Comparison of analgesia and ataxia degree obtained between three dosages of tramadol in cattle

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SUMMARY

Aim - The aim of this study was to evaluate and compare the analgesia and ataxia degree between three dosages of tramadol in cattle.

Methods - Thirty Friesian cows undergoing transrectal and transvaginal ultrasound examination were enrolled. They were randomly divided into three groups, A, B, and C. Each group consisted of 10 subjects. Tramadol was administered intravenously as follow: 1 mg/kg (group A), 1.5 mg/kg (group B) and 3 mg/kg (group C). Heart rate, respiratory rate, non-invasive systolic pressure, ataxia score (range 0-3) and stimulus response score (range 0-4) were recorded before tramadol administration and at 10, 20, 30, 60 and 90 minutes after tramadol administration. A cumulative pain score (CPS, range 0-12) was performed. When the CPS was > 10 and stimulus response score was equal to 4, the animals received flunixin meglumine 3.3 mg/kg intravenously as rescue analgesia.

Results - Heart rate of cows treated with tramadol 3 mg/kg was significantly lower at 20, 30, 60 and 90 minutes ($p < 0.001$) compared to those of other groups. Cows treated with tramadol 1.5 mg/kg showed a significant increase ($p = 0.010$) in the degree of ataxia at all times compared to other groups.

The CPS recorded in group C was significantly lower ($p = 0.028$) compared to those of other groups at all times. Group B showed a significant lower ($p = 0.028$) stimulus response score compared to those of other groups. In group C, we observed phenomena of excitability and slight transient muscle fasciculation. No rescue analgesia was administered in any subject.

Conclusion and clinical relevance - Tramadol 1.5 mg/kg provided better ataxia and analgesia compared to other doses. Furthermore, tramadol 3 mg/kg may cause excitatory movements and muscle fasciculation.

KEY WORDS

Tramadol, cattle, ataxia, analgesia.

INTRODUCTION

Local anesthetic techniques are widely used in cattle because many diagnostic and surgical procedures are performed with the animal in standing[1-3]. Nevertheless, in tissues affected by purulent inflammation (e.g., foot diseases, soleari ulcers, podophlemmitis, interdigital dermatitis, nipple injurie, and mastitis), pH tends to acidity, and local anesthetics are ineffective[1,4-5]. In addition, anesthetic blocks may be difficult to performed in case of abdominal surgery. Even though local technique with those agents may be quite effective for pain relief in inflamed tissues, especially if the nerve block is proximal to the affected area, In addition in abdominal surgery where anesthetic blocks cannot be performed; alfa$_2$adrenoceptor agonists[3,6-7], opioids and NSAIDs, represent a valid alternative to local anesthetics[9-17]. Butorphanol, tramadol and other opioid agonist-antagonist provide sedation and analgesia, In various species of ruminants such as camelids and cattle[1,9-16]. NSAIDs are a valid therapeutic choice for the above mentioned surgical pathologies., because this drugs are anti-inflammatory and painkillers[17]. Tramadol is as a racemic mixture of two enantiomers. The positive enantiomer inhibits serotonin re-uptake while the negative enantiomer inhibits noradrenaline re-uptake[1]. Both enantiomers of tramadol are agonists of the mu-opioid receptors. All these effects synergistically induce a good analgesia. Tramadol causes few side effects on cardiovascular, respiratory, and gastroenteric systems. Tramadol has a half-life of about 2 hours in goats and alpacas[10-12]. The 20% of tramadol is bound to plasma proteins (fraction of bound drug), has a high affinity for tissues, and is able to cross the placental barrier. Tramadol is mainly eliminated unchanged with stool and urine (99%), whereas only a very small amount of drug (0.02%) is eliminated by excretion in the milk[1].

These interesting pharmacological and pharmacokinetic effects of tramadol make it very suitable for analgesic therapy in bovine species, especially since the suspension time could be very short[1]. The aim of this study was to compare the analgesic property and the ataxia degree obtained with three dosages of tramadol in cattle.

