

Effects of tramadol slow injection vs fast bolus in the therapeutic balance of the foot in bovine



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SUMMARY

Introduction - A study performed in Brazil on detection and subsequent treatment of pain, by the veterinarian, in cattle and horses showed that tramadol was used by 39% of Brazilian practitioners.

Aim - The objective of the present study is to evaluate the analgesic and sedative effects of slow intravenous injection of tramadol in bovine.

Materials and methods - Twenty bovines (aged 3 ± 1 years and weighing 600 ± 20 kg) divided into two groups received, during the therapeutic balance of the foot, tramadol 1 mg/kg^{-1} by bolus IV (group B) or by slow intravenous injection administered over 10 minutes (group I). Heart rate (HR), respiratory rate (RR), Systolic Pressure (SP), sedation and analgesia were assessed before and up to 15 minutes following drug administration. The sedation was evaluated considering ataxia, assessed through a four-point grading scale and measuring height of the head above the ground. Analgesia was evaluated using Numeric Rating Score scale (NRS 0-10) and a cumulative pain scale (CPS), assigning scores (1-4) to the percentage variations, compared to baseline values of HR, RR and SP. Recorded physiological data were compared using Wilcoxon Test to evaluate changes along the time line, while differences between groups were compared using the Mann-Whitney U test. Ataxia and analgesia scores were compared using the Fischer's exact test with $p < 0.05$ considered significant.

Results and discussion - Heart rate, RR and SP increased, during the therapeutic balance, respect to baseline, in both groups. However, increase in HR, RR and SP in the group B is greater than in the group I. Ataxia scores were low in both groups as follow: group B 0(1-1) and group I 0(1-2). The height of the head above the ground was reduced in the group I ($p = 0.000$). Analgesia scores were significantly lower in the group I, for both NRS and CPS ($p = 0.000$).

Conclusion - The outcomes of the present study showed that the slow intravenous tramadol administration over 10 minutes provided better analgesia and sedation compared to fast bolus administration in cattle.

KEY WORDS

Foot diseases, cattle, animal welfare, tramadol.

INTRODUCTION

Epidural and locoregional anesthesia by administering local anesthetic drugs, alone or combined with anesthetics and opioids, are the most widely used techniques to obtain analgesia in large animals¹. A Brazilian study on detection and subsequent treatment of pain in cattle and horses, performed by veterinarians, highlights that Brazilian practitioners use the following drugs for analgesia in large animals: butorphanol (43.4%), tramadol (39%), flunixin (83.2%), and ketoprofen (67.6%). Horses undergoing explorative laparotomy were commonly (72.9%) administered analgesic drugs, whereas the cattle undergoing surgical abdominal procedures receives only flunixin (58.5%) and/or xylazine (23%) as analgesic treatment. Local anesthesia with lidocaine remains the most used analgesic technique (48%) in cattle. Surgical resolution of fractures is one of the most painful

procedures but the interviewed veterinarians believe they do not have adequate knowledge to deal with pain management. Furthermore, the limited use of analgesic drugs in large animals highlighted in the Brazilian study is similar to that reported in other countries^{2,3}.

Tramadol is a weak opioid consisting of two enantiomers that inhibit the re-uptake of serotonin and noradrenaline. Tramadol has a good analgesic efficacy associated with minor side effects^{4,5}. The 20% of tramadol is bound to plasma proteins (fraction of bound drug) and has a high affinity for tissues. Tramadol is able to cross the placental barrier and small amounts of the drug (0.1%) and its active metabolites (0.02%) are found in mother's milk. The 90% of tramadol is eliminated by the urine. The remaining 10% is eliminated unchanged in the faeces¹⁰. It has been demonstrated that slow intravenous administration of tramadol is more effective than fast bolus in horses^{7,8,9}.

The aim of this study is twofold: to sensitize veterinarians to be aware of detection and prevention of pain in cattle, and to evaluate the analgesic property and sedative efficacy of tramadol in slow intravenous injection compared to the fast bolus in cattle undergoing treatment of foot diseases, which are

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widespread disorders and often treated without analgesic protocols.

