

EVALUATION THE SEDATIVE AND ANALGESIC EFFECT FOR MIXTURE OF TRAMADOL AND METOCLOPRAMIDE IN SHEEP

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ABSTRACT

The aim of study was to explore the analgesic and sedative effects of tramadol and metoclopramide co-administration in sheep. Injection of tramadol intramuscular at 5mg/kg body weight in sheep produced deep sedation, recompense and analgesia in comparison with dose of 2.5mg/kg body weight which produced only mild sedation and failed as analgesic dose. Intramuscular injection of metoclopramide at 20mg/kg body weight in sheep produced deep sedation, recompense and analgesia in comparisons with dose of 10 mg/kg which produced only sedation and failed as analgesic dose. Intramuscular injection of metoclopramide at dose 20mg/kg or tramadol at 5mg/kg body weight in sheep each alone were produced deep sedation, recumbence and analgesia while metoclopramide at 10mg/kg body weight or tramadol at (2.5mg/kg b. W) produced only mild sedation and each dose failed to produced analgesia in sheep. Concomitant administration of tramadol at dose 2.5mg/kg body weight to sheep and metoclopramide at dose 10mg/kg body weight intramuscular as sedatives not analgesia dose produced a significant increase in sedation score and produced deep sedation with recompense as well as good analgesia in comparison with control group and group of tramadol or metoclopramide alone.

INTRODUCTION

Tramadol is an opioid analgesic drug that are giving for patient suffering from moderate, severe or chronic pain (1). This drug has been used as a pre-anesthetic (2). Tramadol is a drug that combined with Mu-receptor in the central nervous system

and inhibition nor epinephrine and serotonin reuptake (3, 4, 5). tramadol use to relief pain sings anxiety, depression(6) and after anesthesia in cow ,dog and mice (7, 8).Metoclopramide is agastropkinetic agent and antiemetic in animals(9)(10) and human (11). This drug act antagonize of dopamine and inhibition of serotonin receptors5-HT₃ (12) and Cholinergic activity(13) metoclopramide has analgesic effect in mice (14) and human (15) . Many researchers were used metoclopramide and fixed the analgesic effect to this drug when used alone or combination with other drug. Metoclopramide was used with ketamine in mice(16).another study used it alone or as a combination with Diphenhydramine in mice and introduced analgesia(17)but not found studies use metoclopramide with tramadol in sheep .Therefore, suggest performing of this study to evaluate the analgesic effect of tramadol alone or as a combination with metoclopramide in a sedative dose in sheep and to study the effect of this mixture as for analgesia.

MATERIAL AND METHOD

Twenty ewe from local market weighing about (35-40)kg with aged about(1-1.5)years were selected for this study. The animals fed with standard diet and water with kept standard animal housing condition.

First Experiment: Detection the Sedative and analgesic dose of tramadol which injected intramuscular in sheep.In this experiment the animals were divided randomly into three groups each every group consist of five animal, in the first group (control group)was injected with normal saline solution while the animals in the second and third groups were injected with tramadol hydrochloride(Tramadol HCL ampul50mg/ml G.L. pharm Gmbh,8502a lannach Austria),the constriction of this drug100mg/2ml at(2.5,5)mg/kg body weight intramuscular in sheep respectively.The dose of tramadol was obtained from previous study(18). Detection of sedative scores pre and after 15,30,45,60 minute from tramadol injection according to (19)as fallows;

0: normal animal (no sedation)

1: dropping of head with normal walking

2: ataxia

3: lying but able to rise

4: recumbence and Loss of righting reflex.

Detection of analgesia by using of electrical stimulates to measuring of pain threshold after stimulating the nasal mucous membrane for ewe (noxious stimulation). The nociception threshold was detected after attachment the electrical polar of electrical stimulation to the nasal mucous membrane and record the volt that which the sheep moved the head for the source of stimulation then detection the pain threshold before the base line and after injection of the drug within 30 minutes.

