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SHORT COMMUNICATION

Comparative analgesic and sedative effects of tramadol, tramadol-lidocaine and lidocaine for caudal epidural analgesia in donkeys (*Equus asinus*)

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Abstract

Objective To compare anti-nociceptive and sedative effects of tramadol, a combination of tramadol-lidocaine, and lidocaine alone for perineal analgesia in donkeys.

Study design Experimental 'blinded' randomized cross-over study.

Animals Six healthy adult donkeys.

Methods Treatments were tramadol (TR) (1.0 mg kg^{-1}), tramadol-lidocaine (TRLD) (0.5 and 0.2 mg kg^{-1} respectively) and lidocaine (LD) (0.4 mg kg^{-1}) given into the epidural space. The volume of all treatments was 0.02 mL kg^{-1}. Nociception was tested at the perineal region by pin prick, followed, if no reaction, by pressure from a haemostat clamp. Times to onset, degree and duration of anti-nociception of the perineal region were recorded. Response was tested immediately after drug administration and at: 2, 5, 10, 15, 30, 45, and 60 minutes post-administration and then at 30 minute intervals thereafter until a response re-occurred. Physiologic data and degree of sedation and ataxia were recorded pre-administration and at intervals for 240 minutes post-administration. Results were analyzed using ANOVA, Kruskal–Wallis tests, and Wilks' Lambda test as relevant. Significance was taken as $p < 0.05$.

Results Times (minutes, mean ± SD) to onset and duration of anti-nociception, respectively were; TR 13 ± 1.6 and 220 ± 4.6; TRLD 6 ± 0.8 and 180 ± 8.5; LD 4 ± 1.4 and 75 ± 4. Onset and duration times were significantly longer with TR than the other two treatments. TR never produced complete anti-nociception, whereas the TRLD and LD induced complete anti-nociceptive effects. Duration was significantly longer with TRLD than with LD alone. Epidural injections of TR and TRLD induced mild sedation.

Conclusions and clinical relevance Epidural combination of TRLD produced an anti-nociceptive effect in the perineum, which was rapid in onset and had a longer duration of action than LD alone. An epidural single dose of TRLD combination would appear to provide an acceptable analgesic effect in the perineal region of donkeys.

Keywords caudal epidural, donkeys, lidocaine, nociception, tramadol.

Introduction

Caudal epidural anaesthesia is used widely in large animals to allow diagnostic, obstetrical, and surgical intervention in the perineal region. Local anaesthetics are the most commonly used drugs for producing epidural anaesthesia. However, with the exception of

bupivacaine and ropivacaine, these agents provide analgesia of relatively short duration and may necessitate re-administration to allow completion of the surgical operation. In addition, local anaesthetic agents unselectively block motor, sensory and sympathetic fibers, and may lead to ataxia, hind limb weakness, and occasionally recumbency (Day & Skarda 1991).

Assessment of the analgesic effects of tramadol administered epidurally has been reported in horses (Natalini & Robinson 2000), cattle (Bigham et al. 2010), dog (Natalini et al. 2007), cat (Castro et al. 2009) and goat (Dehkordi et al. 2012), and it appeared to give prolonged anti-nociception without serious side effects. The pharmacokinetic effect of oral and intravenous tramadol was described in donkeys (Giorgi et al. 2009); however, no data exists on its epidural effects in this species. Therefore, the objective of the present study was to compare the anti-nociceptive effect of tramadol (TR), a combination of tramadol-lidocaine (TRLD), and lidocaine (LD) alone when administered in the epidural space of the donkey.

Materials and methods

The study protocol was approved by the Animal Care Committee of the Kafer-Elsheikh University.

Experimental animals

Six donkeys (*Equus asinus*) were selected for this study (four non-pregnant females and two males). The mean ± standard deviation (SD) age of donkeys was 10 ± 1.4 years, and weight was 230 ± 20.9 kg. All animals were considered healthy on the basis of physical examination and full biochemistry and haematologic analyses. The animals were all kept under the same feeding and other management conditions. Tramadol, LD and TRLD combinations were given into the epidural space.

