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 standing1-3. Nevertheless, in tissues affected by purulent inflammation (e.g., foot diseases, soleari ulcers, podophlemitis, interdigital dermatitis, nipple injurie, and mastitis), pH tends to acidity, and local anesthetics are ineffective4-6. 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; alfa2-adrenoceptor agonists5-7, opioids and NSAIDs, represent a valid alternative to local anesthetics4-6. Butorphanol, tramadol and other opioid agonist-antagonist provide sedation and analgesia. In various species of ruminants such as camellids and cattle8-16. NSAIDs are a valid therapeutic choice for the above mentioned surgical pathologies, because this drugs are anti-inflammatory and painkillers17. Tramadol is as a racemic mixture of two enantiomers. The positive enantiomer inhibits serotonin re-uptake while the negative enantiomer inhibits noradrenaline re-uptake1. 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 gastrointestinal systems. Tramadol has a half-life of about 2 hours in goats and alpacas18-20. 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 milk1. 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 short1. 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. 358/112/18/1986), and USA laws (Animal Welfare Assurance No A5594-01, Department of Health
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.

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:

\[ P \leq 10\% \]
\[ 10\% < P \leq 20\% \]
\[ 20\% < P \leq 30\% \]
\[ 30\% < P \leq 40\% \]
\[ P > 40\% \]

The total score was obtained by summing the three score.

The dosage of tramadol for ataxia was equal to 3.3 mg/kg intravenously as rescue analgesia.

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

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 after tramadol administration (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).
ly, alone or in combination with romifidine. When administered 3 mg/kg of tramadol, administered intravenously slowly, no excitatory effects were recorded in horses that received the same dose given in a rapid bolus in the bovine, no side effects (e.g., excitability and fasciculation) were highlighted. Even though it has been demonstrated that 1 mg/kg of tramadol administered intravenously slowly was more effective compared to the subject received tramadol 1 and 1.5 mg/kg. Other authors have observed the same side effects in in sheep. 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.

**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.

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. Muscle twitching and tremors have been observed in alpacas and in the horse after intravenous administration of tramadol. However, no excitation effects were recorded in horses that received 3 mg/kg of tramadol, administered intravenously slowly, alone or in combination with romifidine.

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. 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.

**Table 1**

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<th>Recorded Data</th>
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<th>60'</th>
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<td>97(72/74)</td>
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</table>

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.
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.

References