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Haemodynamic effects of clonidine injected epidurally in halothane-anaesthetized dogs

The haemodynamic effects of clonidine administered in the epidural space were studied in 16 halothane-anaesthetized dogs. The animals were randomly assigned to two groups: Group I received three doses of 3 ml of normal saline, Group II received three doses of $3 \mu\text{g}\cdot\text{kg}^{-1}$ of clonidine, through an epidural catheter, whose tip was located between L₂-T₁₁. Control haemodynamic measurements were taken one hour after completion of the surgical preparation (period P₁); they were repeated every 45 minutes after each incremental dose (periods P₂, P₃, P₄) and 105 minutes after a total cumulative dose of $9 \mu\text{g}\cdot\text{kg}^{-1}$ of clonidine or 9 ml of saline were given (period P₅). No significant changes over time were observed in Group I. In Group II clonidine produced statistically significant reductions of systemic blood pressure (BP), mean left ventricular pressure (LV), heart rate (HR), cardiac output (CO) and peak LV dP/dt only after a total clonidine dose of $9 \mu\text{g}\cdot\text{kg}^{-1}$ and these changes were sustained. BP fell 15 per cent, CO 21 per cent, HR 25 per cent, LV 20 per cent and peak LV dP/dt 30 per cent when P₅ measurements were compared to control values within Group II ($p < 0.05$). These haemodynamic effects of clonidine are likely due to minimal systemic absorption and/or cephalad spread of the drug towards its site of action in the brain stem. The reductions of HR, CO, BP, and isovolumic indices of contractility are likely explained by a reduction of sympathetic outflow at the spinal cord and medulla oblongata levels as well as increased parasympathetic tone.

If these observations can be extrapolated to clinical conditions, in view of the small haemodynamic changes observed only with the highest dose employed, and the potent analgesic effects, epidural administration of clonidine appears safe and may be useful for management of acute postoperative pain.

Key words

EPIDURAL ANALGESIA: clonidine; HAEMODYNAMICS: epidural clonidine; SYMPATHETIC NERVOUS SYSTEM: clonidine.

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Clonidine, a centrally acting antihypertensive agent,¹ has been reported to have significant antinociceptive properties in animals² and in humans.³ Coombs *et al.*⁴ reported that intrathecal clonidine provided effective pain relief in a patient with malignant pain who had developed narcotic tolerance; however, significant hypotension and bradycardia occurred. Calvillo and Ghignone⁵ suggested that clonidine selectively modulates C fibre input (and therefore nociception) to the spinal cord by presynaptic mechanisms. These studies suggest that the spinal cord mediates the antinociceptive properties of clonidine and, furthermore, that the sympathetic nervous system participates in nociceptive modulation.⁶ This, however, does not rule out the possibility that clonidine also has supraspinal sites of action, as it has been suggested.⁷

Several studies have reported the effects of clonidine administered intrathecally or epidurally on nociceptive threshold and blood pressure in awake and anaesthetized preparations.⁸⁻¹⁰ Intrathecal administration of clonidine in doses ranging from 0.1 to 5 μg in rats resulted in a gradual, prolonged and dose-dependent reduction in BP and HR; larger doses caused a predominant hypertensive response, likely due to systemic absorption.^{8,9} By contrast, continuous epidural infusion of very large doses of clonidine (100 to 600 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$ in chronically instrumented rams) did not produce significant changes in BP and HR.¹⁰ The use of epidural clonidine could become widespread in certain subsets of patients if the haemodynamic repercussions were minimal. This study was designed to investigate the full haemodynamic consequences that follow the acute administration of clonidine in the epidural space of the dog.

