Published online at http://www.amirj.org ISSN: 2349- 6371

AMERICAN MULTIDISCIPLINARY INTERNATIONAL RESEARCH JOURNAL

Interaction between Naloxone and Tramdol in kindling model of seizure in rat

Yazdan Nourian[1],Ramin Ataee[1,2*],Nafiseh Nasei Nasr Abadi[1], Amin Ataei[3], ,Majid Jafari Sabet[4],Ali Morad Heydari Gorji[5]

1-Pharmaceutical sciences research center, Hemoglobinopathy Institute,Mazandaran University of Medical Sciences,Sari Iran

2-Talasemia research center, Hemoglobinopathy Institute,Mazandaran University of Medical Sciences,Sari Iran

3-Pharmacology and Physiology department ,Babol university of medical sciences,Babol Iran

4-Pharmacology department, Iran university of medical sciences,Tehran Iran

5-EDC center,Mazandaran University of Medical Sciences,Sari Iran

*Corresponding author: Ramin Ataee

Abstract

Tramdol is a synthetic opioid receptor agonist which can have analgesic effect as morphine or mepredine.Tramdole can usually induce seizure or aggregate it in overdoses.The mechanisms for seizure inducing effect of tramadol are complicated and many different hypothesis as serotonergic,opioid receptor activation or anti-gabaergic mechanisms are in consider ,so for determination better the pathways in which tramdol can play its' seizure effect, we have planned this study in a kindling model with using Pentylen tetrazol which is a chemical with high seizure effect and known mechanism. In this study, for kindling model of seizure in mice ,PTZ has been administrated at minimum and maximum doses intraperitonealy and tramadol has been administrated 30 minutes before PTZ at doses(0.5,10,15,30,50) mg/kg.The number of mice which have shown mioclonic seizures in each group have been distinguished , quantified and the comparison between groups have been analyzed statistically with Chi-Square and Exact-fisher test.According to results of these experiments,Tramadol in low to moderate doses, could have aggregated the seizure effect of PTZ at minimum and maximum treshold which observed with increasing the quantity of mice with myoclonic presentations.Based on results of this study, it can be concluded that one of mechanisms for seizure effect of tramadol may be its' interaction with GABAergic system based on its' synergism effect with PTZ which has potent anti-GABA activity in CNS.

KEY WORDS : Seizure, Tramadol,PTZ,Kindling model

Introduction

Tramadol is a synthetic analog of codeine and a mild partial agonist of μ opioid receptor(1).Some of analgesic effects of tramadol are through norepinephrine and serotonin reuptake inhibition .Tramadol can be effective as much as morphin or mepridine in mild to moderate pains(1) but in sever and chronic pain is less potent.Tramadol is effective in labor pains and make less infantile reparatory depression(1).

Common adverse effects of tramadol contain nausea and vomiting, diziness, dry mouse,sedation.Respiratory depression with tramadol is less than morphin in equal doses and its' constipation is less than codeine.Tramadol can cause or excite seizure in compatible people(1-6).Although analgesia effects of tramadol cannot antagonized completely with Naloxone (a pure μ receptor antagonist) but depression effect of tramadol can be removed by it(5).

Recently there are some reports about drug abused of tramadol between young individuals(6) but these informations are un-enough and in some are conflicting to explain role of tramadol in seizure though in some reports it has been introduced as seizure-inducing drug in high doses and in others it could have diminished seizure in less doses.

According to these paradoxical informations about role of tramdol in seizures,We aimed this study to assay role of tramdol in kindling model of seizures induced by PTZ in rats .

Chemical kindling is one of procedures in seizure and epilepsy studies(2).in this model, seizure is induced in animal with repeated exciting of brain with administration of a chemical(2).One of the chemicals which used currently in seizure studies is Pentylentetrazole(PTZ) which with antagonizing of Gabaergic receptors in brain and exciting of Sodium and Calcium Channel can make seizure in rat or mouse.Also this model is very similar to absent kind of epilepsy in human(3,4).

Materials and Methods

For this research study,60 mail mice with albino gender have been provided from experimental animal center of Mazandaran university of medical sciences which maintained in animal lab in 12 groups of 5 randomly ,at normal constituents of 21±2 degree and 12 hours light and dark circadian cycle with 30 to 40% humidity .Animals could reach freely to food and water as enough with no limitations.

Experimental groups:

Experiments serial 1:

For determining minimum and maximum doses of PTZ which induced minimum and maximum clonic seizures in mice ,the mice divided in 5 groups of 5 and each group has been administrated 5 increasing doses of PTZ(20,30,40,50,60 mg/kg) intrapritoneally.

