Comparison of the Analgesic Effect of Clonidine and Lidocaine When Administered Epidurally in Cattle

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Abstract

This study was conducted to compare clonidine and saline to lidocaine for epidural analgesia in cows. Four adult mixed-breed beef cattle weighing 1241 ± 268 lb (564 ± 122 kg) were used. Each cow was randomly assigned to receive each of the three treatments, with a 1-week interval between each treatment. Treatments included epidural administration of 1) 5 ml of physiological saline (0.9% NaCl) solution, 2) 0.2 mg of lidocaine/kg of body weight, not to exceed 100 mg (5 ml), and 3) 5 μg of clonidine/kg, diluted with 0.9% NaCl to provide a volume of 5 ml. The site of epidural injection was the first or second caudal intervertebral space. Heart rate, respiratory rate and arterial blood pressure were recorded before injection; at 5, 10, 20 and 30 minutes after injection; and at 15-minute intervals thereafter. Onset and duration of analgesia, sedation and ataxia were recorded. Analgesia was evaluated by the response to an electrical stimulus and to a needle prick. Repeated-measures ANOVA was used to detect differences between treatments.

Lidocaine-induced analgesia occurred within 10 ± 7 minutes and lasted 56.3 ± 40.1 minutes. Analgesia induced with clonidine occurred within 34 ± 11 minutes and lasted at least 6 hours when tested with electrical stimulus, and 11.6 hrs (699 ± 178 minutes) when tested with needle prick. Epidurally administered 0.9% NaCl solution did not induce analgesia. Heart rate decreased significantly at 45 minutes and 30 minutes following epidural administration of lidocaine and clonidine, respectively. Slight to mild sedation and ataxia were observed in three cows, and one cow showed moderate sedation and ataxia following epidural administration of clonidine. Increased salivation and frequency of urination were observed in each cow treated with clonidine.

Résumé

Cette étude a été menée pour comparer la clonidine et la saline à la lidocaine dans l’induction d’analgésie par voie épiderale chez les vaches. On a utilisé quatre vaches de boucherie adultes de race mélangée pesant 1241 ± 268 lb (564 ± 122 kg). Chaque vache était aléatoirement assignée pour recevoir chacun des trois traitements à une semaine d’intervalle. Les traitements comportaient l’induction épiderale de 1) 5 ml d’une solution saline physiologique (0.9% NACL), 2) 0.2 mg de lidocaine par kg de poids n’excédant pas 100 mg (5 ml) et 3) 5 μg de clonidine par kg de poids dilué avec une solution de 0.9% NACL pour obtenir un volume de 5 ml. L’induction épiderale était administrée entre le premier et le second espace intervertébral caudal. Le rythme cardiaque, le taux respiratoire et la pression artérielle étaient enregistrés avant l’induction puis à nouveau 5, 10, 20 et 30 minutes suivant l’induction et enfin à des intervalles de 15 minutes par la suite. Le début et la durée de l’analgésie, de la sédation et de l’ataxie étaient notés. L’analgésie était évaluée à l’aide d’une stimulation électrique et par la piqure d’une aiguille. Des analyses de variance à mesures répétées ont été utilisées pour déceler les différences entre les traitements.

L’analgésie induite par la lidocaïne prise place en moins de 10 ± 7 minutes et dura 56.3 ± 40.1 minutes. L’analgésie induite par la clonidine prise place en moins de 34 ± 11 minutes et dura au moins 6 heures lorsque évaluée par la stimulation électrique et 699 ± 178 minutes lorsque évaluée avec la piqure de l’aiguille. L’administration épidermale de la solution saline physiologique 0.9% NACL n’a pas induit d’analgésie. Le rythme cardiaque diminuait de façon significative 45 minutes après l’induction épidermale de lidocaine et 30 minutes après l’induction de clonidine. Des signes de
sédation légère ou douce et d’ataxie ont été observées chez trois vaches alors qu’une vache montrait des signes de sédation modérée et d’ataxie suite à l’injection épidermale de clonidine. Une augmentation de la salivation et de la fréquence d’urination s’observait chez toutes les vaches traitées avec la clonidine.