MATERIALS AND METHODS

The study was approved by silent consent of the Review Board for Animals Care of the University of Messina. Procedures were performed in accordance with Italian law (D.M. 116192), European law (O.J. of E.C. L. 358/1 12/18/1986), and USA laws (Animal Welfare Assurance No A5594-01, Department of Health and Human Services, USA) in accordance with the Legislative Decree n. 193 of 6th April 2006. Moreover, the owners provided informed consent. Milk, dairy products and meat, have not been sent to commerce. Twenty dry Friesian breed cows, aged 3 ± 1 years and weighing 600 ± 20 kg, underwent functional balance of the foot because of phlegmon and foot ulcer, were included in our study. The cows were weighed with a scale (Mettler Toledo Italy) and, for the acclimation period of 30 minutes, were housed in a Dutch pen (Fontana Italy) adjacent to the barn where the curettage of the foot would be performed. When moving from the weighing area to the pen area and when moving from the Dutch pen to the barn, three operators, who were independent and blinded to treatment, evaluated ataxia assigning scores from 0 to 4 as follow: 0 absence of ataxia, 1 animal slightly staggers, 2 the animal crosses the limbs, 3 animal tends to fall, 4 animal in recumbency.

After placement of animals in the pen, a single operator recorded the following basic parameters: heart rate (HR) using a stethoscope, respiratory rate (RR) evaluating the thoracic excursions, and non-invasive blood systolic pressure (SP), placing the sleeve at the level of the coccygeal vertebrae, using the multi-parametric monitor (CAMS 2). Afterwards, a 14-G venous catheter (Suriflo® catheter) was inserted in the jugular vein and the subjects received tramadol (Altadol 5% Formenti Italy) at the dose of 1 mg/kg^{-1} in fast bolus, group B, and in 10 minutes using an infusion pump (Angel), group I. The patients were randomly assigned to one of two treatment groups by drawing a ticket with the treatment to be administered. Drug treatment was recorded in the barn register. The parameters were recorded before tramadol administration (baseline values), immediately after tramadol injection, and every 5 minutes until 15 minutes after tramadol injection. Balance of the foot started five minutes after the end of the administration of tramadol in both groups.

The height of the head above the ground (HH) was defined as the distance (cm) from chin base to the ground. HH was measured using a meter before tramadol administration and at 15 minutes after tramadol injection. The height of the head and ataxia were used to assess the degree of sedation. Pain assessment was performed by three independent and blinded to treatment observers using a numerical rating scale (NRS)¹¹ with scores from 0 to 10. At baseline, the painful stimulus was performed by applying a foot probe, while, after tramadol administration, the stimulus was the surgical procedure.

Furthermore, analgesia was evaluated using a cumulative pain scale (CPS), assigning scores to the percentage variations of HR, FR and SP, compared to baseline values, according to the following scheme:

- 0 $\leq 0\%$
- 1 = $> 0\%$ but $\leq 10\%$
- 2 = $> 10\%$ but $\leq 20\%$
- 3 = $> 20\%$ but $\leq 30\%$
- 4 = $> 30\%$ but $\leq 40\%$ or more

The final CPS score calculated by summing the scores from the individual scores.

Statistical analysis of data was performed using SPSS 15.0 (IBM Company, Italy). Shapiro-Wilk normality test was performed to verify the normal distribution of data. The data were reported as median and range. The changes along the time line were evaluated using Wilcoxon Test, while differences between groups were compared using the Mann-Whitney U test. Ataxia and analgesia scores were compared using the Fischer's exact test with $p < 0.05$ considered significant.

RESULTS

Kendall's test showed a high level of concordance inter-observer ($W = 1$) for ataxia and pain scores in both groups.

Shapiro-Wilk normality test highlighted that the data were not normally distributed.

Heart rate significantly increased at 10 minutes ($p = 0.002$) and 15 minutes ($p = 0.006$) in the group B, whereas there were no significant differences in HR ($p = 0.293$) in the group I even though HR decreased after tramadol administration compared to baseline value.

Respiratory rate significantly increased after tramadol administration and throughout the therapeutic balance in both groups. The animals in the group B showed RR higher than those in the group I.

Systolic pressure significantly increased after tramadol administration and throughout the therapeutic balance in the group B, whereas, in the group I, SP significantly decreased ($p = 0.000$) during therapeutic balance compared to baseline value.

