Clinical actions of intramuscularly clonidine in cattle

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SUMMARY

To determine the sedative and antinociceptive effects of three doses of intramuscularly (IM) administered clonidine, an alpha-2 agonist, six healthy cattle were used in a randomized study. Each animal was treated on three occasions with intramuscular clonidine at either 4 (CL4), 5 (CL5) or 6 (CL6) mcg/kg bodyweight. Sedation, antinociception, heart rate, arterial blood pressure, respiratory rate and rectal temperature were measured immediately prior (Time 0) and at 5, 10, 15, 30, 60, and every 60 minutes until animals returned to normal alertness after clonidine administration. Serum glucose concentration was measured at time 0, 30, 60 minutes and every 120 minutes. The degree of sedation and antinociception was assessed subjectively by the same observer blinded for all treatments. The three doses produced dose-dependent sedation and antinociception; the highest dose induced the most prolonged sedation (approximately 405 min) and antinociception (approximately 210 min). Heart and respiratory rates decreased significantly from baseline after each treatment but blood pressure was not affected significantly. Hyperglycaemia was recorded with all doses. The results suggest that IM administration of clonidine induces dose-dependent onset and duration of sedation and antinociception in cattle, and all doses induced bradycardia and a decreased respiratory rate with little interference with arterial blood pressure.

Keywords: Clonidine, alpha-2 agonists, sedation, analgesia, cattle.

RÉSUMÉ

Action de la Clonidine par voie intramusculaire chez la vache

Afin de déterminer les effets sédatifs et antinoceptifs de trois doses de clonidine, un agoniste des récepteurs alpha-2 adrénergiques, administrée par voie intramusculaire, six vaches en bonne santé ont été utilisées dans une étude randomisée. Chaque animal a reçu à trois occasions une administration intramusculaire de clonidine à la dose de 4 (CL4), 5 (CL5) ou 6 (CL6) mg/kg de poids vif. La sédation, l’analgésie, la fréquence cardiaque, la pression artérielle, la fréquence respiratoire et la température rectale ont été évaluées immédiatement avant (Temps 0) et aux temps 5, 10, 15, 30, 60 min après l’administration puis toutes les 60 minutes jusqu’à ce que les animaux retrouvent leur niveau de vigilance normal. Les concentrations sériques de glucose ont été déterminées aux temps 0, 30, 60 minutes après l’administration puis toutes les 120 minutes. Les degrés de sédation et d’analgésie ont été estimés de façon subjective et en aveugle par le même observateur pour l’ensemble des traitements. La clonidine a induit une sédation et une analgésie dose-dépendante ; la plus forte dose a entraîné la sédation et l’analgésie les plus prolongées, environ 405 et 210 min, respectivement. Les fréquences cardiaques et respiratoires ont été diminuées significativement par rapport aux valeurs de base pour chacun des traitements mais la pression artérielle n’a pas été affectée de façon significative. Une hyperglycémie a été notée pour toutes les doses. Ces résultats suggèrent que l’induction et la durée de la sédation et de l’analgésie chez la vache varient de façon dose dépendante suite à une administration intramusculaire de clonidine; l’ensemble des doses testées étant associées à une bradycardie et à une diminution de la fréquence respiratoire avec peu d’effet sur la pression artérielle.

Mots clés : Clonidine, alpha-2 agonistes, sédation, analgésie, vache.

Introduction

Alpha-2 agonists, such as xylazine, produce dose-dependent sedation and antinociception in cattle [14]. Although alpha-2 agonists induce moderate to deep sedation and analgesia in cattle, this class of drugs does not result in the required level of anesthesia for painful surgical interventions. The analgesic actions of alpha-2 adrenergic receptors are due to their strategic location on the dorsal horn neurons of the spinal cord, which allows inhibition of substance P (a peptide neurotransmitter) release in response to peripheral stimuli. However, these receptors are controlled by supraspinal sites via the descending medullospinal noradrenergic pathway.

