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Clonidine prolongs canine tetracaine spinal anaesthesia

Using a randomized blind cross-over design, the comparative efficacy of clonidine in prolonging tetracaine spinal anaesthesia was studied in six mongrel dogs.

Lumbar subarachnoid injections (1 ml) of: tetracaine 4 mg with clonidine 150 μg, tetracaine 4 mg with epinephrine 200 μg, tetracaine 4 mg, clonidine 150 μg, epinephrine 200 μg, and five per cent dextrose in H₂O (vehicle) were administered randomly to each animal at 5–7 day intervals.

Subarachnoid tetracaine produced a motor blockade of 186 ± 58 (mean ± SEM) min. Both clonidine and epinephrine produced a similar prolongation of tetracaine motor blockade, 135 per cent (p < 0.01) and 116 per cent (p < 0.05) respectively, compared with tetracaine alone. No motor blockade was observed in dogs receiving clonidine, epinephrine or five per cent dextrose in H₂O. The addition of clonidine to tetracaine spinal anaesthesia produced a significant increase in duration of sensory blockade, 56 per cent (p < 0.01) and 107 per cent (p < 0.01) respectively, when compared to tetracaine with and without epinephrine. Subarachnoid clonidine alone produced a sensory blockade of 76 ± 17 minutes, while only one animal receiving subarachnoid epinephrine had a sensory blockade (40 minutes). No neurologic deficits were observed in any of the animals.

The study concludes that during spinal anaesthesia with tetracaine in dogs, clonidine is as effective as epinephrine in prolonging motor blockade, but is more effective in prolonging sensory blockade.

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Spinal anaesthesia was introduced by August Bier in 1898 and vasoconstrictors were first introduced to prolong spinal anaesthesia by Braun in 1900.[1] Bier[2] and Heinke and Lawen,[3] among others, used epinephrine intrathecally with cocaine in order to prolong the duration of spinal anaesthesia.

Since the initial introduction, the use of vasoconstrictors to prolong spinal anaesthesia has caused controversy among anaesthetists. Bonica *et al.*[4] found that phenylephrine and epinephrine both increased the duration of motor and sensory blockade by 50 per cent, while the effects of ephedrine were much less pronounced. Moore and Bridenbaugh[5] looked at 8,852 patients who had vasoconstrictor drugs injected into the subarachnoid space along with the local anaesthetic solution. In their study epinephrine extended the duration of anaesthesia by 50 per cent compared with 100 per cent for phenylephrine. A recent study by Feldman and Covino[6] examined the effect of vasoconstrictor agents in prolonging the duration of spinal anaesthesia in the dog. Their results showed a 58 per cent increase in duration of motor blockade following subarachnoid administration of tetracaine with epinephrine and a 22.5 per cent increase using phenylephrine when compared with a control solution of plain tetracaine.

Kozody *et al.*[7,8] proposed a hypothesis to explain why epinephrine and phenylephrine prolong the duration of clinically useful tetracaine but not lidocaine or bupivacaine spinal anaesthesia.[9,10] They suggested that a vasopressor mediated inhibition of local anaesthetic-induced regional spinal cord and dural arteriolar vasodilation may be partially responsible for the prolonged duration of tetracaine spinal anaesthesia when epinephrine is used as an adjunct. Vasoconstrictors are believed to affect the absorption of various local anaesthetics to varying degrees depending on the intrinsic vasodilatory activity and lipid solubility of the agent

used. Pharmacologically decreased absorption produces a prolonged regional effect.[7]

Animal studies have demonstrated that the intrathecal injection of alpha-receptor agonists produce analgesia which depending on the agonist, may be comparable to opiate-induced analgesia.[11] Clonidine, a predominantly alpha$_2$ adrenoceptor agonist with some alpha$_1$ stimulating properties, has been shown to have a marked analgetic effect when administered intrathecally.[12,13] Following parenteral clonidine administration, vasoconstriction occurs predominantly via postsynaptic alpha$_2$ adrenoceptor stimulation.[14] Theoretically the pharmacodynamic properties of clonidine would make it a useful adjunct to spinal anaesthesia based on the two proposed mechanisms. The present study was therefore undertaken to assess the comparative efficacy of clonidine and epinephrine in prolonging tetracaine spinal anaesthesia in dogs.