Methods

Anaesthesia was induced in 16 mongrel dogs weighing 18 to 24 kg with thiopentone ($20 \text{ mg}\cdot\text{kg}^{-1}$) and maintained with halothane one per cent end-expiratory concentration (Beckman LB₂ Halothane analyzer, Beckman Instruments, Fullerton, CA) in O₂. Mechanical ventilation was instituted with a tidal volume of $20 \text{ ml}\cdot\text{kg}^{-1}$ via an endotracheal tube. An epidural catheter was inserted at the L₃-L₄ interspace through an 18 gauge Crawford needle. The epidural space was identified by the loss of

resistance technique; radiographic confirmation of the catheter position was obtained by lateral and postero-anterior projections. The catheter tip was located between L₂ and T₁₁. A catheter was placed in the thoracic aorta via the internal carotid artery to monitor systemic blood pressure (BP) and to obtain samples of arterial blood. A thermistor-tipped flow-directed catheter was inserted via the external jugular vein and advanced in a branch of the pulmonary artery where pulmonary artery pressure (PA) and pulmonary capillary wedge pressure (PCWP) were obtained. A second thermistor-tipped catheter was positioned in the right atrium for injection of saline boluses for cardiac output (CO) determination. Thermodilution curves were recorded at least four times in each condition and averaged. The per cent standard error of the mean (SEM%) of the CO measurements averaged four per cent. A catheter-tip manometer (Millar PC 350, Millar Instruments, Houston, TX) was inserted via the femoral artery into the left ventricle (LV) to obtain left ventricular pressure; the signal was differentiated to obtain peak LV dp/dt.

All vascular pressures were referred to the centre of the chest with the animal in the supine position. The transducers' outputs, the ECG, end-tidal halothane concentration and thermodilution curves were displayed on an 8-channel recorder. Heart rate was obtained by a standard limb lead ECG. These preparations were usually completed in about one hour during which time approximately 25 mg·kg⁻¹ of lactated Ringer's solution was infused to adjust the PCWP to approximately 6 mmHg; subsequently the infusion rate was set at 50 ml·hr⁻¹. Baseline measurements (period P₁) of BP, CO, PA, PCWP, LV end diastolic pressure (EDP), peak LV dp/dt and HR were recorded after a stabilization period of at least 60 minutes, during a ten-second apnoeic period at functional residual capacity. The animals were then randomly assigned to two groups. Group I (N = 8), the

control group, received preservative-free normal saline in 3 ml increments through the epidural catheter for a total volume of 9 ml; Group II (N = 8), the clonidine group, was administered freshly prepared clonidine solution (Bohringer Ingelheim, Ridgefield, CT) in three doses of 3 µg·kg⁻¹ (total dose 9 µg·kg⁻¹) in the same volume as in Group I. Subsequent measurements were obtained at 45-minute intervals following epidural administration of either clonidine or saline: periods P₂, P₃, P₄. Final measurements (P₅) were taken 60 minutes after the last epidural injection. Arterial blood gases were sampled hourly and pH was maintained between 7.35–7.45 by administration of sodium bicarbonate or by adjustment of ventilatory rate to maintain PaCO₂ between 30 and 40 mmHg. Temperature was maintained between 37.5 and 38.5°C with a warming blanket. Pulmonary vascular resistance was calculated as PVR = (mean PA-PCWP)/CO, and system vascular resistance (SVR) as mean BP-right atrial pressure/CO.

Analysis of variance employing the Tukey's method was performed; the Bonferroni inequality correction for the t-test was then applied to the haemodynamic data for selected pairs of simultaneous multiple comparisons.¹¹ The differences between control values and values of each of the conditions within and between groups were considered significant when *p* was <0.05.

Results

The haemodynamic data of Group II are reported in the Table. Acute epidural administration of clonidine up to a mean dose of 6 µg·kg⁻¹ resulted in no significant haemodynamic effects. Significant changes of BP, LV, HR, CO and peak LV dp/dt were observed only after a total cumulative dose of 9 µg·kg⁻¹ of clonidine (P₄) and were sustained for the period of observation (P₅).

