Analgesic effects of tramadol hydrochloride administered via caudal epidural injection in healthy adult cattle

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Objective—To evaluate the extent and duration of analgesic effects of tramadol hydrochloride administered epidurally in standing healthy adult cattle.

Animals—5 mixed-breed adult female cattle.

Procedures—1, 2, or 3 mg of tramadol/kg was injected into the first intercoccygeal space of each cow in random order at 1-week intervals. Analgesia, sedation, and ataxia were scored on scales of 0 (no effect) to 3 (complete analgesia or extreme sedation or ataxia) at 5-minute intervals beginning 5 minutes prior to injection and ending 120 minutes after injection. Analgesia was evaluated on the basis of response to pinprick stimuli over 9 caudal regions. Heart rate, respiratory rate, rectal temperature, and rumen motility were assessed 5 minutes before and at predetermined intervals for 120 minutes after tramadol injection.

Results—Analgesia induced via tramadol administration was dose dependent (eg, mean duration of complete analgesia at the perineum was 18 minutes when cows received the 1 mg/kg dose, 60 minutes when cows received the 2 mg/kg dose, and 92 minutes when cows received the 3 mg/kg dose). Slight to mild sedation and ataxia were observed when cows received 2 or 3 mg of tramadol/kg. No significant tramadol-associated changes in heart rate, respiratory rate, rectal temperature, or rumen motility were detected.

Conclusions and Clinical Relevance—Caudal epidural tramadol administration induced analgesia with slight to mild sedation and ataxia in cows. Analgesia in affected regions after administration of 2 or 3 mg of tramadol/kg was considered sufficient to allow common surgical procedures to be performed in standing cattle. (Am J Vet Res 2010;71:720–725)

The chemical name for tramadol hydrochloride is (±)-cis-2-[(dimethylamino)-methyl]-1-(3-methoxyphenyl)-cyclo-hexanol hydrochloride.1 Tramadol is a centrally acting analgesic that is structurally related to codeine and morphine; it consists of 2 enantiomers, which contribute to analgesic activity via different mechanisms. (+)-Tramadol and the metabolite (-)-O-desmethyl-tramadol are agonists of the μ-opioid receptor. (+)-Tramadol additionally inhibits serotonin reuptake, and (-)-tramadol inhibits norepinephrine reuptake, thus enhancing inhibitory effects on pain transmission pathways in the spinal cord.2,3 Tramadol has rarely been associated with respiratory or cardiovascular depression in humans, even in large doses, and this set it apart from other opioid receptor agonists. In addition, a minimal incidence of constipating effects and low likelihood for development of tolerance and dependence make this a valuable agent for clinical use.3,4

Caudal epidural anesthesia is used to provide analgesia and relaxation in standing cattle for surgery of the tail, perineum, penis, anus, rectum, vagina, and vestibule.5 Obstetric indications in large animals include surgical treatment of parturient injuries, the performance of simple embryotomies, and inhibition of straining to facilitate manipulative correction of fetal malpresentations and reduction of the prolapsed uterus.6,7 When local anesthetics agents are administered via epidural injection, they affect motor and sensory nerves. Motor dysfunction resulting in severe ataxia and recumbency is a particular disadvantage for surgery when it is desirable that the animal should remain standing.7

In other studies,8 investigators determined that epidurally administered tramadol induces analgesia in the perineal and sacral regions in horses. In humans undergoing minor surgical procedures with local anesthesia, preoperative administration of tramadol SC extends the pain-free period and decreases the need for additional analgesia after surgery, compared with the effects of lidocaine injection alone.9 Tramadol administered via the epidural route also induces analgesia in humans10,11 and dogs.12 To the authors’ knowledge, no studies have been performed to investigate the effects of tramadol after epidural administration in cattle. The purpose of the study reported here was to evaluate whether tramadol administered via caudal epidural injection induces
perineal analgesia in cattle at a dose of 1, 2, or 3 mg/kg and to determine the duration and extent of analgesic effects. Sedation, ability to control voluntary muscular movements, and effects on heart rate, respiratory rate, and rectal temperature were also assessed.