Introduction

Clonidine (2-[2,6-dichlorophenylamino]-2-imidazoline) est un centralement agissant avec un \( \alpha_2 : \alpha_1 \) récepteur sélectivité rapport de 220:1, qui est intermède entre xylazine (160:1) et detomidine (260:1). Clonidine est utilisée comme un anti-hypertenseur dans l'humain grâce à sa capacité à diminuer le flux sympathique en sortie de l'axe, prurit, nausée, vomissement ou gastro-éматique évident.\(^{12,5,14}\) Presque sûrement, la substance gelatinesque du canal dorsal est le site où clonidine active les postsynaptiques \( \alpha_2 \)-récepteurs pour causer une dépression des flux sympathiques et afférents \( \alpha_2 \) et \( C \) fibres sensitif somatosensory reflexes.\(^{6,9,8}\) Several studies in another species showed that epidural analgesia induced by clonidine is more potent than epidural analgesia induced by morphine.\(^{5,8,11,30}\) In humans, epidurally administrer clonidine has been used for treatment of chronic, intractable pain and perioperative pain associated with various kinds of abdominal surgery.\(^{6}\)

The reported duration of clonidine-induced analgesia varies greatly between species.\(^{9,3,21,26}\) Analgesia lasted 2 heures when clonidine was administrer intrathécalement dans le mouton conscient,\(^9\) however prolonged analgesia (average duration of 6 à 8 heures; range 4 à 72 heures) has been observed when administrer epidural in humans.\(^{16}\) Other \( \alpha_2 \)-agonists such as xylazine, detomidine and medetomidine have been reported to induce prolonged duration of epidural analgesia in animals.\(^{13,22,27}\) To the authors' knowledge, there is no report describing the effects of epidural administrer clonidine in adult cattle. Therefore, the objective of this study was to evaluate the analgesic effect of epidural administrer clonidine in cows.

Materials and Methods

Four healthy, adult (1 to 12 years old) mixed-breed beef cows weighing 1241 ± 208 lb (564 ± 122 kg) were randomly assigned to receive three treatments, with a 1-week interval between treatments. Treatments included epidural administrer of 1) 5 ml of physiological saline (0.9% NaCl), 2) 0.2 mg of lidocaine/kg of body weight, not to exceed 100 mg (5 ml), or 3) 5 μg of clonidine/kg of body weight, diluted with 0.9% NaCl solution to provide a volume of 5 ml. The investigators of this study were aware of each treatment received by every cow.

Cows were restrained in a chute. After the tail head region was surgically prepared prior to placement of a sterile needle, an epidural injection was administrer in the first or second caudal intervertebral space, using an 18-gauge, 1.5-inch (3.81-cm) needle. Correct placement of the needle was determined by the hanging-drop technique or by lack of resistance during injection of a small amount of 0.9% NaCl.\(^{38}\) Each drug or saline was injected over a 1-minute period.

Heart rate (HR), respiratory rate (RR) and arterial blood pressure (systolic [SAP], mean [MAP] and diastolic [DAP] pressures) were recorded at 0 (baseline), 5, 10, 20 and 30 minutes after epidural injection of drug or saline, and then at 15-minute intervals thereafter for 6 heures après l'administration de la drogue. Needle prick was then used to evaluate analgesic effect for the remainder of the experiment until the cow again responded to the stimulus. Arterial blood pressures were measured by using a pressure cuff placed over the caudal artery. A standard-limb lead-II electrocardiogram\(^4\) was monitored continuously to detect arrhythmias for 6 heures, with one lead placed over the right scapula and the other placed over the fifth rib on the right side.