The maximum reduction of BP was 15 per cent when P₅ was compared with control value (*p* < 0.05). The other

TABLE Haemodynamic effects of clonidine administered epidurally (mean ± SD)

	P ₁ Control	P ₂ 45 min after 3 µg·kg ⁻¹	P ₃ 45 min after 6 µg·kg ⁻¹	P ₄ 45 min after 9 µg·kg ⁻¹	P ₅ 60 min after P ₄
CO L·min ⁻¹	1.86 ± 0.21	1.8 ± 0.2	1.65 ± 0.25	1.5 ± 0.27*	1.47 ± 0.27*
HR beat·min ⁻¹	120 ± 31	118 ± 28	106 ± 22	95 ± 24*	90 ± 21*
BP mmHg	112 ± 22	109 ± 20	103 ± 19	97 ± 19*	94 ± 18*
Ao diast mmHg	95 ± 20	95 ± 20	85 ± 21	80 ± 18*	75 ± 18*
Mean LV mmHg	52 ± 12	52 ± 8	50 ± 10	43 ± 11*	42 ± 9*
LV EDP mmHg	9.0 ± 3.5	8.5 ± 3	8 ± 3	7 ± 3	7 ± 3
PCWP mmHg	6.3 ± 3	5 ± 3	6 ± 2.5	5.5 ± 2.6	5.6 ± 2.5
PA mmHg	12 ± 4	11.5 ± 4	11.0 ± 3	10 ± 3.5	11.0 ± 3.5
SV ml	16 ± 5	16 ± 4	16 ± 5	17 ± 5	17 ± 5
Peak LV dp/dt mmHg·sec ⁻¹	2000 ± 654	1883 ± 595	1687 ± 565	1529 ± 498*	1329 ± 430*
SVR dyne·sec·cm ⁻⁵	3880 ± 1840	3914 ± 1892	4033 ± 1931	4211 ± 2011	4299 ± 2023
PVR dyne·sec·cm ⁻⁵	230 ± 43	239 ± 44	242 ± 45	236 ± 43	220 ± 41

**p* < 0.05 when compared with control value.

haemodynamic parameters whose changes reached statistical significance ($p < 0.05$) were HR, CO, LV and peak LV dP/dt in periods P_4 and P_5 , when compared with P_1 within the clonidine group (Group II). The largest reduction of HR, CO, LV and peak LV dP/dt were observed in P_5 and were respectively 25, 21, 20 and 30 per cent of control values ($p < 0.05$). Stroke volume was maintained. No changes in SVR nor PVR were observed. The injection of clonidine by $3 \mu\text{g}\cdot\text{kg}^{-1}$ increments did not result in any transient increase in BP or HR. No significant changes of measured and calculated parameters were observed in the control group (Group I) during the study period.

Discussion

Epidural administration of clonidine resulted in a significant and sustained reduction of BP, HR, LV, CO and peak LV dP/dt only after a total cumulative dose of $9 \mu\text{g}\cdot\text{kg}^{-1}$. BP fell 15 per cent and HR was reduced 25 per cent from control values ($p < 0.05$). These changes are comparable in magnitude to those observed by Yasuoka and Yaksh⁹ after intrathecal administration of $5 \mu\text{g}$ of clonidine in unanaesthetized rats. Intrathecal clonidine, however, in the dose range employed during this investigation (3 to $8 \mu\text{g}\cdot\text{kg}^{-1}$) resulted in marked reduction of BP and HR, approximately 33 per cent of control values, in anaesthetized rats;⁸ yet larger doses (30 – $80 \mu\text{g}\cdot\text{kg}^{-1}$) produced a predominant pressor effect, likely because of systemic absorption.⁹ At variance with the present results, chronic epidural infusion of very large doses of clonidine (100 to $600 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$) in unanaesthetized sheep has been reported to have no significant haemodynamic effects. The epidural route of administration appears therefore to produce a lesser haemodynamic impact as compared to intrathecal administration, despite doses of similar or greater magnitude, likely because of minimal systemic absorption and/or rostral spread of clonidine towards the brain stem. Further, the contribution of a reduced background sympathetic activity and the depression of the baroreflex mechanism¹² resulting from halothane anaesthesia may explain the difference in the haemodynamic response to epidural clonidine observed in the present study when compared to studies in the awake animals reported by Coombs.¹⁰

In tetraplegic patients where there is no significant peripheral sympathetic tone, and where the baroreflex arch is interrupted, clonidine does not affect mean resting systolic and diastolic blood pressures or reduce plasma norepinephrine.¹³ This suggests that descending influences from the brain stem, determining peripheral sympathetic outflow, are of primary importance for the hypotensive effect of clonidine in the resting state.

