Spinal cord blood flow following subarachnoid lidocaine

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Twelve mongrel dogs were randomized into two equal groups. Cervical, thoracic and lumbosacral spinal cord and spinal dural blood flows were measured using the radioactive microsphere technique. Blood flow determinations were made prior to and 20 and 40 minutes following lumbar subarachnoid injection of: (1) two per cent lidocaine (100 mg) or (2) two per cent lidocaine (100 mg) with 1/25,000 epinephrine (200 μg). Dogs receiving subarachnoid lidocaine demonstrated a decrease in mean arterial blood pressure of 23 per cent and 14 per cent ($p < 0.05$), while dogs receiving lidocaine with epinephrine had a decrease of 38 and 34 per cent ($p < 0.05$) at 20 and 40 minutes respectively. Cardiac index was not significantly changed in either group. Lumbar subarachnoid lidocaine (100 mg) produced a rapid regional dural hyperemia (observed at 20 minutes postinjection) and a delayed regional spinal cord hyperemia (observed at 40 minutes postinjection) which were not observed following the addition of epinephrine (200 μg).

Key words

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

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Although lidocaine is a local anaesthetic commonly used for spinal anaesthesia, its effects on the spinal cord arterial circulation are unclear. Following systemic administration of lidocaine in therapeutic doses, decreases in cerebral blood flow and cerebral metabolism have been observed.[1] The effects of systemic administration of lidocaine on the spinal cord circulation are unknown; however, it has been assumed that the spinal cord effects of lidocaine may be similar to those observed in the brain.

The effects of lidocaine following direct application to vessels supplying neural tissue may differ significantly from the effects observed following systemic administration. Direct micro-application of lidocaine to cerebral pial arterioles has been observed to produce a dose-related vasodilation over a concentration range of 0.1–20 $mg \cdot mL^{-1}$.[2] Recently, Dohi *et al.*[3] reported, that 1 mL of five per cent lidocaine did not affect regional spinal cord blood flow at 20–30 minutes following subarachnoid administration in halothane anaesthesized dogs. However, the methodology used by Dohi *et al.* (hydrogen clearance technique) is associated with many artifacts when applied to the investigation of the spinal cord circulation and blood flow determinations may be unreliable.[4]

We have previously observed the differing effects of tetracaine and bupivacaine, two highly lipid soluble agents, on the spinal cord circulation in dogs.[5,6] The present study was undertaken to evaluate the effects of lidocaine, a local anaesthetic agent with a lower lipid solubility (in comparison to tetracaine and bupivacaine) on the spinal cord circulation over time. Since the effects of epinephrine when combined with lidocaine for spinal anaesthesia are unclear, spinal cord blood flow was determined following subarachnoid administration of lidocaine and lidocaine with epinephrine.

Methods

Guidelines for the humane treatment of laboratory

animals as outlined by the University of Manitoba were followed.

Twelve mongrel dogs of either sex were studied. The dogs weighed 15–31 kg (24 ± 5 kg ± SD). Anaesthesia was induced with intravenous pentobarbitone 30 $mg \cdot kg^{-1}$ and maintained with a pentobarbitone infusion of 2–5 mg/kg/hr. Following endotracheal intubation the dogs were ventilated with 100 per cent O_2, to a $PaCO_2$ of 35–42 torr.

Following surgery and while maintaining anaesthesia, each animal was allowed to stabilize over 40 minutes. Mean arterial blood pressure (MABP), mean pulmonary artery pressure (PAP) and heart rate (HR) were measured continuously. Pulmonary capillary wedge pressure (PCWP) was determined prior to and between flow determinations. Cardiac output (CO) was determined in duplicate prior to flow determinations.

All dogs were initially fluid loaded with 0.9 per cent saline solution at 38° C to achieve a PCWP of at least 4 mmHg. This PCWP was maintained by subsequent fluid administration as required.