Onset and duration of regional analgesia was determined by use of an electrical stimulus, using a nerve stimulator in the perineal area. An electrical stimulus was applied to cows by use of a square-wave direct current nerve stimulator\(^5\) attached to each cow by means of two platinum electrodes. The electrodes were positioned 5-cm lateral and 3-cm ventral to the anus. During testing, voltage (0 to 80 V, duration 0.5 ms) was increased until a clear avoidance response (avoidance threshold), such as turning the head toward the site of the stimulus or shift of weight of the hindlimbs, became apparent to the investigator. The avoidance threshold for needle prick was also tested at the same recording time and location as the electrical stimulus. Both avoidance thresholds were recorded immediately before injection (baseline), at 5, 10, 20 and 30 minutes after injection, and at 15-minute intervals thereafter for 6 heures. The avoidance threshold for needle prick was recorded continuously beyond 6 heures until the analgesic effect subsided and the cow again responded to the stimulus.

The degree of sedation was evaluated at each of the recording times after administration of the treatments. The grading scale for evaluation was: 0, no sedation, cow appears alert; 1, cow has drooping upper eyelids, but is aware of surroundings; 2, cow has drooping eyelids, was unaware of surroundings, head was lowered, but still above the shoulders; and 3, profound
sedation, cow has drooping eyelids, is unaware of surroundings, and head is held below the shoulders.

The degree of ataxia was also assessed and graded on a scale of 0 to 3 (0, no ataxia; 1, slight ataxia displayed throughout the monitoring period, but knuckling of the fetlocks of the hindlimbs not observed; 2, continuously swaying while standing or attempting to become recumbent, but easily coaxed to continue standing; and 3, knuckling of the fetlocks of the hindlimbs, leaning against the sides of the restraint chute, or recumbency and could not be coaxed to stand). Other effects such as loss of muscle tone in the tail region, salivation and frequency of urination were also monitored. The experimental period lasted 6 hours, after which time the recording of all parameters was discontinued except the analgesic effect, which was assessed hourly by needle pin prick until the cow again responded to the stimulus.

Values for HR, RR, SAP, MAP, DAP and onset and duration of sedation, analgesia and ataxia were analyzed using repeated-measures ANOVA. Values of P ≤ 0.05 were considered to be significant.

Results

Results are summarized in Table 1.

Physiological saline (0.9% NaCl) solution—Compared with baseline values, significant differences were not observed for HR, RR, DAP and the degree of analgesia at any time after administration of 0.9% NaCl solution. The values of SAP and MAP increased transiently from baseline only at 5 minutes after injection. None of the following effects were observed after epidural injection of 0.9% NaCl solution: analgesia, sedation, ataxia, cardiac arrhythmias, decreased muscle tone in the tail, salivation, increases in frequency of urination or recumbency.

Lidocaine—Heart rate was significantly decreased at 45 and 60 minutes after administration of lidocaine.

### Table 1. Mean ± SD heart rate (HR), respiratory rate (RR), systolic (SAP), mean (MAP), and diastolic (DAP) blood pressure in cattle receiving caudal epidural injection of saline, lidocaine (0.2 mg/kg) or clonidine (5 µg/kg).

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<tr>
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<th>HR (beats/min)</th>
<th>RR (breaths/min)</th>
<th>SAP (mm Hg)</th>
<th>MAP (mm Hg)</th>
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<td>15 ± 5</td>
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<td>95 ± 10</td>
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*Significantly different from baseline (time-0) values (P < 0.05).

*Significantly lower than lidocaine values (P < 0.05).
however, RR, SAP, MAP and DAP remained unchanged during the experiment. Decreased muscle tone in the tail and analgesia were observed within 10 ± 7 (5 to 20) minutes after injection of lidocaine and lasted for 56 ± 40 (25 to 115) minutes. Analgesia (avoidance threshold) was significantly greater than the preinjection value. Sedation and ataxia did not occur and cardiac arrhythmia, salivation, increases in frequency of urination or recumbency were not observed after lidocaine treatment.