Second Experiment: Detection of Sedative and analgesic dose by metoclopramide which injected intramuscular in sheep. In this method the animals also divided into three groups of animals each group consist of five animals. First group represented as control group which injected with normal saline solutions while second and third groups injected with metoclopramide at dose (10, 20 mg/kg) / intra muscular in sheep respectively. Detection of sedative score after injection of animal by same method in the first experiment. Using of electrical stimulator by same method in first experiment to measuring the pain threshold

Third Experiment: In this experiment the animals divided into four groups. each group consist of 5 animals. first group of animal (control group) injected with normal saline at (1 ml/kg intramuscular) while second group injected with tramadol at dose 2.5 mg/kg and third group injected with metoclopramide at dose 10 mg/kg while the animals in the fourth group injected with tramadol at 2.5 mg/kg and metoclopramide 10 mg/kg intramuscular separately. Detection of sedative score and analgesic effect of each other group by same method in the first experiment.

Statically Analysis: The parametric Data which include more than 2 factors statically analyze by tow Way analysis of variance (20). The non-parametric data analyze by using Mann-Whitney test (21) the data inform scores and the Significant difference plane least from 0.05.

RESULTS

Injection of sheep with tramadol at 2.5 mg/kg body weight intra muscular Produced mild sedation and calm of the animal was significant increase in sedation scores at minute (15, 30, 45, 60) after injection in comparison with zero time of the

same dose as well as significant increased at the time minute (45,60) in comparison with the time(15) of the same dose. When injection of sheep with tramadol at the 5mg/kg body weight intra muscularly in sheep there was a significant increase in the sedative scores in the animals treated with tramadol at minute(15,30,45,60)in comparison with zero time of the same dose and significant increase at minute (45,60)in comparison with time minute (15) at the same dose .This dose was the good analgesic dose in comparison with dose at 2.5 mg/kg of tramadol which failed to produce analgesia in the treated animals.

Injection of metoclopramide at dose(10mg/kg) intramuscular body weight produced mild sedation and increased in The onset time of sedation, there was significant increase in sedation scores at minute (15,30,45,60) in comparison with zero time of the same dose, as well as a significant increase in sedation scores at minute(30,45,60) in comparison with minute (15) of the same dose .injection of metoclopramide at dose 20mg/kg b.w. i.m. in sheep produced deep sedation (head down, ataxia ,recompense and significant increase in sedation scores at minute (30,45,60) in comparison with minute(15)of the same dose. this dose was produced a good analgesia in the animals in comparison with dose (10 mg/kg b.w. of metoclopramide. There was a significant increase in pain thresholds at the minute(30) after injection in comparison with zero time of the same dose as well as increased in pain threshold in comparison with the control group and group treated with metoclopramide at10mg/kg b.w.

Table(1) Sedation scores which result from Tramadol and metoclopramide injection each alone or as a combination in muscle in sheep.

Dose	Time15 minute	Time30 minute	Time45minute	Time minute
Control	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0
Tramadol 2,5mg/kg	1.0 ±0.0 ^b	1.6±0.2	2.0±0.0*	2.0±0.0*
Tramadol 5mg/kg	0.1±0.0 ^b	1.4±0.2	1.8±2.0 *	2.0±0.0*
Metoclopramide 10mg/kg	1.2 ±0.2 ^b	2.0 ± 0.0*	3.0±0.0* ^a	3.0±0.0* ^a
Metoclopramide mg/kg20	1.4±0.2 ^b	2.6 ± 0.2*	3.0±0.0*	3.6±0.2*
Tramadol2.5mg/kg+ metoclopramide10mg/kg	2.8±0.2 ^{bcd ef}	3.6 ± 0.2	4.0±0.0*	0.0*±4.0

*The Value significant different at minute 15 at plan least from 0.05 at the same dose.

a: Value significant different at minute30 at plan least from 0.05 at the same dose .