Core temperature was continuously measured. $PaCO_2$, PaO_2 and pH were measured at 5–10 minute intervals and immediately preceding each flow determination. $NaHCO_3$ was infused to maintain the pH similar to control values.

Following the stabilization period, control arterial blood flows to both the spinal cord and the dura were measured by the radioactive microsphere technique.[7,8]

Following control blood flow measurements, a lumbar dural puncture was performed at the L_5-L_6 or L_6-L_7 interspace using a 22 gauge spinal needle. Free flow of one to two drops of cerebrospinal fluid from the needle hub assured successful dural penetration.

Animals were randomly assigned to receive one of two solutions intrathecally:

a two per cent lidocaine (100 mg) preservative-free – 5 ml.

b two per cent lidocaine (100 mg) preservative free with 1/25,000 epinephrine (200 μg) – 5.2 ml.

The common clinically used commercial preparation of epinephrine containing 0.1 per cent bisulfite was used in the present study.

Subarachnoid 0.9 per cent saline (5 ml) has been previously demonstrated by our laboratory as having no effect on SCBF and therefore a time control was not repeated.

All solutions were warmed to 37° C and injected at a standardized rate of 0.5 ml/sec. Following injection, the needle was removed and the dogs were placed supine. Blood flow measurements were performed at 20 and 40 minutes after intrathecal injection.

With flow measurements completed, the arterial line was opened, and the animals exsanguinated. The spinal cord and dura were removed *en bloc* and divided into cervical, thoracic, and lumbosacral regions. The dura was dissected from the spinal cord and microsphere counts were performed on each cord and dural specimen. Blood flow to the spinal cord and dural regions was calculated as previously described.[6]

The data were analyzed as follows: The assumptions of an analysis of variance were tested using Tukey's Test and Bartlett's Test. Logarithmic transformations were performed on data with non-homogeneous variances. Repeated measures ANOVA was then performed on paired data, while unpaired data was analyzed using a completely randomized ANOVA. Multiple comparisons were performed where the effect was significant. 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 both groups PCWP was initially similar and did not change significantly during the study (Table I). Heart rate (HR) was initially similar in both groups but decreased significantly (26 per cent) at 20 minutes in dogs receiving subarachnoid lidocaine. HR did not change significantly in dogs receiving subarachnoid lidocaine with epinephrine. Cardiac index (CI) in the two groups was initially similar. There was a tendency for CI to increase in dogs receiving lidocaine with epinephrine; however, it did not reach statistical significance. The tendency was presumably secondary to systemic absorption of epinephrine and a direct myocardial effect. Mean arterial blood pressure (MABP) decreased significantly in both groups following subarachnoid injection. MABP decreased 23 and 14 per cent at 20 and 40 minutes respectively in dogs receiving subarachnoid lidocaine and 38 and 34 per cent at 20 and 40 minutes respectively in dogs receiving lidocaine with epinephrine.

PaO_2, $PaCO_2$, pH and temperature values were

TABLE I Haemodynamic parameters before and after intrathecal injection (mean ± SEM)

Groups	*MABP (mmHg)*	*PCWP (mmHg)*	*CI (ml/kg/min)*	*H.R. (beats/min)*
Lidocaine (n = 6)				
Preinjection	123 ± 2	7 ± 1	230 ± 32	149 ± 5
20 min postinjection	93 ± 5*	7 ± 1	204 ± 35	110 ± 6*
40 min postinjection	106 ± 3*	7 ± 1	203 ± 36	129 ± 6
Lidocaine with epinephrine (n = 6)				
Preinjection	123 ± 4	8 ± 1	185 ± 20	173 ± 7
20 min postinjection	76 ± 6*	10 ± 1	240 ± 18	150 ± 6
40 min postinjection	82 ± 5*	8 ± 1	228 ± 32	153 ± 8

*$p < 0.05$ when compared to preinjection measurements.

not statistically different in the two groups during the study (Table II).