Clonidine—Analgesia and decreased muscle tone in the tail were detected within 34 ± 11 (20 to 45) minutes. Analgesia to the electrical stimulus lasted for at least 6 hours, and analgesia to the needle prick lasted for 699 ± 178 (480 to 855) minutes. Slight to mild sedation (n = 3 cows) and slight ataxia (n = 4 cows) were detected at 24 ± 15 minutes and 31 ± 10 minutes after injection, respectively. Sedation lasted 90 to 200 minutes and ataxia lasted 40 to 72 minutes. One cow exhibited moderate sedation for 60 minutes. The HR and RR decreased significantly from baseline values at 30 minutes and 5 minutes, respectively, after drug administration, and lasted until the end of the experiment. SAP and MAP were lower than baseline values at 60 and 30 minutes post-administration, respectively. DAP values remained unchanged. Cardiac arrhythmia was not observed. An increase in salivation and frequency of urination were evident in all cows receiving clonidine treatment.

The HR and RR of cows administered clonidine was significantly (P ≤ 0.05) less than the HR and RR of cows treated with lidocaine from 5 to 60 minutes and 30 to 60 minutes after drug administration, respectively. The RR was significantly lower for cows treated with clonidine than those treated with 0.9% NaCl or lidocaine. Mean values for SAP and MAP were significantly lower 30 minutes post-administration in cows receiving clonidine than those receiving the other two treatments, and remained lower through 120 and 60 minutes, respectively. The HR, RR, SAP, MAP and DAP of cows given 0.9% NaCl or lidocaine were not significantly different. Onset of analgesia was significantly (P ≤ 0.05) slower for cows receiving clonidine than those receiving lidocaine. Sedation was observed in cows receiving clonidine.

Discussion

Clonidine was the first α₂ agonist extensively studied for use as a spinal analgesia in laboratory animals prior to its clinical application to human patients. These studies indicated that there is a high density of specific clonidine binding to the superficial laminae of the dorsal horn in sheep spinal cord, an area important for nociceptive sensory processing. In addition, the potency of clonidine in blocking withdrawal response to a noxious stimulus was found to be greater after epidural administration than after IV administration. While no direct relationship was demonstrated between antinociceptive effect and plasma clonidine concentration, a close correlation was observed between antinociception and CSF clonidine concentration, suggesting a spinal site of action. These studies also indicated that epidural clonidine produced analgesia rapidly and effectively, but with a short duration (2–4 hours), which seemed to be in agreement with rapid absorption, efficient dural transfer (14% of the administered dose) and rapid elimination of the drug in CSF of sheep.

Unlike the effect of clonidine in sheep, our study shows that the analgesic effect induced by epidural clonidine in cows has a slow onset of action with long lasting perineal analgesia. Timmermans et al. and Savola et al. reported that clonidine has a low lipophilicity and a pKa of 8.1 with a high degree of ionization (33%) at physiologic pH (7.4). Generally, ionized drugs have low lipid solubility, thus they have difficulty diffusing across cell membranes to either reach the site of action or to be removed from the site of action. As a result, drugs with a high degree of ionization normally have slow onset and long duration of pharmacologic actions. Therefore, clonidine should have a slow onset but long duration of analgesic action because of its low lipophilicity and high degree of ionization. Results of our study support this observation.

The reason for the longer duration of analgesia from epidurally administered clonidine in cattle compared to sheep is not clear. The differences in location for drug deposition and total dose administered may have contributed to the difference in onset and duration of analgesia between these two species. Clonidine was deposited epidurally at the lumbosacral interspace in studies with sheep, while it was administered into the caudal intervertebral epidural space in cows. The total dose of clonidine administered was also different between these two species, 6.7 μg/kg (300 μg) in sheep compared to 5 μg/kg (2,820 μg) in cows.

In veterinary medicine, α₂ agonists are usually administered parenterally to induce profound sedation. Sedation is reported to be one of the side-effects of epidurally administered clonidine in humans, but in dogs the dose of clonidine that induces maximum antinociception after intrathecal administration does not induce sedation. In our study, slight to mild sedation was observed in cows during epidural clonidine analgesia. Slight ataxia occurred at approximately the same time as did sedation, but ataxia was short-lived and with no apparent disruption of normal hindlimb motor function.