Clonidine, an imidazoline, is a partial alpha-2 adrenergic agonist (alpha2/alpha1=200:1). The high liposolubility of clonidine (partition coefficient octanol: water=114:1) explains its predominant distribution in the nervous system. Because of its highly lipophilic structure, an alpha-2 adrenergic agonist can easily penetrate into the CNS, reproducing the effects of activation of the medullospinal noradrenergic pathway [1]. Clonidine decreases blood pressure by activating alpha-2 adrenergic receptors at the cardiovascular control centres of the CNS; such activation suppresses the outflow of sympathetic nervous system activity from the brain [8]. Clonidine can also affect non-adrenergic pathways that contribute to the hypotensive effects [3]. Clonidine has a good margin of safety, few cardiorespiratory effects and low cost. The purpose of this study was to evaluate the sedative, antinociceptive, and systemic effects of three doses of administered intramuscularly clonidine to cattle.
Materials and Methods

The study was approved by the Ethics Committee of the Federal University of Mato Grosso do Sul. Six healthy cattle of undefined breed under 2 years of age (three males and three females) weighing 175–260 kg were studied. All animals were housed in stalls in the Faculty of Veterinary Medicine facilities during the experimental period. Feed was withheld for 24 hours and water for 12 hours before the experiment. The order of treatment was randomized, and each animal received each treatment at weekly intervals. Ambient temperature were around 25 °C during these experiments. The observer was blinded to the drug dose administered at each treatment. On the morning of the experiment, a 16-gauge, 5-inch catheter was inserted, aseptically, into the jugular vein to collect blood for serum glucose analysis. Animals were administered with either 4 (CL4), 5 (CL5) or 6 (CL6) mcg/kg bodyweight of clonidine (Clonidin 150 mcg/mL; Cristália Chemical and Pharmacological Products Ltd, Brazil). All treatments were injected intramuscularly (IM) as a single injection into the gluteal muscle.

Heart rate (HR), respiratory rate (RR), arterial blood pressure (systolic [SAP], diastolic [DAP], and mean [MAP] arterial pressure), rectal temperature (RT), degree of sedation and antinociception were recorded immediately before (Time 0) and at 5, 10, 15, 30, 60 min, and every 60 min thereafter until return of normal alertness as it was in the beginning of the experiments. Sedation and antinociception were assessed by the same blinded observer according to the following criteria. Sedation was assessed using a 4-point scale: (1) no sedative effect; (2) reduced alertness but standing; (3) sternal recumbency, marked drowsiness; and (4) sternal recumbency, marked drowsiness with the neck extended. The degree of antinociception was evaluated by the pedal withdrawal response to pinching an interdigital web (superficial antinociception), and using a needle-prick subcutaneously between the ribs (deep antinociception). Lack of antinociception (e.g. a strong positive response to a noxious stimulus) was ensured by drug administration. The baseline stimulus was done with the animals standing in the holding chute. The following scale was used: (1) normal response: strong reaction to a painful stimulus; (2) slightly impaired: no response to skin pinprick, but tail swishing and restlessness; (3) clearly weak: no tail swishing, no response to skin and deep muscle pinprick, and turning toward site of painful stimulus; and (4) absent: animals calm and indifferent to a painful stimulus. Panniculosis response and muscle twitches alone were not considered a painful response to these stimuli. The latent period (time from administration of the dose of clonidine to recumbency), the sedation and analgesic period, and recovery time (from the first spontaneous movement to standing) were recorded. Blood samples (5 mL) to evaluate glycemia were collected from the jugular vein at time 0 and at 30, 60, 120 min, and every 120 min until animals returned to normal alertness. Heart rate (HR) was assessed by auscultation using a stethoscope; respiratory rate (RR) was assessed by observing chest movements/min and rectal temperature (RT) was measured with a digital thermometer (BD, Becton Dickinson, Inc, Ottawa, ON, Canada). Arterial blood pressure (SAP, systolic arterial pressure; DAP, diastolic arterial pressure; and MAP, mean arterial pressure) was measured using a cardiac monitor (EMAI-RX 300 Equipamentos Médicos Hospitales, Brazil) by a non-invasive mechanism with a Velcro cuff (12-19 cm size) around the tail in order to measure the pressure in the coccygeal artery.

All data were analyzed using the Statistical Analysis System (SAS Institute Inc., Cary, NC, USA). A randomized block design was used for each drug dose, in which time was the treatment and each one of the six animals was a block. For dependent variables HR, RR, SAP, DAP, MAP, RT and glucose, an analysis of variance was performed, and the post hoc Dunnett’s test was applied when the treatment response differed from baseline (time 0). For sedation and antinociception dependent variables, the non-parametric Friedman’s test was used, followed by multiple comparisons for ranked data using Dunnett’s test, with time 0 as a baseline. In each analysis, differences were considered significant if p<0.05.

