Evaluation the sedative and analgesic effects of tramadol and chlorpromazine alone or as a combination in chicks
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Abstract
The goal of this study was to assess the pain-relieving action of tramadol alone or when administered with chlorpromazine and screening for analgesic effects by using sedative non-analgesic doses of tramadol and chlorpromazine when injected together in chicks. the analgesic ED$_{50}$ of tramadol was 0.8 mg/kg body weight (intra muscular injection), and the sedative ED$_{50}$ of chlorpromazine was 8.6 mg / kg of body weight (intraperitoneal injection). Based on Isopolographic analysis, the type of drug interaction between tramadol and chlorpromazine was determined when injected together in a ratio by 1: 1, 1: 0.5 and 0.5: 0.5 from the median effective dose (ED$_{50}$) of tramadol and the median effective dose of chlorpromazine was synergetic interaction. Thus conclude that combination of tramadol and chlorpromazine with sedative non-analgesic doses is ideal for a good analgesic effect of pain in chicks.

Keywords: sedation , analgesia , electro stimulator, chlorpromazine, tramadol.

Introduction
Tramadol is a weak opioid agent which inhibits noradrenergic and serotonergic neurotransmission, it have analogous and analgesic efficacy to meperidine but less sedative effect on human(1). It is a centrally acting analgesic agent which activates the 5-hydroxytryptamine( 5HT) & µ-opioid adrenergic receptor (2) The drug prevents the re-uptake of norepinephrine & serotonin (3), this drug is rapidly cross blood brain barrier and has a large distribution volume(4) it is metabolized in
the liver by the cytochrome enzymes P450 (5, 6). Chlorpromazine is a phenothiazine derivative of anti-hepatic drugs (7, 8) in addition to sedative drugs that inhibit dopamine neurotransmitter activity (9), the mechanism of action of this drug inhibits activity of neurotransmitter dopamine& thus closes the dopamine receptors as well as the closure of the activity of the histamine H1, H2, alpha1 and alpha2, and the muscarinic and serotonin receptors (10), and also binds to the opioid µ receptor in the central nervous system µ (3).

**Materials and methods**

In this study used, the chicks broiler type (Ross) of both sexes. The broiler was raised under standard conditions at a temperature of (32–35°C), Ventilation and illumination were carried out until experiments at the age of seven days. The weight of chicks (50–70g) The size of injections was 5 ml / kg body weight and used the electrical stimulator type of 100 (company, Bioscience England) to measure the pain of the chicks. This device was used by other researchers to measure the analgesic effect of pain of xylazine in sheep (11).

**The first experiment**

In this experiment five animals were used to determine the median effective dose(ED50) of tramadol injected (i.m) in chicks, was adopted on up and down method (12) by using electrical stimulator, and determined the least voltage caused pain (calling in chicks) in a primary dose of 1 mg / kg depending on (5,6), and the amount of ascension and descent dose 0.3 mg / kg of body weight.

**The second experiment**

The chicks were injected with chlorpromazine a dose (8.6mg/kg)i.p and it was observed for 30 minutes to see the sedation signs on it. The animal adopted the method of ascension and descent dose. The primary dose of 10 mg / kg depending on (5,6), and the amount of ascension and descent dose 2 mg/kg of Bwt.

**The third experiment**

Determination the type of drug interaction between tramadol was injected i.m and chlorpromazine was injected i.p in chicks in ratios 1:1, 1:0.5, 0.5:0.5 from analgesic ED50 of tramadol and sedative ED50 of chlorpromazine of chicks. The first animal was injected tramadol i.m and chlorpromazine i.p(tramadol, chlorpromazine) in ratio 1: 1, 1:0.5, 0.5: 0.5 of the ED50 of tramadol and chlorpromazine in chicks.

The voltage of the first animal of each group were determined by using an electrical stimulator, the chick was injected Tramadol and chlorpromazine in ratio (1: 1, 1:0.5 and 0.5: 0.5) and left for 30 min. before exposure to the same voltage and recording incidence or lack of pain relief, the method of up and down with dose was adopted in the three groups of chicks 25% of the primary dose for both tramadol and chlorpromazine.

**Data Analysis**

The data of this study was analyzed by Isopolographic-analysis as Shaban Evaluated of the anti-nociceptive effect of dipyrone, xylazine, & tramadol in alone or as a combination in chicks (5, 6).

**Results**

The median effective analgesic dose(ED50) of tramadol injected (i.m) in chicks, which leads to analgesia in 50% of the experimental animal was 0.8 mg/kg of Body Weight, while the median effective sedative dose of chlorpromazine (i.p) injected in chicks was 8.6mg / kg B.w. (Table 1).