By contrast its analgesic effects may occur predomi-

nantly at the spinal level and are due to depression of synaptic efficacy in spinal nociceptive pathways.⁵ Halothane anaesthesia, therefore, may potentiate the haemodynamic response to clonidine in view of inhibition of the baroreflex response and reduction of the background sympathetic activity. It is conceivable then that the haemodynamic consequences of epidural clonidine would be less pronounced in nonanaesthetized humans, as the results obtained in awake sheep suggests.¹⁰ While the reduction of BP is of central origin and due to inhibitions of the tonic vasomotor centre located in the lower brain stem, clonidine has effects occurring independently of the supraspinal cerebral structures.

Neurons involved in tonic and reflex control of BP¹⁴ project to the intermediolateral column of the spinal cord.¹⁵ In this region, which contains the cell bodies of the sympathetic preganglionic neurons that innervate directly the adrenal medulla and the sympathetic ganglia, a very dense noradrenergic innervation and α_2 -adrenoceptor binding sites have been identified.¹⁶ Activation of presynaptic α_2 -adrenoceptors reduces transmitter release (dependent on intensity of stimulation) in response to neuronal activity;¹⁷ this results in reduction of sympathetic outflow¹⁸ and of plasma norepinephrine.¹⁹ The extensive distribution of noradrenergic fibres and α_2 -adrenoceptors throughout specific sites of the spinal gray matter, i.e., intermediolateral column and dorsal horn neurons, suggests that descending noradrenergic systems have potentially important and widespread connections with spinal neurons involved in regulating autonomic and sensory activity.

The slowing of the heart rate produced by clonidine is thought to result both from a reduction of sympathetic drive and a simultaneous increase in parasympathetic tone. While the reduction of the sympathetic drive is of central and peripheral origin, the increase in vagal tone is due to a central mechanism which involves the reduction of tonic sympathetic influences on the excitatory cardiovascular neurons, and occurs only in presence of intact vagal pathways.²⁰ Therefore, the most likely mechanisms involved in the slowing of the heart rate after epidural clonidine are the decrease of the firing rate of preganglionic sympathetic neurons located in the intermediolateral column of the spinal cord and of the neurons in the medulla involved in the cardiovascular control and the increased vagal tone, particularly at the highest doses. Inhibition of the postganglionic sympathetic nerves which requires rather high doses,¹⁷ however, may also have played a role.

The gradual reduction of sympathetic outflow to the heart, rather than a direct effect, explains the reduction of myocardial contractility as indicated by the reduction of peak LV dP/dt. Indeed, clonidine does not have intrinsic

negative inotropic effects on isolated papillary muscle²¹ and in heart-lung preparations.²² In addition to the reduction of sympathetic tone, other factors have to be considered in explaining the depression of peak LV dP/dt observed. While the instantaneous rate of change of ventricular pressure, prior to the opening of the aortic valve, is closely related to the rate of change of wall tension and reflects changes in contractility, changes in fibre length or preload, mean and diastolic aortic pressures and heart rate modify this isovolumic index of contractility.²³ In the present study preload, as indicated by left ventricular end-diastolic pressure (LVEDP) did not change significantly; however, HR, mean and diastolic aortic pressures were significantly reduced, therefore contributing to the depression of LV dP/dt.

Cardiac output was significantly reduced by the highest dose of clonidine administered (Table). The cause of reduction of CO has been previously reported to be the result of multiple factors such as increased vagal activity and loss of sympathetic tone resulting in reduced ventricular performance,²⁴ and reduction of venous return.²⁵

Increased vagal tone may be an important cause of the fall in CO produced by clonidine, especially when heart rate is reduced to frequencies where CO is strongly dependent on HR. However, because of the range of HR observed this is unlikely to have played a major role.

Stroke volume increased slightly and LVEDP did not change significantly, therefore the end systolic volume at a slightly reduced end-systolic pressure either did not change or was slightly reduced. Depression of systolic ventricular performance is thus not explained by an increased end systolic pressure-volume ratio (a sensitive indicator of ventricular contractility)²⁶ and therefore by the reduction of the extent of ventricular shortening, but rather by the reduction of the mean ejection rate as recently reported.²⁷

In addition to the reduction of LV pump performance discussed, the reduction of CO observed with clonidine may be due to a reduction of venous return. The loss of sympathetic tone to the great veins would result in a dilatation of the capacitance vessels, thereby reducing the driving pressure for venous return or mean systemic pressure.

