Caudal Epidural Analgesia in Cattle Using Xylazine

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ABSTRACT

Each of 25 mature Holstein cows were given a single 5 mL epidural injection of one of four different concentrations of xylazine or saline. The onset, magnitude and duration of caudal epidural analgesia was quantitated with the use of a low voltage DC current applied to the perineal area. The dose that produced the longest duration of analgesia and produced the least ataxia or sedation was approximately 0.05 mg/kg (25 mg in 5 mL diluent). The analgesia produced by this xylazine dose was compared to a standard dose of epidural lidocaine (100 mg/5 mL) by the same method. To investigate the role of systemic absorption in the production of epidural analgesia, the previously utilized epidural xylazine dosage was given intramuscularly to four adult cows. Analgesia was quantitated as before and the results compared with epidural xylazine.

Epidural xylazine produced a significantly greater duration of analgesia, as measured by this model, than did epidural lidocaine. Xylazine, given epidurally, produced greater perineal analgesia than did xylazine given intramuscularly.

RÉSUMÉ

Cette expérience portait sur cinq groupes de cinq vaches Holstein; celles de quatre premiers reçurent une injection épidurale de 5 mL de l'une ou l'autre de quatre concentrations expérimentales de xylazine, alors que celles du cinquième ne reçurent que 5 mL de solution saline. Les auteurs déterminèrent ensuite le début, l'ampleur et la durée de l'analgésie qui s'ensuivit, au moyen d'un courant continu de faible voltage qu'ils appliquèrent à la région périnéale. La dose qui produisit l'analgésie la plus longue et le moins d'ataxie ou de sédation se situait aux environs de 0,05 mg/kg, c'est-à-dire 25 mL dans 5 mL de diluent. Les auteurs utilisèrent la même méthode pour comparer l'analgésie ainsi réalisée, à celle d'une dose épidurale standard de lidocaïne, c'est-à-dire 100 mg/5 mL. Pour déterminer le rôle de l'absorption systémique, dans la production de l'analgésie épidurale, les auteurs administrèrent une injection intramusculaire de 25 mg de xylazine, dans 5 mL de diluent, à quatre vaches adultes; ils quantifièrent ensuite l'analgésie, comme précédemment, et comparèrent les résultats avec ceux de l'injection épidurale de xylazine. Le protocole expérimental précité révéla que l'injection épidurale de xylazine produisait une analgésie plus longue que celle de lidocaïne et qu'elle entraînait une analgésie périnéale plus grande qu'en injection intramusculaire.

INTRODUCTION

Caudal epidural analgesia is routinely used in cattle for a variety of surgical and obstetrical procedures and may be described as "high" or "low" (1). Both techniques employ the injection of a volume of local anesthetic solution into the epidural space, between the last sacral and first coccygeal vertebrae, or in the first coccygeal interspace (Cy1-Cy2)(2). High caudal epidural analgesia involves the administration of a relatively large volume of local anesthetic to provide analgesia to more cranial body regions and is used for performing hindlimb and flank surgery (2,3). Low caudal epidural analgesia is more frequently used than the high epidural technique and differs only in the volume of the local anesthetic solution injected. A range of dosages are present in the literature, however a commonly recommended dose for adult cattle is 5-7 mL of 2% lidocaine (1,4). This technique produces analgesia restricted to the caudal perineal region and is useful for several diagnostic and surgical procedures.

Perhaps the most common complication of low caudal epidural analgesia is unintentional overdose, causing ataxia or even recumbency. This event can lead to the injury of the animal or may complicate the intended procedure or both (5). Overdose may occur with the initial injection of a local anesthetic or may follow a second dose of the drug, as the effects of the initial block wane. The duration of analgesia from a 5-10 mL dose of 2% lidocaine is variable, however a conventionally reported range is one to two hours (5-7). On occasion, procedures conducted under caudal epidural analgesia exceed this duration, and require a second dose to be given, increasing the risk of unintentional overdose.

Caudal epidural analgesia using local anesthetics is produced by the inhibition of conduction of impulses of sensory nerves located in the cauda equina (8). The action of local anesthetics is nonselective and depression of autonomic and motor nerves accompanies desensitization. It is this nonselective depression of motor nerves that may result in recumbency.