MATERIALS AND METHODS

The study was approved by the Review Board for Animals Care of the University of Messina (protocol N 031/2019). 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

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and Human Services, USA) in accordance with the Legislative Decree n. 193 of 6th April 2006. Moreover, the owners provided informed consent. The dairy products were removed from the food supply chain for at least thirty days after the administration of tramadol.
Thirty Friesian female cow undergoing transrectal and transvaginal ultrasound examination and biopsy tests, aged between 3 and 4 years, and weighing 500 ±40 kg were enrolled in this study. These subjects came from the Province of Ragusa, Sicily, Italy. Water and food were withdrawn twelve hours before the study.
The study involved the evaluation of sedation, through ataxia and, the variation of the following physiological variables: heart rate (HR), non-invasive systolic pressure (NSP), and respiratory rate (RR).
After being weighed with a scale (Zoopiro Italy), the degree of ataxia was assessed. Then, the cows were acclimatized for 30 minutes in their housing pen. Baseline parameters were recorded as follows: heart rate (HR) and non-invasive systolic pressure (NSP), placing the cuff at the base of the tail, were measured through a multiparametric monitor (EDAN Italy); respiratory rate (RR) was recorded by observing chest wall motion.
The evaluation of ataxia (ataxia score) was carried out, by three unsuspecting observers, by means of the assignment of scores according to the following scheme:
0 = no ataxia.
1 = the animal sways slightly but is stable.
2 = the animal sways and spreads its limbs.
3 = the animal sways and bends with respect to the ground.

Then, the degree of analgesia was evaluated using the response to an electrical stimulus. The skin located at three centimeters above the coronary band of the right hind limb was trichotomized. An ultrasound gel was applied to favor electrical conduction, and two electrodes dome-shaped 3 mm diameter were placed. The electrodes were fixed using an adhesive, and electrical stimulation on coronary band was performed using a bipolar stimulator set at 15 mA with alternating current generator (Phasis II electromyograph of Esaote Biomedica IT)[18-19]. The evaluation of the animal's behavioral reaction to the electrical stimulus (stimulus response score) was performed by three independent and unaware observers, assigning a score ranging from 0 to 4 using the following scheme:
0 = No reaction.
1 = No stimulated limb's reaction but the animal raises its head.
2 = The animal lifts its head and slightly subtracts the stimulated limb.
3 = The animal subtracts the stimulated limb.
4 = The animal subtracts the stimulated limb and defends itself.

At the baseline, the response to electrical stimulation was evaluated after recording other variables whereas at 10, 20, 30, 60, and 60 minutes after tramadol administration physiological parameters were recorded after the electrical stimulus to evaluate any changes[13].
A 14-G venous catheter (Suriflo®) was inserted in the jugular vein and the subjects received tramadol (Altadol 5% Formenti Italy) at the following dose: 1 mg/ kg (group A), 1.5 mg/kg (group B), and 3 mg/kg (group C).
The dose of tramadol used in the present study has been selected based on the bibliographical review of the dosages of tramadol used in ruminants[1,9-16].
The dosage of tramadol to be administered, in the three groups, has been established by a lottery.
A cumulative pain score (CPS) was performed assigning scores to the percentage variations of HR, FR and NSP after tramadol administration, compared to baseline, according to the following scheme:
0 = no variation.
1 = > 0% but ≤ 10%.
2 = > 10% but ≤ 20%.
3 = > 20% but ≤ 30%.
4 = > 30% but ≤ 40% or more[20].

The total score was obtained by summing the three score.
When the score of CPS was > 10 and stimulus response score was equal to 4, the animals received flunixin meglumine (Finadyne® Schering-Pough Netherlands) 3.3 mg/kg intravenously as rescue analgesia.
Rescue analgesia was expected above along with the observation. Physiological parameters, stimulus response score, and CPS were recorded before tramadol administration (baseline) and at 10, 20, 30, 60 and 90 minutes after tramadol administration. The time points to collect the variables were chosen only for an alleged intraoperative phase.
Data were analyzed using SPSS 15.0 (IBM Company, Italy). Shapiro-Wilk normality test, Kendall's concordance test, for ataxia and stimulus response score, and a power calculation of sample were performed. The data were expressed with median and range. Differences along the time line and the differences between groups were evaluated using Friedman test $P \leq 0.05$ were considered significant.