Similar to effects reported for sheep, the cardiovascular effects of epidurally administered clonidine in
this study appeared to be minimal. Changes in SAP and MAP were observed only at 60 and 30 minutes post-administration, respectively, which were significantly lower than pre-administration values. Epidural clonidine has been reported to induce a decrease in arterial blood pressure as a result of activation of \( \alpha_2 \)-adrenoceptors on sympathetic preganglionic neurons in the spinal cord.\(^{17} \) Intrathecal injection of clonidine induces a greater decrease in blood pressure when the drug is injected in the thoracic spinal site than when injected in the lumbar site.\(^{8,10,12,15} \) Clonidine administered at the lumbar site may have less influence on blood pressure than the drug administered at the thoracic site because of its greater distance from the sympathetic preganglionic neurons.

Heart rate decreased significantly from 30 minutes after administration of clonidine and remained decreased until the end of the experiment. Epidurally administered clonidine was reported to induce a significant decrease in HR, most likely due to a combination of presynaptic inhibition of norepinephrine release and a vagomimetic effect induced by \( \alpha_2 \)-agonists.\(^8 \)

In the present study epidurally administered clonidine caused a significant reduction in RR in cows, similar to that observed in humans,\(^{23,24} \) dogs\(^9 \) and goats.\(^{28} \) Reports suggest that respiratory depression is greater when clonidine is administered epidurally than when administered systemically, but there is no scientific data to support this observation.\(^{23,24} \)

Increased frequency of urination follows administration of \( \alpha_2 \) agonists. Cattle appear to be more susceptible to this effect than other species, with urine output increasing at least seven-fold.\(^{24} \) Proposed mechanisms for this effect include inhibition of release of antidiuretic hormone from the pituitary,\(^{19} \) antagonism of the renal tubular effect of antidiuretic hormone,\(^{20,31} \) an increase in glomerular filtration rate\(^{32} \) and the release of atrial natriuretic factor.\(^5 \) Increased salivation subsequent to parasympathetic stimulation and decreased swallowing occurs during xylazine sedation of ruminants.\(^{20} \) Though systemic effects of clonidine, other than sedation and ataxia, have not been studied extensively in domestic animals, increased salivation also occurred in cows in our study. Interestingly, by subjective observation increased salivation seemed to coincide with the onset of sedation and analgesia. Clonidine should be used with great caution in dehydrated animals as the increases in salivation and urine output may be detrimental to these animals.

Lidocaine is the most commonly used anesthetic for local and regional analgesia in veterinary practice. In this study, after epidural administration of lidocaine, onset and duration of perineal analgesia and loss of muscle tone of the tail were similar to that reported by other investigators.\(^{26} \) Lidocaine is frequently reported to induce disruption of hind limb motor function and ataxia. Occasionally, animals may become recumbent as a result of severe ataxia, but the cows in this study did not become recumbent. In comparison, cows receiving clonidine appeared to be more ataxic than those receiving lidocaine. However, all cows in either group remained standing throughout the experiment period. Importantly, the duration of analgesia induced by clonidine in the present study was significantly longer than that of lidocaine.

Chronic epidural clonidine infusion in dogs has been shown to cause no pathologic effect on the spinal cord,\(^{23,28} \) therefore clonidine is likely safe for treatment of persistent straining in cows. Though pregnant women receiving clonidine treatment have delivered full-term, healthy babies,\(^{18} \) administration of clonidine to pregnant ruminants may cause premature parturition since ruminants are known to be more sensitive to \( \alpha_2 \)-agonists than are other species.

**Conclusion**

Results of our study indicate that epidurally administered clonidine may be useful in ruminants requiring long-lasting perineal analgesia for standing surgery and pain relief with minimal side-effects.

