

Evaluation the sedative and analgesic effects of tramadol and chlorpromazine alone or as a combination in chicks

Manahel Allawi Abdulla Aljbori Rawnaq Faris Abdulqader Alshalchi
Ghada Abdulmunem Faris

Department of Physiology, Biochemistry and Pharmacology, College of Veterinary
Medicine, University of Mosul, Mosul, Iraq

E-mail address: rawnaqfaris8111@gmail.com Mobile no. **07717531406**

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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 ED₅₀ of tramadol was 0.8 mg/kg body weight (intra muscular injection), and the sedative ED₅₀ 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(ED₅₀)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.

تقييم الفعل المسكن والمهدئ لمزيج الترامادول والكلوروبرومازين في أفراخ الدجاج

غادة عبد المنعم فارس رونق فارس عبد القادر مناهل علاوي عبد الله
كلية الطب البيطري – جامعة الموصل

الخلاصة

كان الهدف من هذه الدراسة تقييم الفعل المسكن والمهدئ لمزيج الترامادول والكلوروبرومازين في أفراخ الدجاج. تم تقييم التأثير المسكن (Analgesic ED₅₀) للترامادول وحده (0.8 ملغم / كجم من وزن الجسم) والتأثير المهدئ (Sedative ED₅₀) للكلوروبرومازين (8.6 ملغم / كجم من وزن الجسم) عند حقنهما معاً في أفراخ الدجاج. تم تحديد نوع التفاعل الدوائي بين الترامادول والكلوروبرومازين عند حقنهما معاً بنسبة 1:1 و 1:0.5 و 0.5:0.5 من الجرعة المسكنة للترامادول والجرعة المهدئة للكلوروبرومازين. استنتج من نتائج التحليل أن مزيج الترامادول والكلوروبرومازين بالجرعة المهدئة غير المسكنة يعد مثالياً لإحداث تسكين جيد للألم في أفراخ الدجاج.

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 pheno-thiazine 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 H_1 , H_2 , α_1 and α_2 , 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 (ED_{50}) 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 a ratios 1:1, 1:0.5, 0.5:0.5 from analgesic ED_{50} of tramadol and sedative ED_{50} 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 ED_{50} 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

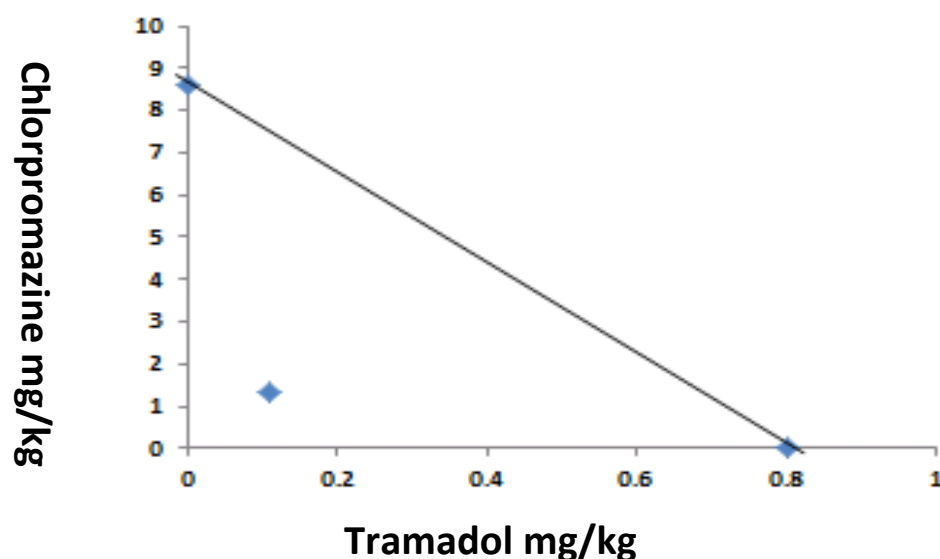
The median effective analgesic dose (ED_{50}) of tramadol injected (i. m) in chicks, which leads to analgesia in 50% of the experimental animal was 0.8 mg/kg of Body Weight, while the median effective sedative dose of chlorpromazine (i.p) injected in chicks was 8.6mg / kg B.w. (Table 1).