It has been shown in a number of species that opioids and alpha-

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adrenergic agents produce selective caudal epidural analgesia, by activating specific spinal receptors (9,10). Stimulation of these spinal receptors results in the inhibition of rostral transmission of nociceptive (pain) impulses. Therefore, a potential advantage of such agents is the production of selective sensory blockade, without the unfavorable depression of motor or autonomic neurons. Xylazine, an $alpha_2$-adrenergic agonist, was recently investigated for epidural use in the horse. It resulted in safe and effective analgesia and produced much less depression of motor function than that produced by lidocaine (11). The purpose of this study was to determine if xylazine produces caudal epidural analgesia in cattle and to compare the analgesia of xylazine with the recommended dose of lidocaine.

MATERIALS AND METHODS

The experiments followed the guidelines of the "Guide to the Care and Use of Experimental Animals", Volume 1 of the Canadian Council on Animal Care.

PART 1: DETERMINATION OF THE ANALGESIC EFFECTS OF EPIDURAL XYLAZINE

Twenty-five adult dairy cows (weighing between 475 and 550 kg) were involved in this portion of the experiment. Each cow was restrained in a stanchion and given a single epidural injection of one of four different concentrations of xylazine (Rompun, Mobay Corporation, Shawnee, Kansas) or a control solution (saline) between Cyl and Cy2, using an 18 gauge 3.7 cm hypodermic needle. Xylazine dosages were diluted in sterile saline to a final volume of 5.0 mL, and all treatments were blinded. The specific composition of the xylazine solutions were: 1 mg/mL, 3 mg/mL, 5 mg/mL and 7 mg/mL. Each of the solutions was given to five different cattle (total number of injections = 25). Accurate placement of the needle in the epidural space was determined by the presence of negative pressure (hanging-drop technique) and negligible resistance to injection. Cattle with epidural injections not fulfilling both criteria were replaced. No cow received more than one epidural injection. The onset, magnitude and duration of the analgesia were quantitated with the use of a continuous-output, low voltage, direct current (Grass SD9 stimulator, Grass Instruments, Quincy, Massachusetts) applied to the perineal area of the cows. A maximum stimulus of 80 volts was used. The electrodes, in the form of alligator clamps, were located approximately 5 cm on either side of the vulva. An electrical conducting paste was not used. The lowest voltage that produced a clear avoidance response (avoidance threshold) was recorded. An avoidance response included any of: purposeful movements of the tail, lifting of a hindlimb, as in preparation to kick, or depression of the hindquarters. The cows were tested immediately prior to the epidural injection (baseline) and at 15 minute intervals thereafter for a minimum of 1.5 hours or until the avoidance threshold returned to baseline. Clinical estimates of analgesia (perineal stimulation with a needle or hemostat) corresponded to an avoidance threshold of approximately 40 volts, so that this voltage was considered the acceptable minimum. In addition to quantitating the avoidance thresholds, a subjective assessment of ataxia and sedation was made and recorded by two observers independently. Ataxia was evaluated by the ability of the cow to compensate when gently pushed or pulled, while in the stanchion. Sedation was subjectively evaluated by the attitude of the cow, including the response to noise, and carriage of the head. The presence of excessive salivation was also recorded. The dose that produced the longest duration of analgesia and produced the least ataxia or sedation was selected for use in part 2 of the experiment.

PART 2: COMPARISON OF XYLAZINE WITH LIDOCAINE HYDROCHLORIDE

An additional nine adult dairy cows of similar weights were used in this portion of the experiment. Seven randomly selected cows were given an epidural injection of 100 mg of lidocaine hydrochloride (Lidocaine injectable, Vet Labs Ltd., Lenexa, Kansas) (5.0 mL of a 2% solution). Another two cows were given the optimal epidural dose of xylazine selected from part 1 of the protocol (25 mg in a 5.0 mL volume). Thus, seven cows received epidural lidocaine, and these animals were compared to a total of seven receiving epidural xylazine. Avoidance thresholds were determined in a manner similar to that in part 1. As for part 1, the two observers were unaware of the identity of the treatments received by the cattle.

The mean duration of an avoidance threshold greater than 40 volts was compared using a Student's t test. The magnitude of avoidance threshold was compared with a Kruskal-Wallis H test. Statistical significance was set at the 5% level.