Methods
Guidelines for the humane treatment of laboratory animals as outlined by the Canadian Council on Animal Care were followed. Six mongrel dogs of either sex weighing 17 kg were studied using a randomized blind cross-over design. Following induction of anaesthesia (intravenous thiopentone 15–30 mg·kg^{-1}) and tracheal intubation, the animals were placed on an operating table in the right lateral decubitus position with a 10° head-up table tilt. Anaesthesia was maintained with $N_2O:O_2$ (2:1) and isoflurane (1.5–2 per cent). The low back region (L_1–S_1) was shaved and the skin prepared with povidone iodine. The lumbar region was draped and a lumbar puncture was attempted with a 22 gauge 3½-inch spinal needle at the L_6–L_7 interspace. If this was unsucessful a repeat attempt was performed at the L_5–L_6 interspace. Successful dural puncture was confirmed by the free flow of one to two drops of CSF from the needle hub.

Each animal received the following solutions in 1 ml D5/W in a randomized order at five- to seven-day intervals: tetracaine 4 mg, tetracaine 4 mg with clonidine 150 μg, tetracaine 4 mg with epinephrine 200 μg, clonidine 150 μg, epinephrine 200 μg or five per cent dextrose H_2O (vehicle). Following completion of the subarachnoid injection, anaesthesia was discontinued and the animals were allowed to recover in the right lateral decubitus position.

Time from intrathecal injection to arousal was recorded for each animal and on awakening the endotracheal tube was removed. Following arousal the animals were assessed for motor and sensory blockade at 20-minute intervals for one hour and at 15-minute intervals thereafter. The end point for recovery of motor function was the ability of the animal to stand unsupported on its hind limbs.

Sensory blockade was assessed using a modified method of Eger et al.[15] A ten-inch rubber shod haemostat was applied (first rachet) longitudinally to the proximal one third of the shaved tail. The haemostat was moved continuously for a 60 second application or until an avoidance response was elicited. A reproducible avoidance response was interpreted as a return of sensation. All assessments of motor and sensory blockade were performed by an observer unaware of the drug administered. Following regression of motor and sensory blockade the animals were returned to the central animal boarding facilities and observed for a five- to seven-day period.

The data were analyzed using a one way analysis of variance with post-ANOVA multiple comparisons being performed, using Duncan's Test. A value of $p < 0.05$ was considered statistically significant.

Results
The time from subarachnoid injection to arousal was 19 ± 2 (mean $\pm$ SEM) minutes. Although a tendency for prolonged somnolence was observed in animals receiving subarachnoid tetracaine with clonidine and clonidine alone, no significant difference was observed between the groups (Figure 1). One dog in the clonidine group was eliminated from the study, because of prolonged time to arousal (> 90 min) and inability to assess sensory function. The prolonged time to arousal was the result of increased anaesthetic induction requirement necessitating a total dose of thiopentone exceeding 40 mg·kg^{-1}.