In support of this explanation, clonidine produced reduction of venous return by increasing the volume of capacitance vessels in dogs on cardiopulmonary bypass;²⁵ this would account for the reduction of LVEDP observed. However, the small changes in preload, despite dilatation of capacitance vessels suggest that reduction of alpha sympathetic tone may result in diminished resistance to venous return, therefore reducing the impact of capacitance vessels dilatation on venous return and CO.

In summary, changes in autonomic tone, particularly

the reduction of sympathetic tone with its repercussions on ventricular pumping performance, cardiac frequency and venous return could explain the reduction of CO observed. No changes in SVR occurred, therefore the reduction on BP is thus explained by the reduction in flow. A reduction of total resistance would have been expected in view of the reduction of the sympathetic tone; however, the passive stretching of the vessel wall by the ejected blood was likely reduced, and resulted in no net change.²⁹

Clonidine has been shown to have potent analgesic properties both in experimental animals and humans.^{2,3} The spinal site of the analgesic effect³ associated with the lack of respiratory depression²⁹ and of neurotoxicity,¹⁰ the minimal haemodynamic changes observed in the anaesthetized dog in the present study, and in the awake¹⁰ sheep, despite the high dose given, point out the safety of the epidural route of administration of clonidine. If these experimental observations can be extrapolated to clinical situations, the results of this study suggest that epidural clonidine may be clinically useful in the management of acute postoperative pain, or as an adjunct to local anaesthetic for epidural anaesthesia.

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Résumé

Les effets hémodynamiques de l'administration de clonidine dans l'espace épural étaient étudiés chez 16 chiens anesthésiés à l'halothane. Les animaux étaient divisés en deux groupes d'une façon randomisée: le groupe I a reçu trois doses de 3 ml de physiologique, le groupe II a reçu trois doses de $3 \mu\text{g}\cdot\text{kg}^{-1}$ de clonidine, à travers un cathéter épural dont le bout distal était localisé entre L_2 et T_{11} . Les mesures hémodynamiques de contrôle étaient prises une heure après l'accomplissement de la préparation chirurgicale (période P_1); elles étaient répétées chaque 45 minutes après chaque dose de rajout (période P_2 , P_3 , P_4) et 105 minutes après avoir atteint une dose cumulative totale de $9 \mu\text{g}\cdot\text{kg}^{-1}$ de clonidine ou 9 ml de salin (période P_5). Aucun changement significatif à travers le temps n'a été observé dans le groupe I. Dans le groupe II la clonidine a produit une diminution statistiquement significative de la tension artérielle systémique (BP), de la pression du ventricule gauche (LV), de la fréquence cardiaque (HR), du débit cardiaque (CO) et dP/dt maximal uniquement après avoir atteint la dose maximale totale de $9 \mu\text{g}\cdot\text{kg}^{-1}$. La BP a diminué de 15 pour cent, CO de 21 pour cent, HR de 25 pour cent, LV de 20 pour cent et le dP/dt de 30 pour cent quand les mesures faites au temps P_5 étaient comparées aux valeurs de contrôle dans le groupe II ($p < 0.05$). Ces effets hémodynamiques de la clonidine sont probablement dus à une absorption systémique minime et/ou à une diffusion vers le haut du médicament vers son site d'action dans le cerveau. La diminution de la fréquence cardiaque, débit cardiaque et la tension artérielle ainsi que les indices isovolumiques de contractilité sont probablement expliqués par une réduction de la réponse sympathique de la moëlle épinière et du bulbe rachidien ainsi qu'une augmentation du tonus parasympathique.

Si on pouvait extrapoler ces observations expérimentales aux conditions cliniques et parce que les effets hémodynamiques ont été observés uniquement avec des fortes doses de clonidine qui est un puissant analgésique, l'administration épidurale de cette drogue apparaît sécuritaire et pourrait être utile au point de vue thérapeutique contre les douleurs aiguës postopératoires.