PART 3: COMPARISON OF EPIDURAL XYLAZINE TO INTRAMUSCULAR XYLAZINE

To investigate the possibility that the analgesic properties of epidural xylazine may be the result of systemic absorption, 25 mg of xylazine in 5.0 mL of saline were given intramuscularly (semimembranosus/semitendinosus) to four adult cows and four cows were given an intramuscular injection of 5.0 mL of saline. The range of weights of the cattle were as before. Avoidance threshold data were obtained as in parts 1 and 2 and the treatments were blinded to the observers. The magnitude of the avoidance thresholds at each interval were compared to the same epidural dose of xylazine using the Kruskal-Wallis H test ($p < 0.05$).

RESULTS

PART 1: DETERMINATION OF THE ANALGESIC EFFECTS OF EPIDURAL XYLAZINE

An avoidance threshold of at least 40 volts was observed in epidural xylazine dosages of 15 mg, 25 mg and 35 mg. The elevation of the avoidance threshold was inconsistent and short-lived with the 15 mg dose and there was not a substantial difference in the duration of the avoidance threshold elevation in the 25 mg and the 35 mg dose (2.4 ± 0.67 h and 2.5 ± 0.06 h respectively) so that the 25 mg dose (5 mL of 5 mg/mL) was selected for investigation in parts 2 and 3. Mild ataxia and sedation were consistently observed at both the 25 mg and 35 mg dosage. Treated cows held their heads lower than before treatment, were less reactive to noises and movement in the barn and were

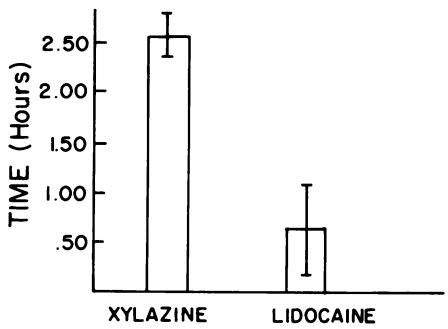

Fig. 1. Mean duration of avoidance threshold > 40 volts (Time) using epidural xylazine (25 mg/5 mL) and epidural lidocaine (100 mg/5 mL) in adult dairy cows. Bars represent mean duration (h) and standard error of the mean.

cautious when moving in their stanchions. Subjectively, the duration and intensity of these side effects were correlated with the elevation of the avoidance threshold. Flaccidity of the tail was observed in all cattle given either of these dosages, which persisted until the avoidance threshold values began to decline from the 80 volts maximum. A single cow receiving 35 mg xylazine became recumbent 20 min following injection but rose without assistance when encouraged to do so.

PART 2: COMPARISON OF XYLAZINE WITH LIDOCAINE HYDROCHLORIDE

The magnitude and duration of analgesia with lidocaine and xylazine (25 mg) is illustrated in Fig 1. Epidural xylazine produced a significantly greater ($p = 0.003$) duration of avoidance threshold exceeding 40 volts than epidural lidocaine (2.54 ± 0.23 h compared with 0.62 ± 0.45 h). The onset of elevation in the avoidance threshold occurred sooner with lidocaine than xylazine, but this difference was not significant. The avoidance threshold voltage was significantly greater with xylazine than lidocaine from 1.25 h through 3 h postinjection. Mild sedation and ataxia were observed in all cows receiving 25 mg of epidural xylazine. Two of the cows treated with lidocaine were noticeably ataxic and one became recumbent. This lidocaine treated cow became ataxic and went down. She remained recumbent for 30 min.

PART 3: COMPARISON OF EPIDURAL XYLAZINE AND INTRAMUSCULAR XYLAZINE

The cattle given 25 mg of xylazine in 5 mL of diluent by epidural injection were compared to those given 25 mg of xylazine intramuscularly in a similar volume. There was a significant difference in avoidance threshold from 60 min following injection to the end of the test period. The peak elevations in avoidance thresholds were less in intramuscularly treated cattle than for those with epidural administration. An avoidance threshold exceeding 40 volts was recorded only once in a single cow, 30 min following intramuscular injection. Sedation was more marked in cattle treated intramuscularly and one of these cows became recumbent. This animal remained recumbent for 30 min, rose when stimulated, and went down for another 15 min. Profuse salivation was recorded in two of the four cattle given intramuscular xylazine, whereas none of the epidurally treated animals showed ptyalism.

DISCUSSION

Epidurally administered xylazine, at a dose of approximately 0.05 mg/kg, provided caudal epidural analgesia for a significantly longer duration than does epidural lidocaine at approximately 0.2 mg/kg. The mean duration of avoidance threshold elevation produced by xylazine was approximately four times that of lidocaine. Epidural lidocaine, at a dose of 100 mg produced a mean duration of "surgical analgesia" (avoidance threshold > 40 volts) of approximately 40 min. This short period of desensitization was probably related to the testing method. The relatively high standard error of the means related to marked individual variation and small sample sizes. The magnitude of the avoidance threshold elevation was comparable between epidural lidocaine and epidural xylazine treated cattle. Both agents usually eliminated an avoidance response to an electrical stimulus of 80 volts.

