

Dose-response Relationship of Clonidine in Tetracaine Spinal Anesthesia

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The study was undertaken to define a dose-response relationship for clonidine in prolonging canine tetracaine spinal anesthesia. Using a randomized blind cross-over design, six mongrel dogs were given subarachnoid injections (1 ml) of the following solutions over an 8-week period: tetracaine 4 mg (control), or tetracaine 4 mg with clonidine in doses of 10, 25, 50, 100, 150, 200, and 300 μ g. With clonidine doses equal to or exceeding 50 μ g/ml, motor and sensory blockade were significantly ($P < 0.01$) prolonged, when compared to the control times. Analysis of data by second order polynomial regression analysis produced a relationship defined by $Y = 23.241 + 1.104(x) - 0.0023(x^2)$ with $r^2 = 0.92$ and $P < 0.001$ for sensory blockade and $Y = 38.7072 + 1.64425(x) - 0.004125(x^2)$ with $r^2 = 0.90$ and $P < 0.005$ for motor blockade. From these curves, a plateau in clonidine dose-response for both sensory blockade and motor blockade occurred at 150 μ g. The increase in duration of spinal anesthesia with clonidine may be related to a direct post-synaptic α_2 adrenoceptor arteriolar effect, a spinal cord pre- or post-synaptic α_2 antinociceptive action or supraspinal α_2 modulation of nociception. No animals showed evidence of neurologic dysfunction during the study. The authors conclude that a well-defined dose-response relationship exists for clonidine in canine tetracaine spinal anesthesia. (Key words: Adrenoceptor agonist: clonidine. Anesthetics, local: tetracaine. Anesthetic techniques: subarachnoid block. Sympathetic nervous system, catecholamine: norepinephrine.)

CLONIDINE, AN α_2 and α_1 adrenoceptor agonist, has been shown in animals to provide analgesia equal or superior to opioids when given parenterally.¹ Given intrathecally, clonidine is analgetic through actions at both the level of the brain and the spinal cord.²⁻⁴ Recent reports have shown clonidine to be a good adjunct to narcotic analgesia when given *via* the intrathecal or epidural routes in humans.^{5,6} The effect of clonidine on antinociception may be prolonged, lasting as long as 18 h.⁵ Furthermore, animal work and human studies have not demonstrated neurotoxic or respiratory depressant effects following intrathecal administration.^{5,7}

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¶ Coombs DW, Allen C, Meier FA, Fratkin JD: Chronic intraspinal clonidine in sheep. *Regional Anesthesia* 9:47-48, 1984.

Clonidine has vasoactive properties, and, when given as a bolus parenterally, produces transient hypertension, followed by hypotension. It is known to stimulate α_1 and α_2 adrenoceptors, but is primarily an α_2 adrenoceptor agonist on the systemic vasculature. Post-synaptic α_2 adrenoceptors have been shown to produce vasoconstriction of vascular smooth muscle, and appear responsible for the transient hypertension seen with parenteral clonidine.⁸⁻¹³ Since it is believed that adrenergic mediated inhibition of tetracaine-induced vasodilation of the spinal cord and dural arteriolar circulation prolongs spinal anesthesia,¹⁴ the pharmacodynamic properties of clonidine make it an attractive adjunct in spinal anesthesia.^{15,16}

The purpose of the present study was to define a dose-response relationship for clonidine in canine tetracaine spinal anesthesia.

Materials and Methods

Dogs were utilized from a central animal care facility and 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 16-21 kg were studied using a randomized blind cross-over design. Anesthesia was induced with thiopental 20-30 mg/kg injected through a cephalic vein. Following induction, the animals were placed on an operating table in the right lateral decubitus position with a 10° head-up tilt. Anesthesia was maintained with nitrous oxide, oxygen (2:1), and isoflurane (1.5-2.0%) delivered by a funnel mask to the spontaneously breathing dog. The low back region was shaved and prepared with povidone iodine from the level of the L₁ to the S₁ vertebrae. The animal was draped and lumbar puncture was performed with a 22-gauge 7-cm spinal needle at the L₆-L₇ interspace. If this was unsuccessful, the L₅-L₆ space was utilized. Successful dural puncture was confirmed by free flow of CSF from the needle.

Each animal received tetracaine 4 mg with clonidine in doses of 0, 10, 25, 50, 100, 150, 200, and 300 μ g in a randomized manner.