**Acknowledgements**

This study was supported by USA and Research Center, Orion Cooperation, Farmos, Turkku, Finland and Food Animal Health and Disease Research Funds of the College of Veterinary Medicine, Auburn University, Alabama. The protocol for this study was approved by the Auburn University Institutional Animal Care and Use Committee.

**Footnotes**

a Lidocaine HCl Injection, Abbott Laboratories, North Chicago, Ill.
b Duraclon (Clonidine HCl Injection), For Epidural Injection, Roxane Laboratories, Inc, Columbus, Ohio.
c Dinamap, Veterinary Pressure Monitor 8300, Critikon Inc, Tampa, Fla.
d Spacelab, A Squibb Co, Redmond, Wash.
e Grass S88 Stimulator, Grass Instruments Co, Quincy, Mass.
f SAS Inc, Cary, North Carolina

**References**


AABP Officers

President

Dr. Patty Scharko, Lexington, Kentucky

Patty was raised in Columbia, South Carolina and became interested in food animals upon her arrival at The University of Georgia undergraduate campus. She was very involved with the Block & Bridle and Pre-Vet Clubs. Patty received her DVM degree from the University of Georgia in 1983, followed by an internship at Tufts University Ambulatory. A residency in production medicine was completed at North Carolina State University in conjunction with a Masters in Public Health in Epidemiology in 1989 from the University of North Carolina-Chapel Hill. Patty taught at the Atlantic Veterinary College in Prince Edward Island, Canada, in the Ambulatory section for six years following her residency. She became a Diplomate of the American College of Veterinary Preventive Medicine in 1993, studying while she was on maternity leave. In 1995, Patty moved to Lexington, Kentucky, and is the extension ruminant veterinarian at the University of Kentucky involved with both dairy and beef cattle.

Patty has been active in AABP with involvement on the Information Management Committee, as coordinator of Computer Practice Tips and Computer Technology Sessions, General Sessions chair, AABP-L list manager, and District 12 Director.

Patty has been involved with several international groups. She spoke at a dairy producer Brazilian conference and a women’s veterinarian conference in Mongolia. When not at meetings or traveling, Patty enjoys time with her family, Tommy and Melissa.

President’s Message

Dear AABP Members:

AABP members are recognized as leading advisors and experts in cattle health and well being. As an AABP member, you have access to many resources to keep you current on this information: Bovine Practitioner publications, Proceedings, monthly newsletters and inserts, annual conference, pre-conference specialty seminars, AABP members-only section on the web, and AABP-L.

The future of food animal veterinarians is a significant concern for AABP. AABP leaders are meeting with other food animal specialty groups in a Food Animal Summit to discuss the opportunities and threats in our profession. Changes in the industry have altered the veterinary profession and the kind of services that are required. It is important that we adequately understand what the needs will be for the future new graduates and that we attract, train, and graduate bovine veterinarians who will be successful.

Students are acknowledged as an important part of our membership. Low student membership dues, free conference registration, funds for student chapters, and job database are part of our effort to improve opportunities for careers in bovine medicine. Students have an opportunity to compete at the conference in Student Case Presentation; the AABP Board of Directors has increased the award amount for the Columbus conference (see “blank” www.aabp.org/scrp.htm for more information). Second year students may apply for Amstutz Scholarships, currently $1,500 per award, based on merit and a submitted paper; fourteen scholarships were given in 2002. The Student Externship Program has up to $500 funds available to fund a 2-week externship, with preference given to food animal interest and limited past exposure to food animal practice; thirty were awarded in 2002. AABP must do all that it can to expose students and recent graduates to food animal practice and all the rewarding career opportunities available.

AABP spends a considerable amount of time and resources on liaisons with animal health groups and agencies. It is important that AABP remains involved and participates in the discussion of cattle issues. I am grateful for all the volunteers who spend countless hours and time away from their families to represent AABP at state, national, and international meetings.

I encourage you to get involved in AABP activities, if you are not already. Come to the Columbus conference and join one of the committees that will meet on Thursday morning during the conference. These committees continue to interact through e-mail dialogues on important issues.

Shalom,

Patty Scharko