Results

There were no treatment differences during baseline for any of the parameters measured. Sedation and antinociception occurred in all cattle following intramuscular administration of each of the three doses of clonidine. The degree of sedation induced by CL4, CL5 and CL6 was adequate (grade 4 – sternal recumbency, marked drowsiness with the neck extended) but lasted for different durations. Time to onset of sedation was similar between treatments (CL4, CL5 and CL6) (15 min) but delayed with CL4 (30 min; difference not statistically significant). CL6 produced a significantly (p<0.05) longer duration of sedation (375 ± 75 min; mean ± standard deviation) than CL5 (270 ± 61 min) or CL4 (204 ± 52 min; Fig. 1). The onset of effective antinociception (grade 4) was faster with the highest dose, beginning at approximately 30 min, whereas with the low or intermediate doses it began at approximately 60 min. The duration of antinociception was dose-dependent: for the low dose (4 mcg/kg) it was approximately 90 min; for the intermediate dose (5 mcg/kg) approximately 120 min, and for the high dose (6 mcg/kg) approximately 210 min (Fig.2). The duration of the antinociception obtained was shorter than the period of sedation by variable degrees. Glucose concentrations was increased at all doses (Fig.3).

All doses of clonidine induced a significant decrease in HR compared to baseline (Table 1). Following CL4 bradycardia began at 15 min, and with CL5 it began at 5 min, which remained unchanged until 180 min post-treatment for both doses. Following CL6 a significant decrease in HR (p<0.05) at 5 min and stayed low for the remaining test period (600 min). There were no significant changes in arterial blood pressure compared to baseline for any treatment (Table 1). There was a significant decrease (p<0.05) in respiratory rate following all treatments compared with baseline. The CL4 treatment of clonidine produced the longest period of decline in RR (15–240 min), the CL5 and CL6 treatments produced a similar period of decrease in RR, of between 30 and 180 min. CL4 and CL5 caused an increase (p<0.05) in rectal temperature that started at 30 min and lasted until 360 and 480 min, respectively.
Figure 1: Median score for sedation in response to intramuscular administration of 4 (CL4), 5 (CL5) or 6 (CL6) mcg/kg liveweight of clonidine in six cattle. Sedation score was as follows: (1) no sedative effect; (2) reduced alertness but standing; (3) marked drowsiness, rising with difficulty; and (4) marked drowsiness and inability to rise. *abc* Value for *a*CL4, *b*CL5 and *c*CL6 differs significantly (n=6; p<0.05) from the respective baseline (time 0) value for each dose.

Figure 2: Median analgesia score in response to a pedal withdrawal response to pinching an interdigital web or by the needle-prick subcutaneously between the ribs after intramuscular administration of 4 (CL4), 5 (CL5) or 6 (CL6) mcg/kg liveweight of clonidine in six cattle. The following scale was used: (1) normal response to a painful stimulus; (2) slightly impaired; (3) clearly weak; and (4) absent. *abc* Value for *a*CL4, *b*CL5 and *c*CL6 differs significantly (n=6; p<0.05) from the respective baseline (time 0) value for each dose.

Figure 3: Mean ± SD of serum glucose levels (mg/dl) in six cattle after intramuscular administration of 4 (CL4), 5 (CL5) or 6 (CL6) mcg/kg of clonidine in six cattle. *abc* Value for *a*CL4, *b*CL5 and *c*CL6 differs significantly (n=6; p<0.05) from the respective baseline (time 0) value for each dose.
The present study has demonstrated that administration of each of the three IM doses of clonidine (4, 5 and 6 mcg/kg) in cattle resulted in clinically relevant dose-dependent sedation and antinociception. On the basis of other studies involving other species, we selected the doses above as our original doses. In a pilot investigation, intramuscular clonidine 2 or 3 mcg/kg caused minimum sedation/antinociception in cattle. A study in humans that used a dose of 2 mcg/kg of clonidine IM demonstrated that the duration of drowsiness was correlated with the duration of antinociception [2]. In our study, the period of sedation was two or three times longer than the period of antinociception. In humans, a single dose of clonidine given either epidurally or intramuscularly produces antinociception of limited duration [2]. However alpha-2 adrenoceptor agonists induce moderate to deep sedation and antinociception in cattle [14].