RESULTS

Shapiro-Wilk normality test showed that the data were not normally distributed.
The Kendall's concordance test showed a high degree of agreement between the observers: 100% for ataxia scores, and 99%-100% for stimulus response scores.
The size of the sample is not enough to be representative of the population of dairy cattle present in the province of Ragusa.
Table 1 showed the data regarding HR, RR, NSP, ataxia score, cumulative pain score, and stimulus pain score.
HR was significantly different between groups at all times (p = 0.000). HR recorded in the group C was significantly lower compared to HR recorded in the other groups at 20, 30, 60 and 90 minutes (p = 0.000).
RR was significantly different between groups at all times (p = 0.000). RR in group C was significantly lower compared to RR of the other groups at all times (p = 0.000) but it did not change from baseline, in contrast to groups A and B in which modest, even though significant, variations have been observed, compared to baseline values.
NSP showed significant differences in groups A and B compared to baseline values (p = 0.000). In group C, NSP remained stable and no significant difference was recorded.
Ataxia scores did not show any significant differences at all times in all groups.
However, in group B the ataxia scores were higher than those recorded in groups A and C.
After tramadol administration (p = 0.010).

Table 1

Recorded Data	Groups	B	10'	20'	30'	60'	90'
HR (beats/min)	A	99(97/100)§#‡	95(93/97)§#‡	96(95/97)§#‡	98(97/99)§#‡	100(99/101)§#‡	105(98/110)§#‡
	B	90(91/89)§#‡	89(88/90)§#‡	87(86/88)*§#‡	90(89/91)§#‡	87(86/88)§#‡	89(85/90)*§#‡
	C	98(97/101)§#‡	99(98/100)§#‡	73(72/74)*§#‡	75(74/76)*§#‡	74(72/75)*§#‡	78(73/75)*§#‡
RR (breaths/mi)	A	35(34/36)§#‡	37(35/38)*§#‡	35(34/36)§#‡	34(33/35)*§#‡	35(34/37)*§#‡	34(33/35)§#‡
	B	38(37/40)§#‡	39(38/40)*§#‡	40(39/41)*§#‡	45(44/47)*§#‡	45(44/46)*§#‡	44(43/46)*§#‡
	C	20(19/22)§#‡	20(18/24)§#‡	20(19/24)§#‡	20(19/22)§#‡	20(20/22)*§#‡	20(18/22)§#‡
NSP (mmHg)	A	145(143/146)§#‡	159 (158/160)*§#‡	170(168/171)*§#‡	152(150/153)*§#‡	141(139/142)*§#‡	146(144/148)*§#‡
	B	128(126/129)§#‡	135(134/134)*§#‡	136(134/135)*§#‡	134(132/135)*§#‡	135(134/136)*§#‡	136(135/137)*§#‡
	C	100(99/103)§#‡	100(99/101)§#‡	100(98/102)§#‡	100(99/101)§#‡	100(99/102)§#‡	100(98/102)§#‡
Ataxia scores (scale 0/3)	A	0(0/0)	0(0/0)	0(0/0)	0(0/0)	0(0/0)	0(0/0)
	B	0(0/0)	1(0/1)	1(0/1)	1(0/1)	1(0/1)	1(0/1)
	C	0(0/0)	0(0/0)	0(0/0)	0(0/0)	0(0/0)	0(0/0)
CPS (Scale 0/4)	A		0(1/1)	(0/2)	0(1/1)	0(1/1)	0(1/1)
	B		1(0/1)	1(0/1)	1(0/2)	1(0/2)	1(0/2)
	C		0(0/0)‡	0(0/0)‡	0(0/0)‡	0(0/0)‡	0(0/0)‡
Stimulus response score: recorded Scores (Scale 0/4)	A	4(4/4)	2.6(2/3)*	2.6(2/3)*	2.6(2/3)*	3(2/3)*	3(2/3)*
	B	4(4/4)	1(1/2)*	1(1/2)*	1(1/2)*	2(1/3)*	2(1/3)*
	C	4(4/4)	2(1/3)*	3(2/3)*	3(2/3)*	3(2/3)*	3(2/3)*

