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Evaluation of antinociceptive effect of tramadol in chicks

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Abstract

In this study the ED50 of tramadol was evaluated and it was found to be equal to (0.85 mg/kg). The analgesic effect of tramadol (1 mg/kg) by subcutaneous route was investigated in chicks by using electrical stimulator. The drug induce a safe and effective analgesia within 30 minute and lasted for 90 minute after injection. Tramadol also produce sedative effect within 40 minute after administration and last up to 80 minute, presented by dropping of the head and wings, ataxia, lying but able to rise and recumbency then loss of consciousness. The administration of tramadol produce a dose- depended antinociceptive effect with 10 mg/kg as maximum effective dose. This study concluded that tramadol have a good analgesic activity in chicks.

Keywords: Tramadol, Analgesia, Antinociception, Chicks.
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دراسة التاثير المسكن للترامادول في أفراخ الدجاج

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الخلاصة

تمت في هذه الدراسة تقييم الجرعة المسكنة الوسطية للترامادول المعطى تحت الجلد في أفراخ الدجاج حيث أظهرت النتائج أن هذه الجرعة بلغت تقريبا ٠.٨٥ ملغم/كغم. كما تم قياس الفعل المسكن لدواء الترامادول بجرعة (١ملغم/كغم) بعد حقنه تحت الجلد في أفراخ الدجاج وذلك باستخدام جهاز التحفيز الكهربائي. أحدث الدواء وبفاعلية تسكينا جيدا بدأ بعد ٣٠ دقيقة من الحقن وامتد لمعدل زمني بلغ حوالي ٩٠ دقيقة، كما وأدى إعطاء الترامادول بنفس الجرعة إلى إحداث تسدير في الأفراخ بدأ بعد ٤٠ دقيقة من حقن الترامادول واستمر حتى الدقيقة ٨٠ من التجربة وتمثل بتهدل الأجنحة وإغماض العيون وعدم القدرة على المشي. كما وتبين من خلال الدراسة إن قوة التأثير المسكن للترامادول تعتمد على الجرعة. ان هذه الدراسة تستنتج بان دواء الترامادول يعطي تسكينا جيدا في أفراخ الدجاج.

Introduction

Tramadol, is a CNS depressant and analgesic drug, used for treating moderate to severe pain (1). It is a synthetic 4-phenyl-piperidine analog of codeine which was introduced in Germany in late 1970s (2). It appears to have actions at the μ-opioid receptor as well as the noradrenergic and serotonergic systems (3). Tramadol is widely used in the treatment of pain in human and animals when given in both injectable (intravenous, intramuscular and/or epidural) and oral preparations (4-6). It is exhibits a good analgesic efficacy, with an analgesic potency equals to mepridine and 5 to 10 time less than morphine (3,7). It had been suggested that tramadol could be effective for alleviating symptoms of most types of neuralgia, depression and anxiety (9); because of its action on the noradrenergic and serotonergic systems, the involvement of which appear to play a part in its ability to alleviate the perception of pain, this inhibition may lead to reduce transmission of pain signal through the spinal cord to the brain (1). The contribution of non-opioid

activity is demonstrated by the analgesic effects of tramadol not being fully antagonized by the μ-opioid receptor antagonist naloxone (8). Clinical experience indicates that tramadol lack many of the side effect typically associated with opioid agonist (5).

Tramadol is used to treat post-operative, injury-related, and chronic (e.g. cancer-related) pain in dogs as well as cattle and many small mammals including mice and rats (4,6,7,10,11).

The objective of this study was to evaluate the analgesic properties of tramadol and to measure the ED_{50} of tramadol in chick due to the lack of evidence on the use of tramadol in chicks.

Materials and Methods:

Experimental animals:

Chicks used in this study were purchased from local market. Aged ranged from 2-3 weeks, and their body weight from 30-35 gm. The chicks were in excellent health, food but not water was withheld the morning of each treatment day.

The drug used was tramadol injection (Taridol 100mg /2ml) from ALPA LABORATORIES LTD, Syria.

The experiments were preformed as a randomized design. Each chick was treated with specific dose of tramadol, all doses were given subcutaneous (SC) with a volume of injection equals to 5 ml/Kg. All dilution were prepared using normal saline as vehicle (6).