Based on Isopolographic analysis and using different ratios of the median effective analgesic dose of tramadol and the median effective sedative dose of chlorpromazine when injected together intramuscular and intraperitoneal injection respectively, at 1: 1, 1: 0.5 and 0.5: 0.5, the type of drug interaction between the two drugs was synergistic (Table 2). (Figures1,2,3 ).
Table (1): Determination ED$_{50}$ of tramadol i.m injection and ED$_{50}$ of chlorpromazine i.p injection in chicks.

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Tramadol mg/kg</th>
<th>Chlorpromazine mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>ED$_{50}$ of analgesia</td>
<td>..........</td>
<td>..........</td>
</tr>
<tr>
<td>ED$_{50}$ of sedation</td>
<td>8.6 mg/kg</td>
<td>8.6 mg/kg</td>
</tr>
<tr>
<td>Range of doses</td>
<td>0.7-1 mg/kg</td>
<td>8-10 mg/kg</td>
</tr>
<tr>
<td>Primary dose</td>
<td>1 mg/kg</td>
<td>10 mg/kg</td>
</tr>
<tr>
<td>Final dose</td>
<td>1 mg/kg</td>
<td>10 mg/kg</td>
</tr>
<tr>
<td>Amount of increase or decrease in dose</td>
<td>0.3 mg/kg</td>
<td>2 mg/kg</td>
</tr>
<tr>
<td>No. of chicks used</td>
<td>(XOXOX) 5</td>
<td>(XOXOX) 5</td>
</tr>
</tbody>
</table>

X= analgesia , O = no analgesia

Figure (1) interaction both injection together of tramadol and chlorpromazine in ratio 50:50 from analgesic ED$_{50}$ of both drugs.
The median effective analgesic dose of tramadol and the median effective sedative dose of chlorpromazine when injected together were (tramadol at 0.8 mg/kg by intramuscular injection and chlorpromazine at 8.6 mg/kg intraperitoneal injection), used by up and down method were (0.17 mg/kg) and (1.23 mg/kg) Respectively (Table 2).

Tramadol at dose of 0.113 mg/kg Bwt., intramuscular injection & chlorpromazine at dose of 1.33 mg /kg B.wt. , by intraperitoneal injection were failed to induced any analgesia and sedation in the experimental animals at each drug alone., while both drugs were successful at The same dosages to induced deep sedation and good analgesia of the experimental animals (Table 2).
DISCUTION
The aim of current study was to evaluate the pain-relieving effect of tramadol on its own or as a combination with chlorpromazine by using electrical stimulator and to examine analgesia by use of sedative not analgesic doses from tramadol and chlorpromazine in chicks. Tramadol centrally act on behalf of anti-nociceptive agent which activate the μ-opioid adrenergic & 5-hydroxytryptamine(5Ht) receptor(13,14,15). Chlorpromazine is phenothiazine derivative (16,17). Chlorpromazine is neuroleptic drug which produce therapeutic effect and unwanted effect in man such as a sedative, autonomic, endocrine & neurological effect (18) and (2) in Camel. The sedative and analgesic effect of tramadol due to a racemic mixture containing of two isomers (-) enantiomer, (+) antimere(M1) has affinity for μ opioid while (19, 20) enantiomer is control the other mechanism (non-opioid) which it inhibits noradrenaline & serotonin reuptakes (21) which inhibition of pain. Chlorpromazine produce sedation in chicks this result agreement with (11,7) because action of chlorpromazine on dopamine antagonist and
Histamine(22) and the median sedative dose for chlorpromazine was(8.6 ) mg/kg B.w.
While injection of tramadol and chlorpromazine together in a different ratio(0.5:0.5,1:0.5,1:1) from median analgesic dose for tramadol and Median sedative dose for chlorpromazine which produce deep sedation this result due to depressive of synergetic effect from two drugs on the central nervous system. This mixture from two drugs which success to induce analgesic effects in a sedative dose compare when use of these drugs alone on chicks, as well as this combination reduce the side effects of two drugs when used alone. It’s thought that block of D2 Receptors this drug produces sedative effect and hypothermia. This result due to action on the receptor system, its antagonist to alpha adrenergic receptor.

Conclusions
We conclude from our results that the combination of tramadol and chlorpromazine with sedative non-analgesic doses is ideal for a good analgesic effect of pain in chicks. Thus, this study will open the way to use this combination as a model in scientific research in chicks.

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Conflict of interest
There exists no.

Authors contribution
Both authors have equal contribution for this manuscript.

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