Materials and Methods

Animals—Five mixed-breed adult female cattle indigenous to Iran (mean ± SD age, 4.8 ± 0.8 years; weight, 177 ± 31.5 kg) were selected for study participation. Cows were randomly selected from a university research herd; criteria for exclusion from the study included pregnancy, signs of lameness, or clinically detectable disease. Cows were determined to be healthy on the basis of results of a physical examination and a CBC. Serum biochemical analysis was not performed. The protocol of the study was approved by the Iranian Society for the Prevention of Cruelty to Animals.

Study design—Three doses of tramadol hydrochloride⁶ (1, 2, and 3 mg/kg) were selected for epidural administration: the lowest dose was that established for use in horses.⁷ The initial volume was calculated for the 3 mg/kg dose for each cow, and the lower doses were made by dilution of the drug with sterile 0.9% sodium chloride solution to achieve the same volume. Each of the 3 treatments was administered to each cow in random order as part of a crossover block design, with a 1-week interval between treatments. Thus, each cow was used in 3 different experiments. The observers were blinded to the drug dose administered at each study. All injections were performed by 1 investigator (AB), all analgesia scoring was done by 1 investigator (FA), and other variables (heart rate, respiratory rate, rumen motility, and rectal temperature) were measured by 1 investigator (FA).

Drug administration and determination of effects—Cows were moved into a restraining chute at the start of each experiment. The first intercoccygeal space (Co1-2) was identified by raising and lowering the tail and palpating vertebral articulations. The hair covering the injection site was clipped, and the skin was aseptically prepared. Epidural puncture was performed with an 18-gauge, 38-mm-long needle directed at an angle of approximately 45° to the skin surface centered on the dorsal midline, and correct needle placement in the epidural space was confirmed by lack of resistance during solution injection.

Analgesia, sedation, and ataxia were each subjectively scored by use of a 4-point scale (ie, scored from 0 to 3). Lack of analgesia (ie, strong positive response [foot stamping or kicking] to a noxious stimulus [superficial pinprick]) was confirmed 5 minutes before the tramadol solution was administered. The extent and duration of analgesia were evaluated on the basis of response to pinprick stimuli at each of 9 locations in the following sequence: the tail (dorsal and ventral surfaces of the base and midregion), anus, perineum, vulva, medial and lateral aspects of the proximal thigh regions, caudal udder attachment region, caudal glands of the udder, and midgluteal regions. For tests that were bilateral (ie, left and right sides), the lowest score for the 2 sides was recorded; for test sites of the tail, the lowest of the 4 values was recorded. Pinprick assessments continued cranially and distally in this manner until a normal response (no sign of analgesia) was observed; then testing was halted until the next time point. Following epidural injection of tramadol, assessments were made at 5-minute intervals until 120 minutes after injection. Analgesia was initially assessed on the basis of responses to 2 or 3 superficial pinpricks accomplished by use of an 18-gauge needle. If no response to superficial pinpricks was observed, 2 or 3 deep muscular pinpricks (≤1 cm deep) were performed in that region to confirm complete loss of response to the stimulus. Analgesia scoring was based on the responses to the superficial and deep pinprick tests and was determined as follows: 0, no analgesia detected (eg, vigorous response [including foot stamping or kicking] to either a superficial or deep pinprick); 1, mild analgesia (slow or less vigorous response to stimulus [eg, head tossing, turning the head toward the tested site, or avoidant movement]); 2, moderate analgesia (substantially diminished response, such as skin twitching); and 3, complete analgesia (no response, considered suitable for surgical procedures). The scores for 9 areas (tail, anus, perineum, vulva, medial thigh region, lateral thigh region, caudal udder attachment region, caudal glands of the udder, and midgluteal region) were determined and added together for each cow (maximum total score, 27).