Pain was induced by application of noxious stimulus (single electrical pulse) delivered from a device of Electrical stimulator type 100 (Bioscience company, England) using a modified (Sandmeire 2000) (12) method for the assessment of duration of application of noxious stimulus. This stimulus was applied to the skin under the wing at 10, 20, 30, 60 up to 120 minute after drug administration and was maintain until chick call were heard, calling of the chicks were recorded as negative result.

Experiment (1):

Five chicks were used in this experiment to determine the median effective analgesic dose (ED_{50}) of tramadol, by using up & down method (13). The noxious stimulus was applied for each chick before treatment to determine pain threshold and after 30 minutes of tramadol administration starting by 0.5mg /Kg dose depending on early polite study. The increase and decrease in the dose was in a constant value of (0.5 mg/Kg). The ED_{50} for tramadol was determined according to Dixon table (13), using the following equation: $ED_{50} = X F + k d$

XF : Last Dose.
K : From Dixon table.
d : constant dose range.

Experiment (2):

Two groups were used in this experiment with five chicks in each group. The first group was given tramadol injection (1 mg /Kg) which produce the best analgesic effect, while the second group was given normal saline injection as a control.

The onset and duration of analgesic effect of tramadol were determined in chicks by using electric stimulator (noxious stimulus) which was applied at 10,20,30,…. until 120 minutes after administration of tramadol, after the electrical stimulus a call to the stimulus was recorded to indicated for pain response.

0 = pain.
X= analgesia.

Experiment (3):

Five chicks were used to determine the degree of sedation after administration of tramadol (1 mg /Kg) SC while another group of five chicks were given normal saline injection as a control.

The assessment of the degree of sedation in chick was recoded using the following score (14):-

0: normal.
1: dropping of head & dropping of wing.
2: ataxia.
3: lying but able to rise.
4: recumbency then loss of consciousness.

Experiment (4):

The dose – response curve of tramadol in chicks were determined in this experiment.

After determination of the pain threshold for chick (base line 9 volt), the chicks were divided in 5 groups, each group contain 5 animals and they were treated by following doses:

group 1: tramadol at 0.5 mg /kg
group 2: tramadol at 1 mg /kg
group 3: tramadol at 2.5 mg /kg
group 4: tramadol at 5 mg /kg
group 5: tramadol at 10 mg /kg

Ten minutes later animal were tested again for the changes in pain threshold by electric stimulator and repeated test every 10 minutes up to 120minut.

Statistical analysis

The result were expressed as a mean ± SD. The non parametric data were analyzed by Fisher exact probability test (15). The level of significance was at $P<0.05$.

Results

Experiment (1):

The analgesic ED_{50} of tramadol injection in chicks were determined using the following equation: $ED_{50} = X F + kd$. It was calculated to be equals' to 0.85 mg /kg according to table (1).

Table (1): Determination of ED_{50} in chicks treated by Tramadol.

Measurements	Result
ED_{50}	0.851 mg/ Kg
Dose range	0.5- 1 mg/ Kg
First Dose	0.5 mg/ Kg
Last Dose	1 mg/ Kg
No. of Chicks	OXOXO
Sings of Analgesia	No Call after electrical stimulation at 9 Volt

Experiment (2):

The mean ± SD onset and duration of analgesia obtained with administration of tramadol (1 mg /Kg) is given in table (2)

The onset of analgesia was started 30 minute after injection of tramadol and last up to 1.5 hours after injection.

Table (2): Determination of the onset and duration of analgesia in chickstreated by (1 mg/ Kg) tramadol SC.

Group	Control	Treated
20	0	0
30	0	100%*
40	0	100%*
50	0	100%*
60	0	100%*
70	0	100%*
80	0	100%*
90	0	100%*
100	0	100%*
110	0	66.6%*
120	0	33.30%

* significant at P<0.05.

Experiment (3):

Administration of tramadol (1 mg /Kg) produce sedation in chicks within 40 minutes, this appear by dropping the head and wing of the chick, closing the eyelid, ataxia and recumbency of the animal. The intensity of sedation decrease after 80 minutes but the recumbency time last about 40 minutes until return to the righting reflex (Figure 1).