Preinjection measurements of spinal cord and spinal dural blood flow were not significantly different in any given region in the two groups (Tables III, IV). In dogs receiving subarachnoid lidocaine, cervical and thoracic spinal cord blood flow remained unchanged from control values. Lumbosacral spinal cord blood flow did not change significantly at 20 minutes post lidocaine injection; however, blood flow increased significantly (138 per cent) at 40 minutes. In dogs receiving subarachnoid lidocaine with epinephrine, no change in spinal cord blood flow occurred over time in any region when compared to preinjection values.

A significant increase in lumbosacral dural blood flow of 232 and 234 per cent occurred at 20 and 40 minutes respectively following subarachnoid lidocaine. In dogs receiving lidocaine with epinephrine no significant change in dural blood flow was observed following injection.

Discussion

In clinical practice the addition of epinephrine to lidocaine spinal anaesthesia does not result in a greater extent of blockade, nor does it decrease the rate of two and four segment regression of sensory blockade. Adding epinephrine to lidocaine spinal anaesthesia is therefore felt to have no effect on clinically useful spinal anaesthesia (as defined above). Adding epinephrine to lidocaine spinal anaesthesia has, however, been demonstrated to prolong the total duration of sensory and possibly motor blockade near the site of injection.[9–11]

Pharmacokinetic data in humans following subarachnoid lidocaine (five per cent) with and without epinephrine suggest that peak plasma concentrations (C_{max}) are lower when epinephrine is added; however, the remaining pharmacokinetic parameters are unchanged.[11] The time taken to achieve peak plasma concentrations (T_{max}) ranged from 58 ± 24 minutes to 71 ± 29 minutes for lidocaine with epinephrine and lidocaine plain respectively,

TABLE II Arterial blood gases, pH and temperature before and after intrathecal injection (mean ± SEM)

Groups	*PaO_2 (mmHg)*	*$PaCO_2$ (mmHg)*	*pH*	*Temperature (°C)*
Lidocaine (n = 6)				
Preinjection	451 ± 26	38 ± 1	7.43 ± 0.01	38.0 ± 0.3
20 min postinjection	447 ± 11	36 ± 2	7.42 ± 0.02	37.9 ± 0.3
40 min postinjection	445 ± 24	39 ± 1	7.39 ± 0.02	38.0 ± 0.3
Lidocaine with epinephrine (n = 6)				
Preinjection	444 ± 19	39 ± 1	7.42 ± 0.01	38.3 ± 0.2
20 min postinjection	439 ± 16	40 ± 1	7.38 ± 0.04	38.3 ± 0.3
40 min postinjection	436 ± 10	38 ± 1	7.40 ± 0.02	38.4 ± 0.3

No significant difference

TABLE III Spinal cord blood flow before and after intrathecal injection (mean ± SEM)

	Regional flow (ml/100 gm/min)		
Groups	*Cervical cord*	*thoracic cord*	*Lumbo-sacral cord*
Lidocaine (n = 6)			
Preinjection	16 ± 2	13 ± 2	21 ± 2
20 min postinjection	13 ± 2	12 ± 2	35 ± 7
40 min postinjection	13 ± 1	13 ± 1	50 ± 9*
Lidocaine with epinephrine (n = 6)			
Preinjection	22 ± 4	17 ± 3	30 ± 4
20 min postinjection	20 ± 3	12 ± 1	24 ± 4
40 min postinjection	19 ± 2	13 ± 3	36 ± 9

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

suggesting a slow absorption of lidocaine from the subarachnoid space.

The present study suggests that adding epinephrine to lidocaine spinal anaesthesia may limit the uptake of lidocaine by preventing spinal cord vasodilation. In view of the delayed vasodilatory effect of lidocaine the immediate uptake following subarachnoid injection of lidocaine may not be significantly altered by epinephrine.[12] The clinical result is no appreciable effect on extent and initial regression of neural block.