Sedation was assessed according to specific criteria and scored as follows: 0, no signs of sedation; 1, reduced alertness with no other signs; 2, lethargy with eyes closing and slight lowering of the head; and 3, overt lethargy with eyes closing and moderate to marked lowering of the head. Ataxia was assessed and scored as follows: 0, no signs of ataxia; 1, altered hind limb position (eg, wide-based stance or shifting of foot position to avoid leaning against the chute); 2, swaying and leaning against the chute; and 3, recumbency. Motor nerve blockade of the tail was confirmed by the lack of voluntary movement and lack of resistance to manual movement of the tail. Anal relaxation was confirmed by dilation of the anal sphincter and lack of contraction of the anal sphincter after pinprick stimulation. Heart rate, respiratory rate, rectal temperature, and rumen motility were assessed 3 minutes prior to tramadol administration and at 5, 15, 30, 45, 60, 75, 90, and 120 minutes after injection. Heart rate was monitored via thoracic auscultation; beats were counted during a 1-minute period. Respiratory rate was determined by counting thoracic and abdominal excursions during a 1-minute period. Rumen motility was evaluated via auscultation of the left paralumbar fossa and determination of the rate of rumen contractions during 2 consecutive minutes. Temperature was measured by use of a digital thermometer⁸ per rectum.

Statistical analysis—Mean analgesia, sedation, and ataxia scores were determined for the 5 cows after administration of each dose of tramadol (1, 2, or 3 mg/kg). The mean total analgesia score for each treatment was determined by adding the scores (determined from analgesia scores for all 9 tested regions) for the 5 cows and averaging the results for the data set. Measurements were compared by use of commercially available statistical analysis software.⁴ Data were
analyzed by use of ANOVA followed by a Tukey test. Values of heart rate, respiratory rate, rectal temperature, and rumen motility were compared with baseline values (measurements determined before tramadol injection) and reported as mean ± SD. Total mean scores for analgesia, ataxia, and sedation were compared among the 3 treatment groups. Differences were considered significant at a value of P < 0.05.

**Results**

No adverse affects were associated with tramadol administration. Onset of motor nerve blockade of the tail (mean time to onset was < 156 seconds for each of the 3 doses of tramadol) afforded reliable evidence that the caudal epidural injection had been administered correctly. Mean duration of motor nerve blockade of the tail increased with the dose of tramadol administered (25, 74, and 91 minutes for doses of 1, 2, and 3 mg/kg, respectively). The duration of this effect in cows that received tramadol at a dose of 2 or 3 mg/kg was significantly increased, compared with the duration of motor nerve blockade of the tail in cows that received the 1 mg/kg dose. Similarly, there were significant and dose-dependent changes in mean duration of anal relaxation (11, 68, and 86 minutes for tramadol administered at doses of 1, 2, and 3 mg/kg, respectively).

An analgesia score of 3 (considered complete analgesia that was suitable for surgery) was not achieved in some cows that received tramadol at a dose of 1 mg/kg, but complete analgesia was achieved in the tail, anus, perineum, vulva, and medial aspect of the thigh regions in all cows that received doses of 2 or 3 mg/kg (Table 1). The difference in mean onset of complete analgesia among the 3 treatment groups was not significant. The mean times to onset of complete analgesia were 5 to 12 minutes for tail, anus, perineum, and vulva and 5 to 30 minutes for lateral thigh region, medial thigh region, and caudal udder attachment region. Complete analgesia was not obtained in the caudal udder attachment region following administration of the dose of 1 mg/kg and was not obtained in the gluteal region following administration of any dose of tramadol. Mean duration

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**Table 1—Mean time to onset (minutes) and duration (minutes) of complete analgesia**

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<th>Tramadol dose (mg/kg)</th>
<th>Region</th>
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<th>D&lt;sub&gt;onset&lt;/sub&gt;</th>
<th>N&lt;sub&gt;complete&lt;/sub&gt;</th>
<th>T&lt;sub&gt;duration&lt;/sub&gt;</th>
<th>D&lt;sub&gt;duration&lt;/sub&gt;</th>
<th>N&lt;sub&gt;complete&lt;/sub&gt;</th>
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*Analgesia was evaluated in 9 regions by responses to pinprick tests and as determined by changes in mean duration of anal relaxation (11, 68, and 86 minutes for tramadol administered at doses of 1, 2, and 3 mg/kg, respectively). Differences were considered significant at a value of P < 0.05.*
of complete analgesia increased according to the dose of tramadol, and values were significantly different in cows that received 3 mg of tramadol/kg, compared with cows that received 1 mg of tramadol/kg.