Subarachnoid tetracaine produced a hindlimb motor blockade of 186 ± 58 min (Figure 2). The addition of clonidine and epinephrine to the tetracaine solution produced a similar significant prolongation of motor blockade, 438 ± 37 min and 402 ± 63 min respectively. The values represent a 135 per cent ($p < 0.01$) and 116 per cent ($p < 0.05$) respective increase in motor blockade duration when
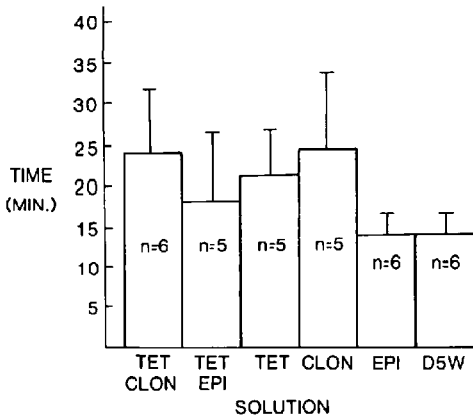
FIGURE 1   Time to arousal. TET CLON: tetracaine 4 mg with clonidine 150 μg. TET EPI: tetracaine 4 mg with epinephrine 200 μg. TET: tetracaine 4 mg, CLON: clonidine 150 μg, EPI: epinephrine 200 μg, D5W: 5% dextrose H_2O (vehicle). No significant difference.
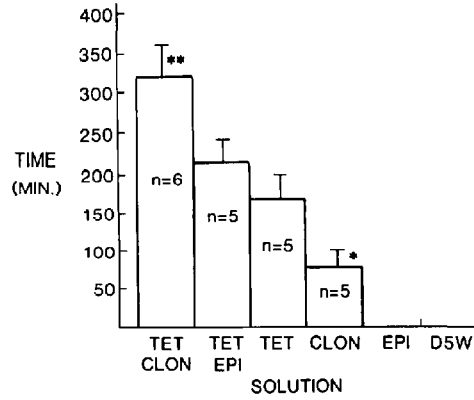

FIGURE 3   Duration of sensory blockade. (Abbreviations as in Figure 1). Results expressed as mean ± SEM. *p < 0.05. **p < 0.01 compared with tetracaine plain.
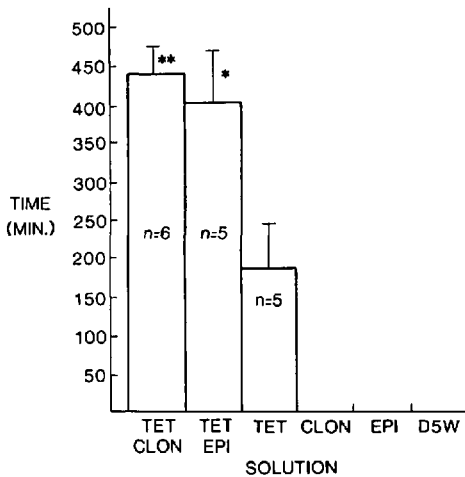

FIGURE 2   Duration of motor blockade. (Abbreviations as in Figure 1). Results expressed as mean ± SEM. *p < 0.05. **p < 0.01 compared with tetracaine plain.

compared with the plain tetracaine solution. One animal was eliminated from each of the tetracaine and tetracaine with epinephrine groups because of the absence of motor blockade on arousal. No hindlimb motor blockade was observed in dogs receiving clonidine, epinephrine or D5/W. In dogs

receiving subarachnoid clonidine a temporary jumping hindlimb gait was observed in four of the five dogs. The remaining animal, an elderly dog with a lethargic gait demonstrated a temporary improvement in gait, which became similar to that observed in healthy young dogs.

Subarachnoid tetracaine produced a sensory blockade of 156 ± 23 minutes (Figure 3). The addition of epinephrine to tetracaine spinal anaesthesia produced a non-significant prolongation of sensory blockade (207 ± 23 min). Clonidine when added to tetracaine spinal anaesthesia produced a significant increase in duration of sensory blockade (323 ± 31 min) compared with tetracaine alone or tetracaine with epinephrine. The respective increases were 107 per cent (p < 0.01) and 56 per cent (p < 0.01). Subarachnoid clonidine alone produced a sensory blockade of 76 ± 17 minutes. One animal receiving subarachnoid epinephrine alone had a sensory blockade of 40 minutes, while no animals receiving subarachnoid five per cent dextrose in H_2O had sensory blockade.

Gross neurologic assessment of the animals between injections and at the completion of the study was normal.