The drugs were not given on a mg/kg basis, to allow preparation of all the solutions prior to administration, to blind the study. Since the cattle were of different weights, a range of dosages were given, however the effects of this were minimized by randomizing the assignment of treatments. The volume of administration was consistent in both lidocaine and xylazine treatments, as volume has been shown to exert an effect on the onset and duration of analgesia produced by epidurally administered drugs (12).

The prolonged duration of epidural analgesia using xylazine was not without disadvantage. Systemic absorption of the xylazine is likely, as treated cattle often showed signs of sedation. Dosages that did not result in sedation inconsistently produced epidural analgesia. Measurement of blood concentrations of xylazine, or its metabolites, were not conducted in this study.

A second disadvantage of epidural xylazine is the somewhat delayed onset of analgesia compared to lidocaine. The delay was not statistically significant in our model, however a delayed onset of desensitization has been noted clinically. This disadvantage may be avoided with the simultaneous use of lidocaine and xylazine, but this combination was not investigated in this study.

The proposed mechanism of action of epidurally administered alpha-adrenergic agonists involves the binding to spinal cord receptors in the dorsal horn, resulting in the inhibition of transmission of noxious stimuli, mediated by substance P. In addition to adrenergic and opiate systems, other spinal receptor systems have been reported to mediate antinociception (analgesia) including serotonin (13), and 5-hydroxytryptamine (14). Neurospinal receptor pharmacology is complex and dynamic; recent studies have shown interactions between opioid and adrenergic systems, including synergy and cross-tolerance (15,16). Also, there appears to be species variation in the nature of these phenomena. There was no apparent difference in the observed incidence of ataxia with either xylazine or lidocaine. The dose of both drugs was relatively modest. The development of ataxia is dose-dependent using lidocaine, an expected phenomenon when using the high caudal epidural technique. Based on the proposed mechanism of action, the incidence of ataxia associated with the use of xylazine would be expected

to be less than lidocaine, however none of the concentrations tested in this experiment produced marked ataxia. Preliminary studies were conducted using xylazine at higher epidural doses. Injections of 0.12 mg/kg (60 mg xylazine in 5 mL diluent in 500 kg cows) produced noticeable ataxia but not recumbency. Ataxia was commonly observed in horses following epidural xylazine in doses exceeding 0.24 mg/kg and was attributed to the local anesthetic properties of xylazine (11). A similar mechanism may have been responsible for the ataxia observed in this experiment. High doses of alpha$_2$-agonists have been shown to produce hindlimb flaccidity in rats (10). Ataxia may be less problematic with the availability of more selective alpha$_2$-adrenergic agonists.

The combination of epinephrine in the local anesthetic solution is reported to result in a substantially prolonged duration of analgesia; up to twice that with lidocaine alone (4,5). A twofold increase in duration of analgesia using an epinephrine-lidocaine combination would not have provided analgesia of comparable duration to that produced using epidural xylazine at 0.05 mg/kg, based on our data. Epinephrine is thought to prolong analgesia by vasoconstriction and delayed absorption of the local anesthetic. A second possibility is that the epinephrine may act via alpha$_2$-adrenergic receptors in a manner similar to that proposed for xylazine (17). The effects of use of combined epinephrine and xylazine in epidural solutions is unknown. An enhanced duration of caudal analgesia may result with such a combination.

The duration of analgesia provided by epidural xylazine may be clinically useful in the treatment of prolapsed viscera in cattle. The extra period of analgesia may be of benefit in reducing the incidence of recurrent prolapses or perineal damage following the reduction of a prolapsed viscus. Relatively prolonged desensitization, with maintenance of motor tone, may allow greater resolution of edema and swelling and reduce the stimulus to straining when the effects of the block wane. Also, analgesia sufficient to perform standing flank surgery may be possible with an appropriate combination of dose and volume of xylazine or other alpha$_2$-adrenergic agonist administered by epidural or intrathecal injection. Dose-response experiments are required to substantiate or refute this latter possibility given the untoward motor effects (ataxia and tail flaccidity) observed with high doses of epidural xylazine.

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