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). (Figures 1,2,3).

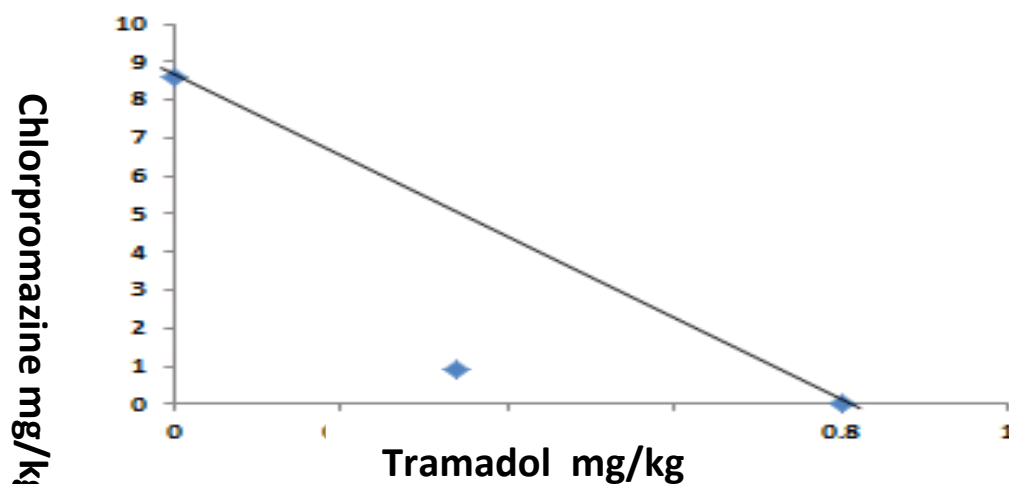
Table (1): Determination ED₅₀ of tramadol i.m injection and ED₅₀ of chlorpromazine i.p injection in chicks.

Measurements	Tramadol	Chlorpromazine
ED ₅₀ of analgesia	Tramadol	
ED ₅₀ of sedation		8.6 mg/kg
Range of doses	0.7-1 mg/kg	8-10 mg/kg
Primary dose	1 mg/kg	10 mg/kg
final dose	1 mg/kg	10 mg/kg
Amount of increase or decrease in dose	0.3mg/kg	2mg/kg
No. of chicks used	(XOXOX) 5	(XOXOX) 5

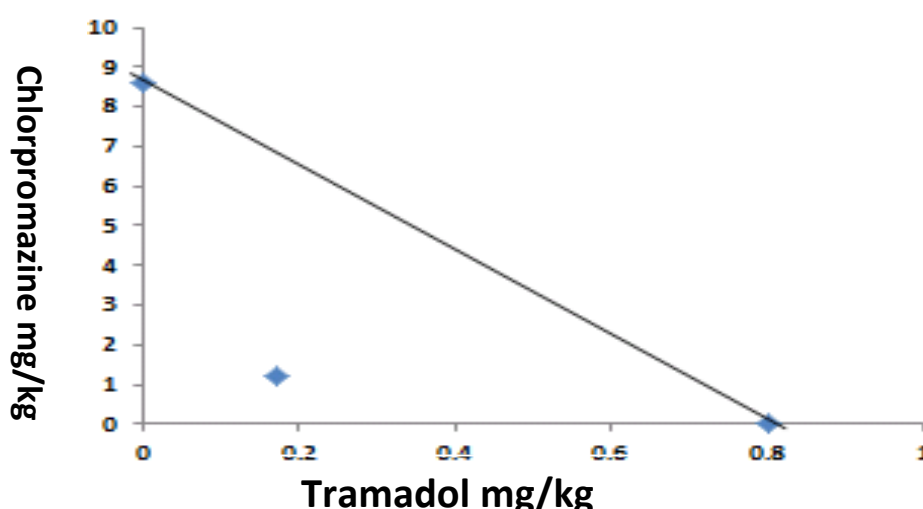
X= analgesia , O = no analgesia



Figur (1)interaction both injection together of tramadol and chlorpromazine in ratio50:50 from analgesic ED₅₀of both drugs.