Study protocol

The experiments were performed as a randomized, cross-over study. On all occasions for anti-nociception, ataxia, and sedation, the same observer was unaware of the drugs used. Each donkey received each of three treatments administered by epidural injection according to a Latin square design and with a period of at least two weeks between experiments. Treatment 1 (TR) was tramadol, 1.0 mg kg^{-1} (Tramadol, 50 mg mL^{-1}, injectable sterilized solution; October Pharma. S.A.E., Egypt). Treatment 2 (TRLD) was tramadol, 0.5 mg kg^{-1}, combined with preservative-free and vasoconstrictor-free lidocaine, 0.2 mg kg^{-1}, (2% Lidocaine Hydrochloride 20 mg mL^{-1}; Hospira, INC., IL, USA). Treatment 3 (LD) was lidocaine (0.4 mg kg^{-1}) alone. The volume of all treatments was 0.02 mL kg^{-1}. All drugs were administered into the epidural space over approximately 30 seconds. For caudal epidural injection, an 18-gauge 5 cm long hypodermic needle was inserted in the second inter-coccygeal space (C2–C3), directing the needle at an angle of 30° from the horizontal. The space was identified by raising and lowering the tail while palpating the depression at the site of the second movable coccygeal articulation. Correct needle placement was confirmed by the hanging-drop method and lack of resistance to injection.

Evaluation of epidural TR, TRLD and LD effects

Anti-nociception was tested at a number of points using a pin prick test (a 22-gauge, 2.5-cm-long needle). This constituted the insertion of the needle through the skin into the underlying tissues at the tail base, anus, perineum and upper hind limb area. The needle was inserted at slightly different sites for each test. Only in the perineum and when pin pricks gave no response, pressure from haemostat clamp (closed to the first ratchet) was used to test for a strong degree of anti-nociception. Positive nociceptive responses to the stimuli were recorded based on the haemostatic clamp test only. A positive response was defined as purposeful avoidance movements of head, neck, trunk, limbs, tail; attempts to kick, and turning of the head toward the stimulation site. The onset time and duration of perineal anti-nociception were recorded. The time from the injection to loss of the sensation was considered as time of onset of effect. The time between loss and reappearance of response to the nociceptive stimuli was considered as duration of the anti-nociceptive effect. Response was tested at: 2, 5, 10, 15, 30, 45, and 60 minutes post-administration and then at 30 minute intervals thereafter until a response reoccurred. The degree of anti-nociception was graded on a scoring system from 0 to 3; 0, no analgesia (strong response to noxious stimulus); 1, mild analgesia (moderate response, with depressed reaction to a painful stimulus); 2, moderate analgesia (very weak and occasional response); 3, complete analgesia (no response to noxious stimulus).

Heart rate, respiratory rate, rectal temperature and degree of ataxia and sedation were assessed before drug administration and at 5, 10, 15, 30, 45, 60, 90, 120, 150 180, 210, and 240 minutes post-administration. The donkeys were evaluated for presence of ataxia by being walked out of the stocks and ataxia was scored on a simple 4 point scale, (0) normal, (1) mild (slight stumbling, easily able to continue walking), (2) moderate (marked stumbling, walking but very ataxic), or (3) severe (recumbency or falling). Sedation was scored on a four-point scale in each donkey for each dose: 0 = alert (no sedative effect), 1 = mild sedation (reduced alertness with no other signs), 2 = moderate sedation (drowsiness and slight drop of head, lips and upper eyelids), 3 = deep sedation (marked drowsiness and drop of head).

Statistical analysis

Statistical analyses were performed using a statistical software program (Graphpad Prism for Windows version 5.0; GraphPad Software Inc., CA, USA). Data were assessed for normal distribution using Kolmogorov-Smirnov test. Kruskal–Wallis with *post hoc* Dunns multiple comparison tests were used to assess statistical differences between treatments of scored parameters at each time point. For heart and respiratory rates and rectal temperature data repeated measures ANOVA were used to determine the main effect of treatment and time. Wilks' Lambda test was selected to evaluate within group interactions and evidence of time group interactions. For the three treatments, onset and duration of analgesia and sedation were analyzed by one-way ANOVA with Turkey *post hoc* multiple comparison tests. Results are presented as mean ± SD, or median (range) as relevant. Differences were considered significant at $p < 0.05$.

Results

Time (in minutes) to onset of anti-nociception was significantly ($p = 0.012$) prolonged following TR in comparison with LD and TRLD (Table 1). TR produced significantly ($p = 0.019$) longer duration of anti-nociception than that produced by LD and TRLD (Table 1). Based on treatment and time, the degree of anti-nociception showed a significant variation between treated groups and with progress of time ($p = 0.032$). Tramadol provoked the most delayed anti-nociception effect, but its effect persisted until 240 minutes post-treatment. However, an effect of LD was evident until 60 minutes post-treatment. Tramadol alone never produced complete anti-nociception, (scores only 1–2), whereas the anti-nociceptive effect of TRLD and LD was complete and scored as excellent (score 3) (Table 1).