The mean total analgesia scores for all 9 regions tested increased as the dose of tramadol administered increased. The values were significantly higher from 15 to 95 minutes after injection in cows that received 3 mg of tramadol/kg, compared with cows that received 1 mg of tramadol/kg. Mean total analgesia scores were also significantly higher at 15, 30, 45, 60, 75, and 92 minutes following administration of doses of 1, 2, and 3 mg of tramadol/kg, respectively. A lesser degree of analgesia was observed thereafter, regardless of dose. Differences in the time to onset of analgesia were negligible, and the onset of analgesia did not appear to be dose dependent. The reported onset of most other epidurally administered drugs in cattle is similar to the mean onset determined for tramadol in the present study: 5 to 6.5 minutes for ketamine hydrochloride,6,16 10 to 20 minutes for detomidine,17 5 to 20 minutes for lidocaine,18 and 5 to 10 minutes for morphine when administered epidurally in humans.10 Other investigators10 determined that the onset of analgesia in horses after epidural administration of tramadol developed more rapidly than the onset of analgesia after epidural administration of morphine because of its higher tissue affinity (which would decrease transit time across the dura mater); however, tramadol was substantially less potent than morphine when administered epidurally in humans.10

The results of the study reported here indicated that the extent and duration of analgesia in cows after tramadol administration were dose dependent, similar to the effects described for tramadol in horses.14 The duration of complete analgesia of the perineum was 18, 60, and 92 minutes following administration of doses of 1, 2, and 3 mg of tramadol/kg, respectively. A lesser degree of analgesia was observed thereafter, regardless of dose. The duration of analgesia provided by the epidural administration of a dose of 2 or 3 mg/kg may

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<th>Variable</th>
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*Rumen motility was decreased significantly (P < 0.05) 15 minutes after injection, compared with rumen motility at baseline.

### Discussion

In the present study, 3 doses of tramadol (1, 2, and 3 mg/kg) administered via caudal epidural injection were selected for use in adult cows. The lowest dose was the dose determined for use in horses;13 use of this dose was based on the results of a pilot study conducted at our facility, which indicated that doses of tramadol < 1 mg/kg may be less effective in cattle. The protocols for scoring analgesia, sedation, and ataxia were based on studies14,15 by other investigators.

Following tramadol injection, analgesic effects were determined by the responses to superficial and deep pinprick tests, which were scored from 0 to 3 (0, no analgesia detected; 1, mild analgesia [diminished response]; 2, moderate analgesia [substantially diminished response]; and 3, complete analgesia [no response; considered suitable for surgical procedures]). The first signs of analgesic effects (motor nerve blockade of the tail) were seen < 3 minutes after injection, but onset of complete analgesia in the anus and perineum occurred in all 5 cows at 7 to 10 minutes after administration of 2 or 3 mg of tramadol/kg. Complete analgesia of these regions was not induced in all cows that received 1 mg of tramadol/kg. Differences in the time to onset of analgesia were negligible, and the onset of analgesia did not appear to be dose dependent. The reported onset of most other epidurally administered drugs in cattle is similar to the mean onset determined for tramadol in the present study: 5 to 6.5 minutes for ketamine hydrochloride,6,16 10 to 20 minutes for detomidine,17 5 to 20 minutes for lidocaine,18 and 5 to 10 minutes for medetomidine.10

Other investigators10 determined that the onset of analgesia in horses after epidural administration of tramadol developed more rapidly than the onset of analgesia after epidural administration of morphine because of its higher tissue affinity (which would decrease transit time across the dura mater); however, tramadol was substantially less potent than morphine when administered epidurally in humans.10