Discussion

A recurrent problem with studies comparing the duration of motor and especially sensory blockade following spinal anaesthesia is the lack of stan-

dardization of assessment. Duration has been assessed in a number of differing ways including: time to two-segment or four-segment regression of analgesia, time to disappearance of adequate operative analgesia, time to regression of motor blockade, or time to first administration of postoperative analgesic. Careful standardization of assessment and the use of a randomized double-blind methodology is necessary for a true comparison. In our study, the method of sensory assessment used would be considered equivalent to time to regression of adequate operative analgesia. The duration of non-operative "analgesia" although not addressed in the present study, may be prolonged with subarachnoid clonidine, compared with other alpha adrenergic agonists.[13] The 56 per cent increase in duration of sensory blockade to a surgical stimulus seen with tetracaine plus clonidine versus tetracaine with epinephrine, could offer additional benefits in the form of prolonged postoperative analgesia.

Clonidine may prolong the sensory blockade observed with tetracaine through a spinal cord presynaptic alpha$_2$ adrenoceptor mechanism, a post-synaptic alpha$_2$ adrenoceptor arteriolar effect and/or a supraspinal alpha$_2$ antinociceptive action. Nociceptive sensory input has been shown in previous studies to be associated with central and spinal adrenergic neurons.[11,12] Regions in the rat CNS where alpha$_2$ binding sites are found are innervated by norepinephrine and epinephrine containing neurons. The neurophysiological functions of the various brain regions having high densities of alpha$_2$ binding sites correlate with the various pharmacologic effects of clonidine. In a study by Luttinger et al.[16] subcutaneous clonidine elicited antinociception, and this effect was attenuated by pretreatment with the alpha$_2$ adrenergic antagonist yohimbine.

Since Yaksh et al. demonstrated that spinal cord alpha adrenergic stimulation produces antinociception the relative contribution of alpha$_1$ and alpha$_2$ adrenoreceptor has been debated. Zemlan et al.[17] observed a dose-related analgesia using clonidine in the spinal rat which was blocked by pretreatment with the alpha adrenergic receptor blocker phenoxybenzamine. Fleetwood-Walker et al.[18] demonstrated the presence of specific adrenergic receptors at sites in the dorsal horn that could mediate similar effects from descending noradrenergic systems. The selective effect of nor-

adrenaline on inhibiting the responses to noxious cutaneous stimulation of spinocerebellar tract and dorsal column postsynaptic neurones was mimicked by clonidine. Antagonism of the noradrenaline effect by yohimbine confirmed the involvement of an alpha$_2$ receptor. The lack of selective effects of the alpha$_1$ and beta agonists phenylephrine and isoprenaline, further supported the conclusion that an alpha$_2$ mechanism mediates the noradrenaline effect. It appears that alpha$_2$ agonists can exert a significant inhibitory effect on spinal presynaptic neurons.[19] This is substantiated by the recent work of Calvillo and Ghignone[20] who demonstrated that clonidine caused primary afferent depolarization of intraspinal cutaneous C fibres, thereby decreasing transmitter release through presynaptic inhibitory mechanisms. These studies support the role of alpha$_2$ adrenoreceptor mechanism in selective inhibition of nociceptive input at the spinal level.

Marwaha et al.,[19] however, caution against ascribing the effects of intrathecal administration of lipophilic drugs like clonidine solely to actions in the spinal cord. They reported that low doses of intrathecally administered clonidine (6–25 $\mu g \cdot kg^{-1}$) consistently inhibited locus coeruleus neuronal firing. They ascribed this inhibition as secondary to the rapid diffusion of clonidine from the spinal subarachnoid space into the general circulation.

A third possible mechanism of clonidine-induced prolongation of analgesia is through adrenoreceptor mediated vasoconstriction. Kiowski et al.[20] suggest that, apart from the classical alpha$_1$ adrenoreceptor, there is a second type of adrenergic receptor on smooth muscle cells that can mediate vasoconstriction, resembling the alpha$_2$ adrenoreceptor pharmacologically and these receptors may mediate vasoconstriction to exogenous catecholamines.