In all donkeys, TR and TRLD induced mild sedation (score 1) (Table 1) and no difference in onset of sedation was detected between the two treatments ($p = 0.081$). All animals remained calm and appeared to be unaware of their surroundings. The duration of sedative effect of TR was significantly ($p = 0.015$) longer than that of TRLD (Table 1). LD provoked no sedative effect.

Mild ataxia (score 1) was noted in donkeys with epidural injection of LD and TRLD, but was not

Table 1 Onset, duration and maximal effects of perineal antinocipetion and sedation following three epidural treatments in donkeys: tramadol (TR) (1.0 mg kg^{-1}), tramadol-lidocaine (TRLD) (0.5 and 0.2 mg kg^{-1} respectively) and lidocaine (LD) (0.4 mg kg^{-1})

Variable	TR	TRLD	LD	*p* value
Anti-nociception				
Onset (mean ± SD)	13 ± 1.6[a]	6.0 ± 0.8[b]	4.0 ± 1.4[c]	0.012
Duration (mean ± SD)	220 ± 4.6[a]	180 ± 8.5[b]	75 ± 4[c]	0.019
Maximum score (median)	1[a]	3[b]	3[b]	0.032
Sedation				
Onset (mean ± SD)	15 ± 1.1	16 ± 1.5	0	0.081
Duration (mean ± SD)	55 ± 6[a]	35 ± 5[b]	0[c]	0.015
Maximum score (median)	1[a]	1[a]	0[b]	0.025

All times are in minutes. Anti- nociception score was graded from 0 (no analgesia) to 3 (complete). Sedation score was graded from 0 (no sedation) to 3 (marked drowsiness). [a,b,c]Means and medians with different superscript letters in the same row are significantly different at $p < 0.05$.

observed in TR epidural injection. None of donkeys in the TRLD and LD groups' experienced severe ataxia.

Rectal temperatures, heart and respiratory rates did not change significantly following any treatments. Moreover, no adverse reactions were observed after administration.

Discussion

The epidural dosage of tramadol in donkeys is not well established. In the present study, the dose was selected based on the previous studies carried out in horses and goats (Natalini & Robinson 2000; Dehkordi et al. 2012). Epidural TR showed prolonged onset and duration of the antinociceptive effect compared with TRLD and LD. This result is in agreement with that reported in horses, cattle and goats (Natalini & Robinson 2000; Bigham et al. 2010; Dehkordi et al. 2012). Murthy et al. (2000) found a low volume of distribution for epidural tramadol that may relate to the prolonged antinociception effect. Furthermore, it has been suggested that the vasodilatation due to sympathetic blockade produced by epidurally injected local anaesthetic agents such as LD decreases the duration of analgesia (Go¢mez de Segura et al. 2000), and this might be an explanation for the shortened duration of action in the TRLD compared with TR alone.

Tramadol provoked mild to moderate anti-nociception, which was never complete. Tramadol is a weak μ-receptor agonist, which promotes analgesia by the binding of its (+) enantiomer to μ-opioid receptors, by the analgesic properties of the main active metabolite, O-desmethyltramadol (M1) or by inhibiting the reuptake of norepinephrine and serotonin (Giorgi et al. 2009; DeRossi et al. 2013). However, potent anti-nociceptive effects of TR have been recorded in horses and goats (Natalini & Robinson 2000; Dehkordi et al. 2012). The present result may be attributed to rapid metabolism of TR to its inactive form. This speculation is supported by the results of the pharmacokinetics of intravenous TR in donkeys (Giorgi et al. 2009).

Donkeys that received TR alone or in combination with LD were mildly sedated (mild sedation, score = 1), probably as a result of the systemic absorption of TR. In horses, epidural TRLD at the same dose as used in the current work was not reported produce behavioural changes (DeRossi et al. 2013).

Mild ataxia was observed after the epidural administration of LD and TRLD, but ataxia was not observed following the TR administration. These results are similar to those previously reported in horses, cattle and goats (Natalini & Robinson 2000; Bigham et al. 2010; Dehkordi et al. 2012).

In the present study, the scoring system is subjective which may not allow ideal evaluation of the sedative and analgesic effects. To minimize this error, the person who recorded the scores was unaware about the treatments. The other limitation of this experiment is lack of information about the pharmacokinetics of epidural tramadol in donkeys. Consequently, these limitations should be considered in further studies.

Epidural tramadol-lidocaine combination induced more potent anti-nociceptive effect and rapid onset than tramadol. In clinical practice, utilizing a tramadol-lidocaine combination, long duration anti-nociceptive effect could commence relatively soon after single-dose epidural administration to enable surgical and obstetrical procedures to be completed. Further research is required to determine whether the analgesia is sufficient for surgical procedures.

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