Alpha-2 agonists cause bradycardia, although the exact mechanism of this effect is uncertain. It is thought that clonidine decreases blood pressure and heart rate by enhancing parasympathetic nervous system activity at brain stem sites [7]. In our study, high, intermediate and low doses of clonidine decreased HR significantly; this effect was more prolonged with the highest dose (600 min), and continued beyond the end of the period of sedation or antinociception. In goats, the decrease in heart rate returned to baseline values at approximately 5.5 h, concomitant with the waning of the analgesic effects of clonidine [13]. The difference in effects on heart rate between our results and previous animal studies may be species or dose related.

In our study, none of the treatments caused any affect on arterial blood pressure. A study in humans demonstrated that low, intermediate, and high doses of epidural clonidine reduce blood pressure, with the intermediate dose causing the largest decrease [7]. The fact that the higher doses did not result in the largest decrease in arterial blood pressure may be a reflection of a peripheral alpha receptor effect [13]. It is probable that the three doses of clonidine used in this study were higher, considering the sensitivity of ruminants to alpha-2 agonist drugs. The most pronounced decrease in blood pressure is obtained using the epidural rather than an IM route, probably due to inhibition of sympathetic outflow in the spinal cord [10]. Although no animal required treatment for hypotension or bradycardia in this study, the risks associated with these effects suggest the need to be cautious in the case of hypovolemic or hemodynamically unstable animals.

Epidurally administered clonidine in low doses (2 and 3 mcg/kg) in cattle does not produce effects on heart or respiratory rates [5]. More recent reports have described arterial hypoxemia and pulmonary oedema in sheep after using the newer alpha-2 agonist’s detomidine, medetomidine, dexmedetomidine and romifidine [4]. In this study, each of the three doses of clonidine given IM induced a significant decrease in the respiratory rate in all animals, but it was more evident with the lowest dose.

**Table I**: Heart rate, arterial blood pressure, respiratory rate and rectal temperature values in six cattle receiving different doses of clonidine (mean ± SD).

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**HR**, heart rate (beats/min⁻¹); **RR**, respiratory rate (breaths/min⁻¹); **SAP**, systolic arterial pressure (mmHg); **DAP**, diastolic arterial pressure (mmHg); **MAP**, mean arterial pressure (mmHg); **RT**, rectal temperature (°C); **CL4**, clonidine (4 mcg/kg); **CL5**, clonidine (5 mcg/kg); **CL6**, clonidine (6 mcg/kg); **ND**, not determined; *Significantly different from baseline (n=6; p<0.05).
Serum glucose concentrations were increased in the post injection period after administration of the high, intermediate or low dose of clonidine IM. There are many investigations of the hyperglycaemic effects of the alpha-2 adrenergic drugs like xylazine or clonidine [6, 9]. The hyperglycaemia and hypoinsulinaemia induced by alpha-2 agonist drugs are mediated by alpha-2 adrenergic receptors, situated in pancreatic islet beta cells that inhibit the release of insulin [9].

Hypothermia is an expected consequence of alpha-2 adrenoceptor agonist administration in cattle because of decreased heat production and a direct effect on thermoregulation. In contrast, our results with lower doses showed a significant increase in the rectal temperature. It is probable that the clonidine-induced increase in body temperature in our study was mediated by alpha-2 (postsynaptic) adrenoceptors [11] or by stress. Therefore, the higher dose kept the RT slightly increased (not significant) because the alpha-2 agonists may allow for better maintenance of body temperature due to the peripheral vasoconstriction and central redistribution of blood [12].

In conclusion, this is the first study to document the sedative and analgesic effects of IM clonidine in cattle. Clonidine administered IM produced dose-dependent sedation and antinociception in all animals. The highest dose of clonidine caused more prolonged sedation and antinociception, and all doses induced bradycardia and a decreased respiratory frequency with little interference with arterial pressures. Further studies are needed to establish a dose-response for the sedative and antinociceptive effects of clonidine, using a wider range of doses.

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