Heart rate (HR), respiratory rate (RR), non-invasive systolic pressure (NSP), Cumulative Pain Scale (CPS 0/4).
Baseline (B), minutes (10, 20, 30, 60, 90) after 1 mg/ kg group A, 1.5 mg/kg group B and 3 mg/kg group C of tramadol injection.
* Significant differences along the time line.
§ Significant difference between group A and the other two groups, # Significant difference between group B and the other two groups,
‡ Significant difference between group C and the other two groups. The differences between the groups was considered significant for $p < 0.05$.

CPS did not show any significant differences along the timeline in all groups.
The CPS of group C were significantly lower compared to CPS of the other groups at all times ($p = 0.000$).
The stimulus response scores have been significantly reduced along the timeline in all groups. The stimulus response score of the group B was significantly lower compared to those of the other groups ($p = 0.000$).
Rescue analgesia was not administered in any subject. In two cows belonging to the group C, we observed phenomena of excitability and transient slight muscle fasciculation.

DISCUSSION

This study demonstrates that tramadol doses of 1, 1.5, and 3 mg/kg are effective to produce analgesia in cows. Furthermore, the side effects (excitability and slight muscle fasciculation) highlighted in some cows treated with tramadol 3 mg/kg were mild and transient.
The same side effects were reported in cattle administered 1 mg/kg of tramadol combined with 0.02 mg/kg of romifidine and in horses administered 1, 2, and 3 mg/kg of tramadol intravenously[14,21].
Even though it has been demonstrated that 1 mg/kg of tramadol administered intravenously slowly was more effective compared to the same dose given in a rapid bolus in the bovine, no side effects (e.g., excitability and fasciculation) were highlighted[1].
Muscle twitching and tremors have been observed in alpaca and in the horse after intravenous administration of tramadol[12,21].
However, no excitatory effects were recorded in horses that received 3 mg/kg of tramadol, administered intravenously slowly, alone or in combination with romifidine[18].
In the present study, we observed a better level of analgesia in the cows received tramadol 1.5 mg/kg. In fact, these animals had a lower degree of response to the noxious stimuli compared to the subject received tramadol 1 and 3 mg/kg. Paradoxically, the cows that received tramadol 3 mg/kg showed no ataxia nor a higher level of analgesia, but phenomena of excitability. Furthermore, the subject administered tramadol 3 mg/kg showed recorded lower values of heart rate, respiratory rate and non-invasive systolic pressure than animals administered tramadol 1 and 1.5 mg/kg. Other authors have observed the same side effects in in sheep[10]. It is likely that group C (3 mg/kg) had the lowest CPS score because 3 mg/kg of tramadol in cattle could be a too high dosage and can cause the appearance of the side effects of opioids. In fact, these effects could be due to activation of the opioid receptor, which gives excitatory effects that can mask the analgesia obtained[1,14,18,22].
There are several limitations the study mainly related the nature of the subjects. First, phenomena of excitability recorded in the group C make difficult the evaluation of the stimulus response scores, and it is likely that these side effects probably could have distorted the results.
Slow intravenous administration of tramadol would not have resulted in the appearance of excitability phenomena, and the evaluation of the analgesia would have been more reliable[1,18].
The lowering of the head is a parameter commonly used to evaluate sedation in cattle[14].
Unfortunately, this method was difficult to apply in the subjects enrolled in the present study due to their nature.
Third, the study was limited to the evaluation of analgesia and sedation in a potential intraoperative phase lasting 90 minutes. We aim to evaluate the half-life and pharmacokinetics of tramadol in cattle with further studies. Finally, another limitation of the study is the low number of subjects.

CONCLUSION

Tramadol 1.5 mg/kg is safe and effective, and provides analgesia compared to tramadol 1 and 3 mg/kg in cattle. The degree of ataxia obtained is not significant with the three tramadol dosages committed in the study, however, in group B the ataxia scores were higher than those recorded in groups A and C.

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