Figur (2)interaction both injection together of tramadol and chlorpromazine in ratio1:50 from analgesic ED₅₀ of both



Figur (3)interaction both injection together of tramadol and chlorpromazine in ratio1:1 from analgesic ED₅₀of 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 (0.17mg/kg) and (1.23mg/kg) Respectively (Table2).

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).

Table (2):Determination ED₅₀ of tramadol i.m and ED₅₀ of chlorpromazine i.p when injected together at different rates.

Measurements	Tramadol: Chlorpromazine		
	0.5 : 0.5	1:0.5	1:1
ED₅₀ Analgesia Tramadol (mg/kg)	0.11	0.34	0.17
Range of doses (mg/kg)	(0.4-0.2)	(0.8-0.5)	(0.8-0.2)
Primary dose(mg/kg)	0.4	0.8	0.8
Final Dose(mg/kg)	0.2	0.5	0.2
Amount of increase or decrease in dose%25 (mg/kg)	0.1	0.1	0.2
No. of chicks used	(x0xx0)5	(xx0xxx)6	(xx0xx)6
ED₅₀ Sedation Chlorpromazine (mg/kg)	1.33	0.94	1.23
Range of doses (mg/kg)	(4.7-2.35)	(4.7-1.12)	(8.6-1.6)
Primary dose(mg/kg)	4.7	4.7	8.6
Final dose (mg/kg)	2.35	1.12	3.8
Amount of increase or decrease in dose %25(mg/kg)	1.175	1.18	2.4
No. of chicks used	(x0xx0)5	(xx0xxx)6	(xx0xxx)6

X= analgesia, O= no analgesia

DISCUSSION

The aim of current study was to evaluate the pain-relieving effect of tramadol on your own or as a combination with chlorpromazine by using electrical stimulator and to Exam 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 un wanted 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 antagonize 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 antagonize to alpha adrenergic receptor.

Conclusions

We conclude from the 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.

REFERENCE:

1. AshaRani, K.N.M. (2016). Effect of intramuscular tramadol hydrochlorid alabor analgesic in primagravidae. International Journal of Reproduction, contraception, obstetrics and gynecology; 5(3), 615 – 619.
DOI:http://dx. doi.org/10.18203/2320-1770.ijrcog20160460.
2. Rashidpour, M., Ahmad, A., Hosseinzadeh, N.T., Dehpour, A.R., Alaeddini, M., Javadi, E., Noroozi, H.(2012). Effect of tramadol (μ -opioid receptors agonist) on orthodontic tooth movements in a rat model. Jou. of Dentistry.9(2), 83-89.
3. Ide, S.M., Minami, K., Ishihara,G.R., Uhi, S.K., Ikeda, A. (2006). Mu opioid receptor _depended and independent component in effects of tramadol . Neuropharmacology.51,651-658https://doi.org/10.1016/j.neuropharm..05.008Get rights and content.
4. Lee, I., Seo, J., Son, W., Gang, S. (2011). Sedative and analgesic effects of intravenous xylazine and tramadol on horses. J. Vet. Sci., 12(3), 281-286.
5. Shaban, K.A., Faris, G.A. (2012). Evaluation of the analgesic effect of xylazine, dipyrone and tramadol in a single dose or as acombination in chicks.AL-Anbar.J Vet Sci. 5(2), 197-21.
6. Shaban, Kh.A., Ibrahim, M.H., Faris, G.A.(2020). Evaluation of the antinociceptive effect of xylazine and it's interaction with metoclopramide in the acute pain model in mice. Iraqi Journal of Veterinary Sciences 34 (2), 384-388 . DOI: [10.33899/ijvs.2019.126070.1226](https://doi.org/10.33899/ijvs.2019.126070.1226),
7. Anatoly, A., Mokrushin,. (2017). Specific effects of antipsychotic chlorpromazine on glutamatergic ionotropic mechanisms. Novel target for treatment schizophrenia. Int. Jou. Brain Disord Treat. Vol.31(1),1-7. .DOI: 1410020/5866-2469/10.23937.
8. Hassan, M.M.(2018). Evaluation the sedative and analgesic effects of xylazine and chloropromazine alone or as a combination in chicks.Iraqi J Vet Sci.; Vol.32(2), 9-13.
9. Pawson, P. (2008).Sedatives,In:Maddison,J.(editor),Small animal clinical Pharmacology,2nd.,Saunders Elsevier,Philadelphia,USA , 113_125.
- 10.Finkel, R., Cubeddu, L.X., Clark, M.A. (2009).Lippincott Illustrated Review Pharmacology,4th Edition. 65_159.
11. Abdullah, M.A., Faris, G.A. (2013). Evaluation the sedative and analgesic effect of xylazine and chloropromazine alone or as a combination in sheep.AL- Anbar.J Vet Sci.6(1), 109-118.
12. Dixon, W. (1980). Effect analysis of experimental observation. Annu Rev Pharm Toxicol. 20, 441-426.
13. Leppert ,T.(2009). Tramadol as an analgesic for mild to moderate cancer pain. Pharmacological reports, 61(6), 978-

