine was 0.4 per cent and that of epinephrine was 1/25,000. Although total dose is an important factor in determining the extent and duration of spinal anaesthesia the regional effect at any spinal cord level is probably related to regional concentration. The initial concentration of drug in the C.S.F. is dependent on the volume and concentration injected, local dilution by C.S.F., and the regional tissue uptake. The actual concentration to which the spinal cord is exposed will therefore be lower than the injected concentration.

The mechanism by which tetracaine produces an increase in the spinal cord blood flow is unknown. Possible mechanisms may be related to sympathetic vascular deafferentation, a direct vascular effect or both. The mechanism remains to be elucidated.

Cervical, thoracic and lumbosacral spinal dural blood flow remained unchanged following subarachnoid 0.9 per cent saline. In a previous study we reported a significant increase in lumbosacral dural blood flow following subarachnoid administration of 0.9 per cent saline.⁹ The difference in dural response to 0.9 per cent saline appears to be related to the temperature of the injectate. Subarachnoid injection of 5 ml of 0.9 per cent saline at

20° C produced a dural hyperemia while 5 ml of 0.9 per cent saline at 37° C used in the present study had no significant effect. Temperature of injectate therefore, appears to be an important variable influencing dural blood flow. Tetracaine had a marked vasodilatory effect on the dural circulation. The mechanisms by which tetracaine produces vasodilation of the dural circulation are unknown, but may be similar to those proposed for the spinal cord circulation.

Subarachnoid injection of tetracaine with epinephrine (200 µg) did not significantly change spinal cord or spinal dural blood flow. Flows in the spinal cord and spinal dural remained similar to pre-injection values. The mechanisms of action of epinephrine on the circulation of the intact spinal cord are presently unclear.

The addition of epinephrine 200 µg to subarachnoid tetracaine prevented the spinal cord and dural hyperemia seen with tetracaine alone. Spinal cord blood flow, however, did not decrease below pre-injection values with the addition of epinephrine (200 µg).

Our study suggests that the mechanism of epinephrine augmented prolongation of tetracaine spinal anaesthesia is through prevention of tetracaine

induced spinal cord and spinal dural vasodilation. By preventing vasodilation, epinephrine would limit the rate of tetracaine uptake permitting a higher and more prolonged CSF tetracaine concentration following subarachnoid injection. These results appear to explain the clinical effect of a neural blockade which is several segments higher and more prolonged when tetracaine spinal anaesthesia is augmented with epinephrine.

The addition of epinephrine to tetracaine spinal anaesthesia is claimed to prolong the duration of anaesthesia by a mean of 50 per cent. However, in clinical practise the response is variable ranging from minimal to > 100 per cent prolongation.

The variability of spinal cord blood flow responses to intrathecal tetracaine seen in our study may help explain why the prolongation of block with the addition of epinephrine is highly variable. If the spinal cord circulation dilates markedly with tetracaine then the addition of epinephrine would prolong the duration of spinal anaesthesia. If, on the other hand, the vasodilatory effect is minimal, the addition of epinephrine may have little effect. Unfortunately at present we have no way of predicting an individual response to subarachnoid tetracaine.

If the above concept is correct, then dural and epidural uptake of intrathecally administered tetracaine must be low. The relative influence of spinal cord hyperemia versus the dural hyperemia in regards to tetracaine uptake is at present unknown.

In conclusion, we have demonstrated that subarachnoid 0.4 per cent tetracaine (20 mg) produces a regional spinal cord and a generalized dural hyperemia in dogs. The hyperemia can be prevented by the use of adjunctive 1/25,000 epinephrine (200 µg) intrathecally. We propose that the mechanism by which epinephrine prolongs tetracaine spinal anaesthesia is through prevention of vasodilation rather than by vasoconstriction of the spinal cord circulation.

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Résumé

Le flux sanguin de la moelle épinière et de la duremère a été mesuré dans les régions cervicale, thoracique et lombo-sacrée par microsphère radioactive chez 18 chiens bâtards. Les mesures ont été effectuées avant, 20 et 40 minutes après l'injection rachidienne de l'un des produits suivants: 1) soluté physiologique, 2) tétracaïne 20 mg ou 3) tétracaïne 20 mg avec épinéphrine 200 µg. On n'a pas observé de changement notable de la perfusion médullaire ou de la duremère à la suite de l'injection du soluté physiologique ou de la tétracaïne avec épinéphrine. Les chiens qui ont reçu la tétracaïne sans épinéphrine ont présenté une augmentation de la perfusion de la moelle épinière au niveau lombo-sacré et de la perfusion de la duremère au niveau thoracique et lombo-sacré 20 et 40 minutes après l'injection. La perfusion duremérienne cervicale a montré une augmentation 40 minutes après l'injection de tétracaïne. L'injection subarachnoïdienne lombaire de tétracaïne (20 mg) produit une augmentation de la perfusion de la moelle épinière à ce niveau et une hyperémie généralisée de la duremère, phénomènes qui sont éliminés par l'addition d'épinéphrine à la solution (200 µg).