Tetracaine crystals were dissolved in 10% D/W, while clonidine crystals were dissolved in sterile H₂O. The final solution injected was made up to a volume of 1 ml in D5/W. The solution was injected intrathecally over 10 s. Following the injection, anesthesia was dis-

TABLE 1. Duration of Motor and Sensory Blockade and Time to Arousal with Intrathecal Clonidine

Clonidine ($\mu\text{g/ml}$)	Duration of Motor Blockade (Min)	Duration of Sensory Blockade (Min)	Arousal Time (Min)
0	188 \pm 28	125 \pm 19	23 \pm 6
10	253 \pm 21*	155 \pm 7	18 \pm 3
25	303 \pm 20†	158 \pm 28	23 \pm 4
50	384 \pm 21†	220 \pm 21†	30 \pm 10
100	405 \pm 25†	219 \pm 16†	33 \pm 10
150	430 \pm 41†	253 \pm 15†	39 \pm 8
200	455 \pm 27†	270 \pm 27†	36 \pm 11
300	425 \pm 34†	277 \pm 8†	41 \pm 2

Values expressed as mean \pm SEM. N = 6 in each group.

* $P < 0.05$; † $P < 0.01$ compared to no clonidine.

continued and the animal remained in a 10° head-up tilt for 1 min, following which it was allowed to recover in the horizontal right lateral decubitus position.

The time to arousal, defined as spontaneous movement of ears, eyes, or head, was recorded. Following arousal, sensory and motor blockade were assessed every 20 min for the first hour and every 15 min thereafter.

Motor blockade was assessed using hind limb function, the end point being the ability to stand unsupported using both hind limbs. Sensory blockade was assessed using a modified method of Eger *et al.*¹⁷ A 25-cm rubber-shod hemostat was applied to the proximal third of the shaved tail for 30 s. Return of sensation was noted when a reproducible avoidance response occurred. All assessments were performed by one ob-

server unaware of the solutions being used. Following complete recovery of sensory and motor function, the animals were returned to the animal boarding facility and observed for 4–7 days. Prior to each subsequent injection, all dogs were examined for gross neurologic dysfunction.

The data were analyzed using second-order polynomial regression analysis and a randomized block ANOVA. Post-ANOVA multiple comparisons were performed using Duncan's Test. A value of $P < 0.05$ was considered to be statistically significant.

Results

Time from subarachnoid injection (table 1) to awakening showed a second-order polynomial relationship to the dose of clonidine administered (fig. 1). This relationship was defined by the equation, arousal time = $20.3903 + 0.1504(\text{dose}) - 0.0003(\text{dose})^2$, with $r^2 = 0.82$ and $P < 0.003$. Regression analysis showed a strong correlation of increasing arousal time to larger doses of intrathecal clonidine, with a maximal effect being reached at 150 μg . An apparent but nonsignificant antagonism of sedation was observed with 10 μg of clonidine.

Both motor and sensory blockade were significantly prolonged ($P < 0.01$) when clonidine in a dose of 50 μg or greater was administered intrathecally compared to tetracaine alone (table 1). We also analyzed our results as a percentage change of control, where control was blockade time observed with tetracaine alone. This is mathematically expressed as:

$$\frac{\text{Observed Blockade Time} - \text{Control Blockade Time}}{\text{Control Time}} \times 100$$

These data points were analyzed using second-order polynomial regression analysis. The mean data are shown in figure 2.

Sensory blockade duration showed a strong correlation to the dose of intrathecal clonidine being defined by the equation: sensory blockade percentage change = $23.241 + 1.104(\text{dose}) - 0.0023(\text{dose})^2$, with $r^2 = 0.92$ and $P < 0.001$. Motor blockade also showed a good correlation with the dose of clonidine administered being defined by the equation: motor blockade percentage change = $38.7072 + 1.64425(\text{dose}) - 0.004125(\text{dose})^2$, with $r^2 = 0.90$ and $P < 0.005$. Both curves constructed from the above equations demonstrate a plateau of clinical effect at a clonidine dose of 150 μg .

No dog showed evidence of neurologic dysfunction after each individual injection. At the conclusion of the

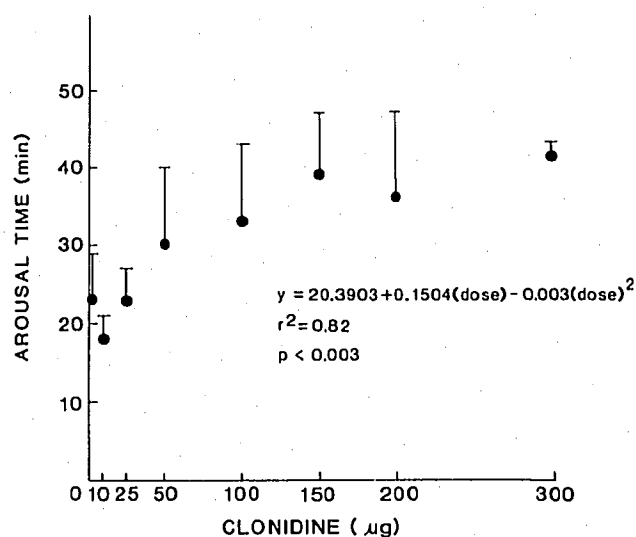


FIG. 1. Time to arousal following increasing doses of intrathecal clonidine. n = 6 in each group. Values expressed as mean \pm SEM. Maximal effect is observed with clonidine 150 μg . A possible non-significant antagonism is observed with clonidine 10 μg .

study, performed over an 8-week period, all dogs were in good health and without signs of gross neurologic damage.