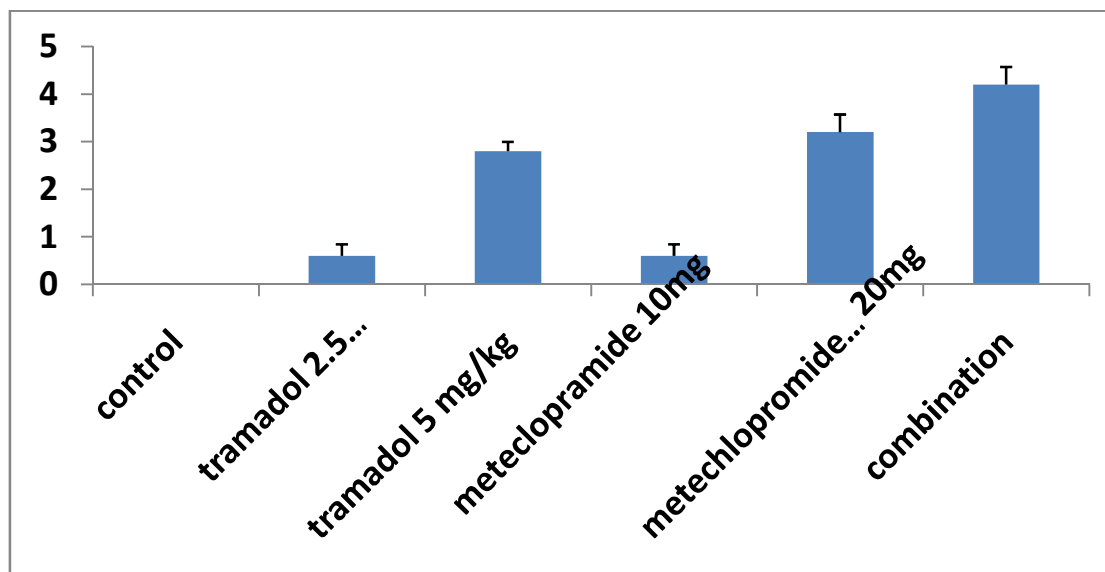
b:The Value significantly differ from control group at plan least from 0.05 at the same time.

c:The Value significantly differ from tramadol group at 2.5mg/kg plan least from 0.05 at the same time.

d:The Value significantly differ from tramadol group at 5mg/kg plan least from 0.05 at the same time

e:The Value significantly differ from metoclopramide group at 10mg/kg plan least from 0.05 at the same time

f.The Value significantly differ from metoclopramide group at 20mg/kg plan least from 0.05 at the same time.



(Figure 1) Sedation scores which result from Tramadol and metoclopramide injection each alone or as a combination in muscle in sheep.

In this experiment the animals which injected with tramadol at(2.5)mg/kg i.m. or metoclopramide at(10mg/kg b.w.) each alones sedatives not analgesic dose this doses produced mild sedation and not produce analgesia while concomitants injection at the same dose of tramadol and metoclopramide produced deep sedation and decrease in the onset of sedation .

There was significant increase in the sedative scores at minute (45,60) in comparison with minute (15) of the same dose and significant increase in pain threshold compare with animal treated with tramadol or metoclopramides each alone. The combination of tramadol and metoclopramide at(sedative dose not analgesic)induced good analgesia in comparison with control group and group treated with tramadol or metoclopramide each alone.

(Table2): Change in voltage caused to pain as a result from tramadol or metoclopramide injection in muscle in sheep .

Dose	Mean $\pm$ stander error
Control	0.0 $\pm$ 0.0
Tramadol2.5mg/kg	0.6 $\pm$ 0.2*
Tramadol5mg/kg	2.8 $\pm$ 2.0* ^a
Metoclopramide10mg/kg	0.6 $\pm$ 0.5 * ^b
Metoclopramide20mg/kg	3.2 $\pm$ 0.3* ^{ac}
Tramadol2.5mg/kg + Metoclopramide10mg/kg	4.2 $\pm$ 0.3* ^{abcd}

*: The Value significantly differ from control group at least from 0.05 at the same time.