The results of the study reported here indicated that the extent and duration of analgesia in cows after tramadol administration were dose dependent, similar to the effects described for tramadol in horses. The duration of complete analgesia of the perineum was 18, 60, and 92 minutes following administration of doses of 1, 2, and 3 mg of tramadol/kg, respectively. A lesser degree of analgesia was observed thereafter, regardless of dose. The duration of analgesia provided by the epidural administration of a dose of 2 or 3 mg/kg may

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be considered sufficient for most minor surgical procedures of the perineum. Other investigators’ reported that analgesia of the perineal region (anus, perineum, and vulva) induced by epidural administration of lidocaine (0.2 mg/kg) combined with xylazine (0.02 mg/kg) was detectable for up to 150 minutes in calves. Ketamine administered epidurally at a dose of 2 mg/kg induced analgesia for 45 to 60 minutes, whereas a dose of 3 mg/kg provided analgesia for 55 to 70 minutes in cattle. Results of the present study indicated that the duration of analgesia after tramadol administration was shorter than that reported after administration of the combination of lidocaine and xylazine but was similar to the duration of analgesia reported after ketamine administration in cattle.

It has been proposed that tramadol affects sensory and motor nerve conduction by a mechanism similar to that of lidocaine, which acts on voltage-dependent Na+ channels and results in axonal blockage. However, tramadol might establish conduction blocks by a mechanism different from that of lidocaine; increased Ca2+ concentrations in the external medium increased increased concentrations of serotonin and resulting in awareness. Although tramadol is an agonist for µ-agonist morphine and the pure κ-opioid receptor agonist U50488H, because it causes activation of the monoaminergic pathways in the CNS, likely increasing concentrations of serotonin and resulting in awareness. Tramadol-induced inhibition of norepinephrine reuptake is similar to inhibition by α2-adrenoceptor agonists; it may be speculated that ataxia following epidural administration of tramadol could result from the contribution of a similar mechanism (ie, the possibility that inhibition of norepinephrine reuptake causes reduction of sympathetic outflow, leading to enhanced muscle relaxation). Ataxia is also an adverse effect of epidural administration of drugs such as ketamine, xylazine-lidocaine combination, and detomidine in cattle.

Epidural injection of tramadol at any dose had no significant effects on heart rate, respiratory rate, or rectal temperature in cattle in the present study; these findings were in agreement with the results of studies performed in humans, horses, donkeys, and dogs. In cattle in the present study, rumen motility was decreased significantly (P<0.05) 15 minutes after injection, compared with rumen motility at baseline for cows that received tramadol at the 1 mg/kg dose. Because rumen motility was affected at only 1 time point, the authors believe that this was not clinically important.

After IV or IM administration in camels, tramadol and its main metabolite O-desmethyltramadol were detected in enzymatically hydrolyzed urine samples for 24 and 48 hours, respectively. Tramadol also had a short half-life and fast clearance in that species. However, withdrawal information for tramadol in food-producing animals has not been established; thus, taking a cautious approach to meat and milk withdrawal times is advised when administering tramadol, regardless of the route of administration. Further studies are needed to determine other possible undesirable effects of epidural administration of tramadol in cattle.

In horses, duration of analgesia induced by the use of epidurally administered opioids was increased in regions proximal to the injection site, compared with the duration in distal regions. The duration of effect of opioids given via this route may also be influenced by the number of molecules retained in the CSF and spinal tissues and by the dissociation kinetics of the administered drug.

In the study reported here, slight sedation and moderate ataxia were evident following administration of the highest dose of tramadol (3 mg/kg): results of a similar study in horses indicated that lowering of the head was observed in the first hour after administration and persisted for 3 hours, but no change in behavioral response or locomotor activity was observed. The minor sedative effect of tramadol could be explained by the fact that although tramadol is an agonist for µ-opioid receptors, it also increases synaptic release of the neurotransmitter 5-hydroxytryptamine (also called serotonin) and inhibits serotonin reuptake presynaptically, which could be related to awareness and insufficient sedation. In the study of tramadol in horses, it was speculated that tramadol induced a shorter duration of sedation, compared with the µ-opioid receptor agonist morphine and the pure κ-opioid receptor agonist.

References