Discussion

The present study demonstrates a dose-response relationship for both motor and sensory blockade to intrathecal clonidine in tetracaine spinal anesthesia. The duration of sensory or motor blockade did not change significantly with doses of intrathecal clonidine above 150 μ g. Clonidine in a dose of 150 μ g has been shown to prolong tetracaine spinal anesthesia in dogs, and, more recently, bupivacaine spinal anesthesia in humans, without adverse effects.^{15,16}

Parenteral clonidine is a potent α_2 agonist which produces initial vasoconstriction of systemic vessels related to its ability to stimulate post-synaptic vascular α_2 adrenoceptors.⁸⁻¹² In the intact animal following parenteral clonidine, vasoconstriction and hypertension is soon followed by centrally mediated hypotension. This appears related to the central effect of clonidine on the sympathetic nervous system and its ability to decrease catecholamine turnover.¹⁸⁻²¹

The effect of a high dose of intrathecal clonidine (150 μ g) on the spinal cord circulation is vasodilatory, possibly through an α_2 pre-synaptic sympathetic inhibitory mechanism similar to its antihypertensive effect.²² A similar tendency has been demonstrated with high-dose intrathecal norepinephrine and epinephrine (combined α_1 and α_2 adrenergic agonists), which do not produce vasoconstriction, but have a tendency to vasodilation.^{23,24} Low-dose intrathecal clonidine produced by the transdural flux of epidural clonidine may produce a small reduction in spinal cord blood flow, possibly by stimulating post-synaptic α_2 vascular adrenoceptors; however, controlled studies are required.²⁵

Kozody *et al.*¹⁴ proposed that adrenergic agonists prolong the duration of tetracaine spinal anesthesia not through vasoconstriction, but by inhibiting spinal cord and dural arteriolar vasodilation normally induced by tetracaine. The local vasoactive effects of intrathecal clonidine may be sufficient to prevent the early arteriolar vasodilation seen with intrathecal tetracaine and delay its removal from the cerebrospinal fluid. Clonidine may, in part, act through a mechanism similar to epinephrine in prolonging time to two segment regression with tetracaine spinal anesthesia.¹⁵

Clonidine in addition has been shown to have potent analgesic properties when given by the intrathecal, epidural, intravascular, or intraperitoneal routes.^{1-6,26} This analgesia is independent of opioid receptor stimulation because it is not reversed with naloxone.^{1,2,27} The effect of both norepinephrine and clonidine on

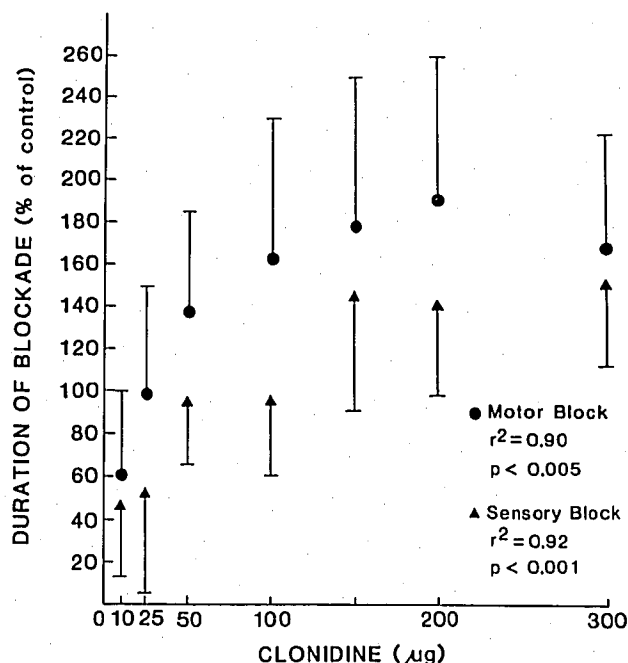


FIG. 2. Effect of increasing doses of clonidine on duration of sensory and motor blockade with tetracaine spinal anesthesia. $n = 6$ in each group. Values expressed as mean \pm SEM. A maximal effect on both sensory and motor blockade is observed with clonidine 150 μ g.

analgesia has been reversed by alpha antagonists, such as yohimbine, tolazoline, phentolamine, and piperoxan.^{2,19,28} Furthermore, the effect of alpha agonists to increase the nociceptive threshold is not reversed by the use of vasodilators, such as isoproterenol, bradykinin or papaverine.^{2,28} Indeed, the nociceptive threshold could not be elevated, using angiotensin-II in an attempt to mimic the effect of vasoconstrictors on analgesia.²