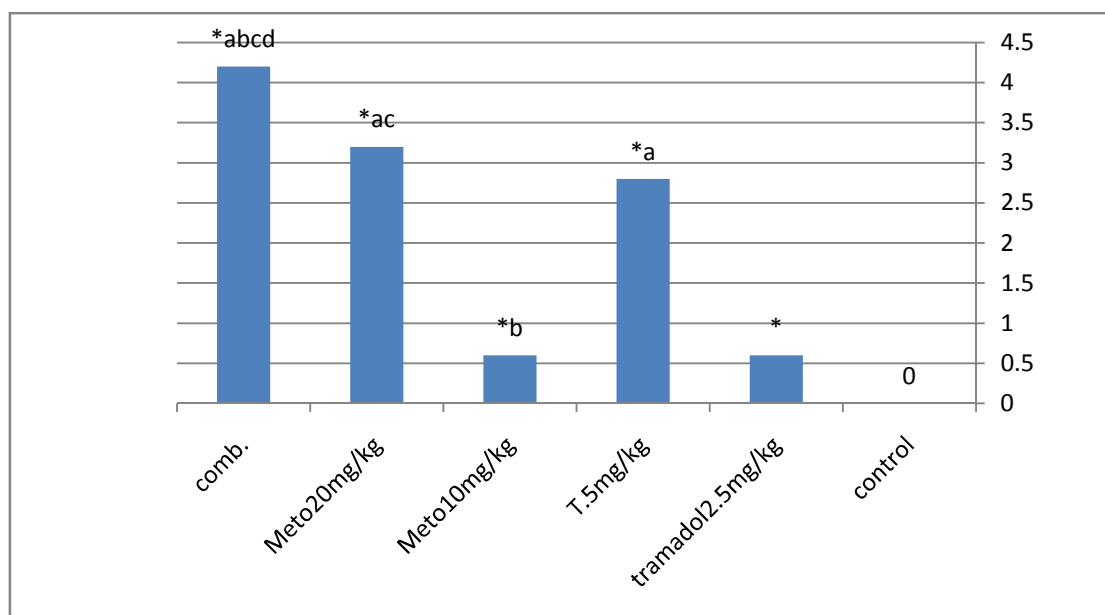
a: The Value significantly differ from tramadol group at 2.5mg/kg plan least from 0.05 at the same time.

b: The Value significantly differ from tramadol group at 5mg/kg plan least from 0.05 at the same time.

c: The Value significantly differ from metoclopramide group at 10mg/kg plan least from 0.05 at the same time.

d: The Value significantly differ from metoclopramide group at 10mg/kg plan least from 0.05 at the same time.

(Figure 2) Change in voltage caused to pain as a result from tramadol or metoclopramide injection in muscle in sheep.



DISCUSSION

Tramadol is centrally acting agent activity at M-opioid adrenergic and and 5-hydroxytryptamine (5-HT) receptors the mechanism of action as are-uptake inhibitor of nor epinephrine and serotonin and agonist of the M-opioid receptor(4). Tramadol used to relief mild to moderate pain in human and veterinary medicine(22) also used preoperatively in veterinary anesthesia to reduces the dose of volatile anesthetics and opioids agent (23).

Metoclopramide is anti-emetic drug recently many studies refers to the analgesic effect of metoclopramide alone (15) or as combination with other analgesic effect of ketamine(16) or with tramadol(24). Intramuscular injection of tramadol at(2.5mg/kg b.w) produced mild sedation without recompense and analgesia while at(5mg/kgb.w) produced deep sedation and sings of sedation was appear(drooping of head with normal walking, ataxia, lying and recompense)as well as produced good analgesia this agreement with previous studies(19) the analgesic effect result from mechanism that is are-uptake inhibitor of nor epinephrine and serotonin and agonist of M-opioid receptor(4).intramuscular injection of metoclopramide in sheep produced sedative effect in form dependant dose this result agreement with(14) which refer metoclopramide produced sedation on the central nervous system in chick also

injection of metoclopramide produced analgesic effect in form dependant dose this result agreement with perilously study(17)(16) which refer to the analgesic effect of metoclopramide in mice this analgesic action due to antagonism action to D receptors which related with opioid system (25) this drug has been increased prolactin(26) as well as agonist of serotonin 5HT(27) and alter Ca^{2+} across through cell membrane(28). Combination of metoclopramide and tramadol in sedatives not analgesic dose which produced deep sedation and analgesia this interaction was a synergism interaction because each drug act on different receptor (pharmacodynamics) and produced their analgesic effect. This combination succeeds to produce analgesia and reduced the side effect for this drug.

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