There was no significant difference in HH in the group B ($p = 0.180$), whereas HH significantly decreased ($p = 0.000$) after tramadol administration in the group I.

As regard with the ataxia scores, there were no significant differences between groups ($p = 0.064$). The NRS score significantly decreased after tramadol administration and throughout the therapeutic balance in both group. The RNS and CPS scores in the group I were significantly lower ($p = 0.000$) than in the group B (Table 1).

CONSIDERATIONS AND CONCLUSIONS

Tramadol 1 mg/kg^{-1} administration in slow injection in 10 min, compared to the rapid bolus administration, gave the cows a better analgesia and sedation without side effects.

The rapid bolus administration or high dosages of opioids determines CNS opioid receptor activation, with transitory excitement and heightened sensitivity to external stimuli⁶.

The local anaesthetics are the most widely used drugs by veterinarians towards the bovine pain management (48%) and only the 39% make use of tramadol³.

However, the most common foot diseases in dairy cow, such as foot ulcer, the podoflemmatitis and the phlegmon,

Table 1

Recorded data	Groups	TIME		Therapeutic foot balance		
		B	AT	5'	10'	15'
HR (beats/min)	B	68(40/80)	68(40/80)	70 (65/88)	<u>75(70/88)</u>	<u>75(65/88)</u>
	I	72(40/80)	70(40/75)	68(65/80)	68(65/88)	68(60/88)
RR (breaths/min)	B	39(37/40)	<u>60(56/65)</u>	<u>80(75/90)</u>	<u>80(70/95)</u>	<u>82(70/90)</u>
	I	40(20/41)	<u>44(40/66)</u>	<u>44(37/66)</u>	45(35/65)	42(34/60)
SP (mmHg)	B	152(143/163)	<u>124(118/135)</u>	<u>157(137/173)</u>	<u>159(140/170)</u>	154(130/169)
	I	160(135/175)	161(150/173)	<u>104(102/107)</u>	135(120/150)	<u>131(125/140)</u>
HH (cm)	B	100(80/100)				99(70/100)
	I	95(90/110)				<u>90(70/90)</u>
Ataxia scores (scale 0/4)	B	0(0/0)	0(0/1)			
	I	0(0/0)	<u>0(0/2)</u>			
Stimulus response scores						
NRS scores (scale 0/10)	B	10(10/10)	<u>9(8/10)</u>	<u>9(8/10)</u>	<u>9(8/10)</u>	<u>9(8/10)</u>
	I	10(10/10)	<u>3(1/10)</u>	<u>3(1/10)</u>	<u>3(1/10)</u>	<u>3(1/10)</u>
CPS scores (scale 0/4)	B		1(0/4)	3(0/4)	3(0/4)	3(0/4)
	I		1(0/3)	2(0/4)	2(0/4)	2(0/4)

Legend: Heart rate (HR), respiratory rate (RR), systolic pressure (SP), height of the head above the ground (HH), ataxia and stimulus response scores (NRS=Numerical Rating scale; CPS=cumulative pain scale) in both groups (B=group B received 1 mg/kg⁻¹ of tramadol in fast bolus; I=group I received 1 mg/kg⁻¹ of tramadol in 10 minutes) before tramadol administration (B=baseline), after tramadol injection (AT) and at 5, 10, and 15 minutes after tramadol administration. Underlined values highlight significant differences along the time line, whereas bold type highlights significant differences between groups (p <0.05).

cause a lowering of pH¹². The local anaesthetics onset time and efficacy, in acid environment, are delayed or absent^{13,14}, so the use of an opioid could be a valid help in animal welfare safeguard.

The present study aims to evaluate analgesic and sedative efficacy of tramadol, administered by slow injection, and to sensitize the veterinarians towards recognition and prevention of pain in cattle.

Article 11 of Legislative Decree 193/2006 permits the use by way of derogation, of medicines, for animals intended for the production of food: the responsible veterinarian may, exceptionally, under his own responsibility to use the said medicines, for safeguarding animal welfare. However, tramadol is excreted unchanged at 100% through stool, urine and milk¹⁰. In conclusion, we believe that the use of this drug can be a valuable aid for the prevention of cow pain, given the low efficacy of local anesthetics in the foot lesions that we have treated.

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