Attempts have been made to localize the site of action of alpha agonist antinociception. This includes spinal cord transection, stimulation, or ablation of individual brain stem centers, and iontophoretic application of putative analgetics. Stimulation of supraspinal brainstem centers, such as the locus coeruleus, raises the nociceptive threshold.²⁹⁻³² Destruction of the locus coeruleus caused a reduction in the nociceptive threshold in animals.³³⁻³⁴ These experiments and others have shown the importance of higher centers in modulating pain. However, it appears the antinociceptive site of action of clonidine is primarily at the level of the spinal cord. Work with catecholamines placed iontophoretically at the level of the spinal cord has shown decreased nociceptive discharge.³⁵⁻³⁷ Spaulding *et al.*⁴ transected spinal cords at the mid-thoracic level and showed that clonidine was equally effective at raising the nociceptive threshold, when compared to the control (intact spinal cord) animals. They concluded that clonidine was act-

ing at the spinal cord level. Zemlan *et al.*³⁸ also demonstrated the same result, and concluded that clonidine produces analgesia by affecting interneurons which cause primary afferent depolarization of cutaneous sensory fibers resulting in attenuation of pain. Calvillo and Ghignone³⁹ showed that clonidine caused primary afferent depolarization of intraspinal cutaneous C fibers resulting in decreased transmitter release. This effect was reversed by yohimbine, thereby implicating α_2 adrenoceptor stimulation. Furthermore, other researchers using subarachnoid catheters placed over the lumbar spinal cord showed a differential effect of clonidine on analgesia of the hind limbs *versus* the forelimbs.^{2,7,27,28}

Clonidine is a lipid soluble drug and, as such, has access to the central compartment. However, when given intrathecally, the effects of systemic access and subsequent supraspinal redistribution appears to have had little effect on pain modulation in the forelimbs of animals given as much 2000 μ g of intrathecal clonidine in the lumbar region.⁷ Presumably, the concentration of clonidine remains high at the injection site and lower in the blood, related to regional binding and rapid redistribution from the vascular compartment. If this was not the case, clonidine should have increased the nociceptive threshold equally in the forelimbs, as was demonstrated in previous work, where intraperitoneal and intravenous clonidine was utilized. We, therefore, believe that, while supraspinal actions are present, especially at the higher dosages, the preceding data indicate that the primary effect of clonidine in prolonging tetracaine anesthesia is at the level of the spinal cord. Further work utilizing systemic clonidine in tetracaine spinal anesthesia is required to validate the hypothesis.

The duration of elevation of nociceptive thresholds has varied in animals, and has been reported to be as long as 18 h in man.⁵ The duration of analgesia appears to exceed the duration of spinal sensory blockade, and may provide continuing postoperative analgesia when the demand for analgesic agents are high. This may allow for early ambulation, since motor function is spared.

There was no gross clinical evidence in any animal of neurotoxicity after each injection or at the conclusion of the study, which took 8 weeks. This agrees with clinical observations in humans given intrathecal^{5,16} and epidural clonidine,⁶ and experimental work in animals involving histological examinations of the spinal cord.⁷¹

The demonstrated dose-dependent effects of clonidine in prolonging time to awakening following general anesthesia are consistent with previous studies showing sedation^{20,40,41} and a reduction in anesthetic requirements.^{42,43} The sedating effects of clonidine have been reversed by administration of α_2 antagonists.^{20,42} It

is believed that clonidine activates presynaptic inhibitory α_2 adrenoceptors located on the noradrenergic neurons of the locus coeruleus, resulting in a decrease in activity with sedation and sleep.²⁰ Clonidine, with a tissue partition coefficient of 39 (incorporates ionization correction), is highly lipid soluble and will cross tissue barriers rapidly.⁴⁴ Following intrathecal administration, vascular access to the supra-spinal C.N.S., rather than C.S.F., circulation is believed to produce sedation.⁴⁵ The mechanism by which clonidine gains access to the C.N.S. may, therefore, be similar to that demonstrated for intrathecal lipid soluble narcotics, such as fentanyl and meperidine.⁴⁶ The C.N.S. sedating properties of clonidine may offer additional benefits in spinal anesthesia, especially in situations where supplemental intravenous sedation was previously required.

In conclusion, intrathecal clonidine, when utilized as an adjunct to tetracaine spinal anesthesia, prolongs the duration of motor and sensory blockade. A dose-response relationship exists with the maximal effect seen, in dogs, at a dose of 150 μ g. We feel that the addition of clonidine to spinal anesthesia may have distinct advantages because of its presently demonstrated ability to prolong motor and sensory blockade and its previously demonstrated ability to elevate the nociceptive threshold, combined with its sedating properties. A possible role in other forms of regional anesthesia remains to be demonstrated.

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