The delayed vasodilatory response to lidocaine (seen at 40 minutes) which is prevented by the addition of epinephrine may result in a higher and prolonged regional lidocaine concentration. Clinically the effect could be translated into prolongation of blockade in the lumbosacral region of the spinal cord following lumbar subarachnoid administration.

Previous work has suggested that prolongation of the total duration of sensory blockade by epinephrine may be secondary to a direct antinociceptive effect (at the dorsal horn) rather than a vascular effect.[13–15] Although this concept may be correct our data suggest that a vascular component may also contribute to prolongation of sensory blockade.

Whether or not prolongation of motor blockade occurs following subarachnoid lidocaine with epinephrine is debated. Recent data suggests that the total duration of motor blockade is prolonged in humans following lidocaine spinal anaesthesia when epinephrine is added.[11] The prolongation of motor blockade by a direct effect of epinephrine on the spinal cord is extremely unlikely with the dosage used in the human studies (150 μg). In Rhesus monkeys a subarachnoid dose of epinephrine of $0.3\ mg \cdot kg^{-1}$ was required before motor abnormalities became apparent.[16] The prolonged motor block following subarachnoid lidocaine with epinephrine can, however, be explained on the

TABLE IV Spinal dural blood flow in dogs before and after intrathecal injection (mean ± SEM)

	Regional flow (ml/100 gm/min)		
Groups	*Cervical dura*	*thoracic dura*	*Lumbo-sacral dura*
Lidocaine (n = 6)			
Preinjection	5.6 ± 1.8	3.6 ± 0.8	5.0 ± 0.8
20 min postinjection	5.2 ± 0.8	7.1 ± 1.8	16.6 ± 3.4*
40 min postinjection	5.4 ± 1.6	6.2 ± 1.4	16.7 ± 2.3*
Lidocaine with epinephrine (n = 6)			
Preinjection	3.7 ± 0.6	2.9 ± 0.2	4.3 ± 0.8
20 min postinjection	4.0 ± 1.1	1.8 ± 0.5	1.6 ± 0.6
40 min postinjection	3.6 ± 1.0	1.7 ± 0.5	2.3 ± 0.7

*$p < 0.05$ compared to preinjection measurements

basis of a decreased regional vascular uptake of lidocaine when epinephrine is added.

Subarachnoid administration of lidocaine (five per cent) in 7.5 per cent dextrose solution has been observed to produce high regional CSF lidocaine concentrations. Regional CSF lidocaine concentrations of 10200 $\mu g \cdot ml^{-1}$ and 550 $\mu g \cdot ml^{-1}$ have been reported at 2 and 30 minutes respectively following the subarachnoid administration of five per cent lidocaine (250 mg) in humans.[17] Although CSF concentrations of lidocaine were not measured in the present study it appears likely that high regional concentrations were present following the subarachnoid administration of two per cent lidocaine (100 mg) in dogs.

Direct microapplication of lidocaine in concentrations of 100 $\mu g \cdot ml^{-1}$ and greater to rat cerebral pial arterioles produces a concentration related vasodilation.[2] The concentration of lidocaine in the CSF of dogs in the present study should have greatly exceeded 100 $\mu g \cdot ml^{-1}$ for over 30 minutes. The dose response curve for regional spinal cord blood flow following subarachnoid lidocaine is unknown, but may parallel that of lidocaine on cerebral pial vessels. Since access of lidocaine to the arterioles within the spinal cord substance is required for a pharmacological effect on regional spinal cord blood flow, diffusion may be a major determinant accounting for the observed delay in vasodilatory response.[18]

Total regional spinal cord blood flow is dependent on the combined blood flow to the regional white and grey matter. In the lumbar region of the spinal cord the ratio of central grey matter to peripheral white matter is higher than in other spinal cord regions.[19] Since blood flow to the central grey matter exceeds that of the peripheral white matter by a ratio of 3:1 in the lumbar spinal cord of dogs,[20] the overall regional blood flow response to pharmacological intervention may be significantly affected by changes in grey matter flow.