The direct antinociceptive effects of intrathecal alpha agonists, however, are unlikely to be secondary to local ischaemia, as they have been shown to be reliably reversible and unaffected in their action by vasodilator agents.[21] A vasoactive interaction between tetracaine and clonidine much like the interaction described by Kozody et al. with tetracaine and epinephrine,[9,10] could be responsible for the prolongation of spinal anaesthesia. The prolongation of sensory blockade could also be explained

by a synergism between the antinociceptive effects of clonidine and the neural blocking actions of tetracaine. However, since clonidine in low doses has little effect on motor function, a synergistic effect between alpha$_2$ adrenoceptor function and tetracaine motor blockade seems unlikely. The likely hypothesis to explain the prolongation of motor blockade appears to be decreased vascular uptake of tetracaine as a consequence of the alpha$_2$ mediated inhibition of tetracaine-induced vasodilation.

Our study confirms the analgetic properties of intrathecal clonidine. In conjunction with tetracaine, clonidine was superior to epinephrine in prolonging sensory blockade following the single intrathecal dose compared. One animal in the epinephrine group displayed a sensory blockade to a surgical stimulus. This agrees with data from Collins *et al.*[22] who reported a significant but incomplete suppression of noxiously evoked activity following 50 μg or 100 μg doses of subarachnoid epinephrine in cats.

No animal studied had any gross evidence of neurologic sequelae. Coombs *et al.*[23] investigated possible neurotoxicity of clonidine in the sheep and concluded that clonidine was not neurotoxic and this is supported by other human and animal studies.[13,21,24]

Administration of clonidine has resulted in "normalization" of sensory-motor and autonomic dysfunctions in the cat following traumatic spinal cord injury.[25] Preliminary studies of the use of clonidine in humans with traumatically injured spinal cords indicates that autonomic dysfunction can be controlled and spasticity minimized. This effect may be similar to the normalization of gait seen in one of our dogs.

Clonidine as an adjunct in spinal anaesthesia may provide advantages over the established vasoconstrictors, including prolonged duration of blockade, improved cardiovascular stability,[26] and postoperative analgesia. Further studies are required to assess dose response, haemodynamic, and regional circulatory effects of clonidine.

Acknowledgements

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Résumé

Avec une étude à double insu randomisée, l'efficacité comparative de la clonidine dans la prolongation d'une rachi-anesthésie à la tetracaïne a été étudiée avec six chiens bâtards.

Des injections sous-arachnoïdiennes lombaires (1 ml) de: tetracaïne 4 mg avec clonidine 150 µg, tetracaïne 4 mg avec épinephrine 200 µg, tetracaïne 4 mg, clonidine 150 µg, épinephrine 200 µg, et cinq pour cent dextrose dans l'eau ont été administrées d'une façon randomisée à chaque animal avec un intervalle de cinq à sept jours.

L'administration de tetracaïne sous-arachnoïdienne a produit un bloc-moteur de 186 ± 58 (moyenne ± SEM) min. La clonidine de même que l'épinephrine ont produit une prolongation identique du bloc-moteur à la tetracaïne, 135 pour cent (p < 0.01) et 116 pour cent (p < 0.05) respectivement, comparativement à la tetracaïne seule. Aucun bloc-moteur n'a été observé avec la clonidine seule, l'épinephrine, ou le cinq pour cent glucose dans l'eau. L'addition de clonidine à la tetracaïne pour une rachi-anesthésie a produit une augmentation significative dans la durée du bloc sensoriel, 56 pour cent (p < 0.01) et 107 pour cent (p < 0.01) respectivement, comparativement à la tetracaïne avec ou sans épinephrine. L'administration rachidienne de clonidine seule a produit un bloc sensoriel de 76 ± 17 minutes, alors qu'un seul chien ayant reçu de l'épinephrine sous-arachnoïdienne a présenté un bloc sensoriel (40 minutes). Aucun déficit neurologique n'a été observé chez aucun de ces animaux.

Cette étude conclut que chez les chiens devant subir une rachi-anesthésie à la tetracaïne, la clonidine est aussi efficace que l'épinephrine dans la prolongation du bloc-moteur et serait plus efficace dans la prolongation du bloc sensoriel.