Experiments serial 2:

To assay the effect of different doses of Tramadol on minimum seizure threshold ,the mice divided to 4 groups of 5 and have received the minimum dose of PTZ for colonic seizure which determined from experiments serial 1 and increasing doses of tramadol(0.5,10,15,30,50 mg/kg) intrapritoneally.

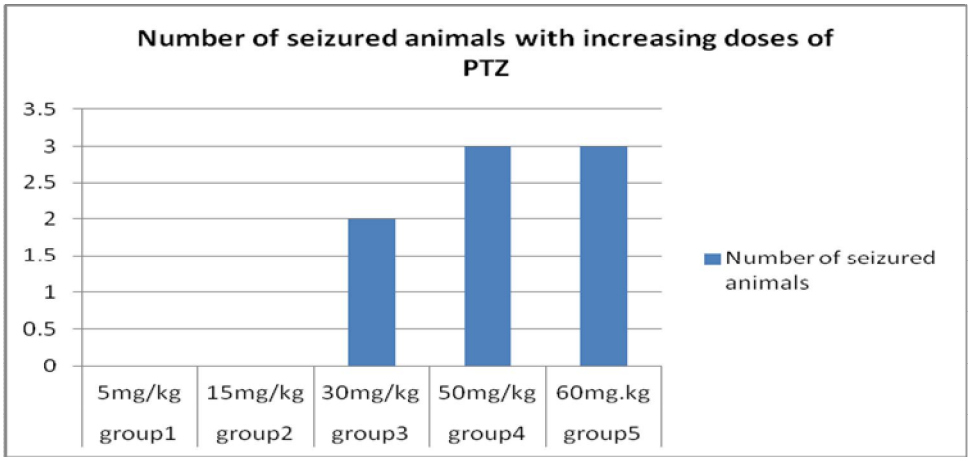
Experiments serial 3:

To assay the effect of different doses of Tramadol on maximum seizure threshold ,the mice divided in 4 groups of 5 and have received the maximum dose of PTZ for colonic seizure which determined from experiments serial 1 and increasing doses of tramadol(0.5,10,15,30,50 mg/kg) intrapritoneally...

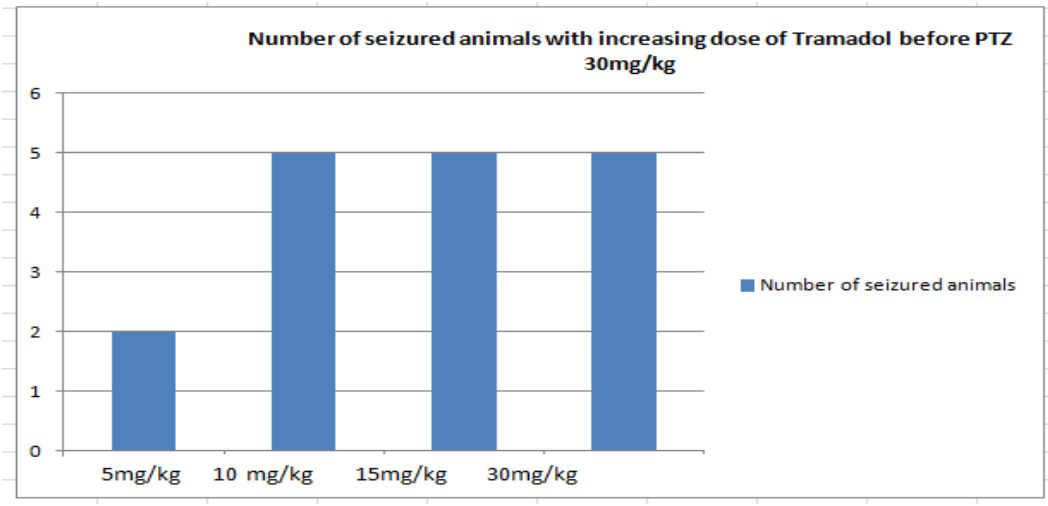
After finishing the kindling experiments in all groups the animals with colonic seizure have been numbered visually and the number of seizured animals in each group determined as seizure index and the comparison between groups has been analyzed statistically by Chi Square and Exact Fisher test.