Following the application of lidocaine topically to the spinal cord (subarachnoid injection) a concentration gradient for the drug is established. The concentration achieved in the central grey matter will be dependent on the concentration gradient of unbound drug, rate of diffusion and rate of uptake. Direct entry into the spinal cord via perivascular channels does not appear to play a major role in the access of lidocaine into the cord substance.[18]

One of the main pharmacological properties influencing the diffusion of local anaesthetics into the spinal cord substance appears to be lipid solubility.[21] Subarachnoid lidocaine in equipotent doses to tetracaine (an agent 27-fold more lipid soluble)[22] appears to have a similar intrinsic vasodilatory effect on the spinal cord. The vasodilatory effect of lidocaine is, however, delayed, being observed at 40 minutes but not 20 minutes, while the vasodilatory effect with tetracaine was observed at both 20 and 40 minutes following subarachnoid administration.[5] The studies suggest that the difference in onset time of vasodilation between lidocaine and tetracaine may be related to differences in lipid solubility.

The observed response of the dural circulation to a high regional concentration of lidocaine is rapid vasodilation. The observed dural arteriolar vasodilatory response to lidocaine is similar to that seen in peripheral vascular beds.[23]

Adding epinephrine to lidocaine spinal anaesthesia resulted in no significant change in spinal cord and dural blood flows from control values. The mechanisms of apparent antagonism of lidocaine induced spinal cord arteriolar vasodilation by epinephrine is unclear.

In summary the study has demonstrated the effects of 2% lidocaine (100 mg) with and without epinephrine (200 μg) on the spinal cord circulation in dogs. The relevance of the present study to the clinical use of lidocaine spinal anaesthesia has been discussed. Possible mechanisms accounting for the observed delayed response of the spinal cord blood flow to lidocaine have been outlined. The present study suggests the need for further research relating to the regional spinal cord circulatory and metabolic effects of agents following subarachnoid administration.

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Résumé

Douze chiens bâtards ont été randomisés en deux groupes égaux. Utilisant des microsphères radioactives, les flots sanguins dans la moelle épinière, dans les régions cervicales, thoraciques et lombosacrées ainsi que celles de la dure-mère ont été étudiés. La détermination des flots sanguins a été faite avant ainsi que de 20 et 40 minutes après injection sous-arachnoïdienne lombaire de: 1) deux pour cent de lidocaïne (100 mg) ou 2) deux pour cent de lidocaïne (100 mg) avec 1/25,000 épinephrine (200 μg). Après injection sous-arachnoidienne, la pression artérielle moyenne a diminué significativement dans les deux groupes. Les chiens ayant reçu une injection sous-arachnoidienne de lidocaïne ont démontré une diminution de 23 pour cent et de 14 pour cent du flot sanguin respectivement à 20 et 40 minutes. Les chiens ayant reçu une injection sous-arachnoidienne de lidocaïne avec épinephrine ont présenté une diminution de 38 pour cent et de 34 pour cent a 20 et 40 minutes respectivement. L'index cardiaque n'était pas changé significativement dans les deux groupes. Aucun changement significatif dans le flot sanguin de la dure-mère n'est survenu après injection sous-arachnoidienne de lidocaïne avec épinephrine. Les chiens ayant reçu une injection sous-arachnoidienne de lidocaïne ont démontré une augmentation significative du flot sanguin de la mœlle épinière dans la région lombosacrée 40 minutes après l'injection. Le flot sanguin de la duremère dans la région lombosacrée a augmenté significativement à 20 et 40 minutes après injection. L'injection sous-arachnoïdienne lombaire de lidocaïne (100 mg) produit une hypérémie rapide dans la dure-mère ainsi qu'une hypérémie tardive régionale qui sera prévenue par l'addition d'épinephrine (200 μg).