992. [https://doi.org/10.1016/S1734-1140\(09\)70159-8](https://doi.org/10.1016/S1734-1140(09)70159-8).
14. Guzman, S., Maria, A., (2007). Tramadol minimizes potential pain during post-oophorectomy in Wistar rats. *Altern Anim Exp*, 14, 91-92.
15. Mashhadane, A. F. , Taqa, A.G., AL-Sandook, A.T. (2013). Effects of tramadol on serum bone alkaline phosphatase, bone morphogenetic protein2 and healing of dental implant in a sheep model. *Int.Jou. of Pharmaceutical, Biological and Chemical Sciences*. 2(4), 13-19. www.ijpbcs.net.
16. Saha, K.B., B0l, Z.S., Xia, j., Sampson, S., Zaman, R.U., (2016). Chlorpromazine versus atypical antipsychotic drugs for schizophrenia(Review).Cochrane Database of systematics Review ,Issue 4.art.no.:cd010631 Doi:10.10002/14651858.CD010631.pub2.
17. S. E. D.(2009). NSIMBA. Effects of daily chlorpromazine administration on behavioral and physiological parameters the rat. *Indian J Physiol Pharmacol* .53 (3), 209–218.
18. Ghada, A., Taqa, G. (2015). Evaluation the Effect of Single and Multiple administration of tramadol on sedation and analgesia in sheep *International Journal of Enhanced Research in Science, Technology & Engineering* ISSN:4 (7), 2319-7463.
19. Papich, M.G. (2007). *Saunders Handbook of Veterinary Drugs*. 2nd ed. North Carolina: State University.
20. Valle, M., Garrido, M.J., Pavon, J.M., Calvo, R., Troconize, I.F. (2006). Pharmacokinetic_pharmacodynamic modeling of the antinociceptive effect of main active metabolites of tramadol,(+) O_desmethyltramadol and (-) O_desmethyltramadol,In rats .j. *Pharmacol .Exp.Ther.*,293, 649_653.
21. Seddighi, M.R., Egger, C.M., Rohrbach, B.W., Cox, S.K., Dohetry, T.J. (2009). Effects of tramadol on the minimum alveolar concentration of sevoflurane in dogs. *Vet. Anaesth'analg*. 36(4), 334-340. <https://doi.org/10.1111/j.1467-2995.2009.00468.x>Get rights and content.
22. Katzung, B.G.(2012). *Basic and clinical pharmacology*.12th ed.,New York:McGraw-Hill. 1091-1099.