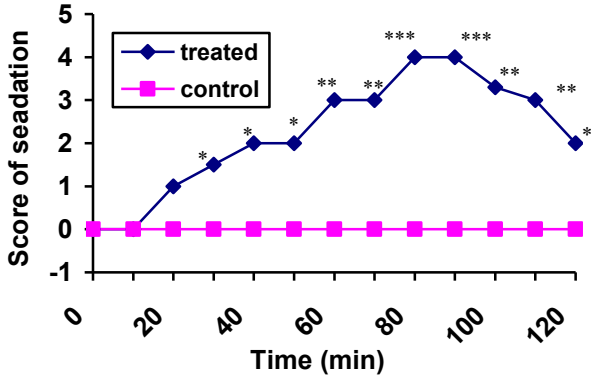

Figure (1): Degree of sedation induced by tramadol (1 mg/ Kg, SC) in chicks.

Experiment (4):

Tramadol produce a dose related increase in analgesia in comparison to base line of pain threshold, the increase in the dose lead to increase in the dose effective curve. The maximum effect occurring at 10 mg /kg SC (Figure 2).

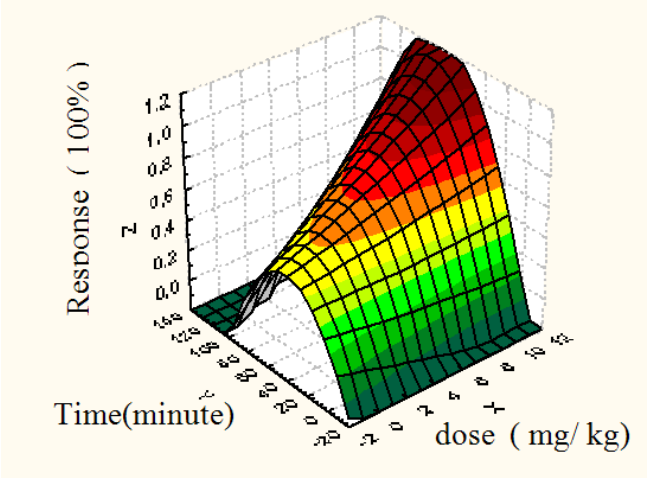

Figure (2): Dose response curve of tramadol in chicks.

Discussion

The use of analgesic drug to prevent or treat post operative pain in animal is increasing now a day (11). Administration of exogenous opioid may cause effective analgesia without CNS adverse effect (12). In this study tramadol was used, it's a centrally acting opioid analgesic.

In the present study, the analgesic properties of tramadol was observed in chicks, these results were in agreement with others study about analgesic effect of tramadol in human (5) and different species of animals intraoperative antinociceptive and postoperative analgesia (4,11,16).

In this study evaluating the ED_{50} of tramadol which lead to analgesia in 50% of treated chick is about 0.85 mg /kg which give a good analgesia from pain induced by electric stimulator.

The potency of analgesic effect of tramadol produce by using single dose fashion showed that analgesic response of tramdol were increased by increasing the dose which lead to increase the duration and the potency of tramadol, and this is correlated closely to results obtained form single dose study for example of morphine and fentanyl determine by single dose test (17) analgesia accompanied with increase a dose and this result agreement with other study observed that each of *Mu*-receptor agonist produce analgesia in dose related manner (16). Noradrenergic descending pathway and serotonergic system innervate all level of the spinal cord and can modulate afferent pain signal at this level (10) to produce antinociception, this may explain the analgesic effect of tramadol due to it's mechanism of action on opioid receptors and on inhibition the reuptake of norepinephrine at the level of spinal cord to produce antinociceptive effect of tramadol (8).

In our study the onset and duration of action were determined, it was about 30 mint and last up to 1.5 hour respectively. and this result is in agreement with other studies which suggest that the onset and duration of analgesic action of tramadol is about (30-60) minutes and last up to (4-6) hour following a single dose of tramadol (11,16). Tramadol is administered as arcemic mixture, that are metabolized in the liver producing an active metabolites of (+)-O- desmethyltramadol and (-)-O- desmethyltramadol which will prolong the duration of action of tramadol (4).

Tramadol produce sedation in chick manifested by dropping of head and wing and closing of the eyes and recumbence of the animal and this may be due to the mechanism of action of tramadol that inhibits the reuptake of norepinephrin and 5-HT (serotonin) (8,17,18). These mechanisms may contribute to the significant anti anxiety or sedative component in the analgesic effect of opioid and tramadol, and produce an important advantage as combination of desirable effects (e.g. analgesia and sedation) in patient with pain (19).

Conclusion

Tramadol at 1 mg /kg SC as a single dose demonstrated a good analgesic and sedative effects in chicks.

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