Results

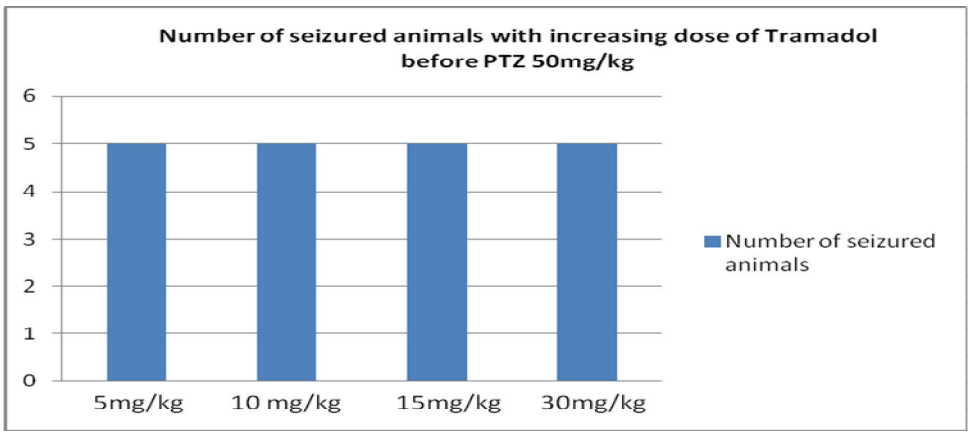
According to experiments serial 1 ,minimum dose of PTZ which induced colonic seizure in mice achieved as 30mg/kg and the maximum dose was 50mg/kg.Also with regarding to experiment serial 2 and 3 ,Tramadol could have increased the seizure index and decreased seizure threshold in each group significantly which received minimum and maximum dose of PTZ (Graphs 1,2,3-tables 1,2).



Graph1:Number of seizured animals with increasing doses of PTZ (5mg/kg-60mg/kg)



Graph2:Number of seizured animals with increasing dose of tramadol before minimum seizure treshold of PTZ(30mg/kg)



Graph3:Number of seizured animals with increasing dose of tramadol before maximum seizure treshold of PTZ(50mg/kg)

Table1,A),B):The results of Chi-Squre and Fisher exact tests for treatment with different doses of tramadole before PTZ(30mg/kg)

A)groupe * tra30_ptz30 Crosstabulation

			tra30_ptz40				Total
			1'+2	1'"+2	1"+2	1+2	
groupe	group1	Count	0	0	0	2	2
		% within groupe	0.0%	0.0%	0.0%	100.0%	100.0%
	group2	Count	5	0	0	0	5
		% within groupe	100.0%	0.0%	0.0%	0.0%	100.0%
	group3	Count	0	0	5	0	5
		% within groupe	0.0%	0.0%	100.0%	0.0%	100.0%
	group4	Count	0	5	0	0	5
		% within groupe	0.0%	100.0%	0.0%	0.0%	100.0%
Total		Count	5	5	5	2	17
		% within groupe	29.4%	29.4%	29.4%	11.8%	100.0%

B)Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)
Pearson Chi-Square	51.000[a]	9	.000	.000
Likelihood Ratio	45.274	9	.000	.000
Fisher's Exact Test	29.727			.000
N of Valid Cases	17			

a. 16 cells (100.0%) have expected count less than 5. The minimum expected count is .24.

Table2,A),B):The results of Chi-Squre and Fisher exact tests for treatment with different doses of tramadole before PTZ(50mg/kg)

A)groupe * tra30_ptz50 Crosstabulation

			tra30_ptz50				Total
			1'+2"	1'"+2"	1"+2"	1+2"	
groupe	group1	Count	0	0	0	5	5
		% within groupe	0.0%	0.0%	0.0%	100.0%	100.0%
	group2	Count	5	0	0	0	5
		% within groupe	100.0%	0.0%	0.0%	0.0%	100.0%
	group3	Count	0	0	5	0	5
		% within groupe	0.0%	0.0%	100.0%	0.0%	100.0%
	group4	Count	0	5	0	0	5
		% within groupe	0.0%	100.0%	0.0%	0.0%	100.0%
Total		Count	5	5	5	5	20
		% within groupe	25.0%	25.0%	25.0%	25.0%	100.0%

B)Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)
Pearson Chi-Square	60.000[a]	9	.000	.000
Likelihood Ratio	55.452	9	.000	.000
Fisher's Exact Test	36.140			.000
N of Valid Cases	20			

a. 16 cells (100.0%) have expected count less than 5. The minimum expected count is 1.25.

Discussion

According to current studie's results ,It was found that tramadol in mild to moderate doses could have increased the seizure intensity of pentylen tetrazole and increased the number of animals with clonic seizure by PTZ. Previously. It was demonstrated some mechanisms for seizures induced by tramadole as serotnergic or opioid receptor agonistic mechanisms (1,5), but it was not cleared exactly the precise mechanisms for tramadole seizures.In serotonergic hypothesis tramadole in toxic concentrations can prevent serotonin reuptake in neural terminals and increase the concentration of serotonin(5).Also in Santos JG Jr et al's study,Venlafaxin , a non-typical antidepressant drug could enhance the intensity of seizures induced by PTZ in mice(5). According to other previous studies ,tramadol can bind to opioids receptors with low affinities and also can inhibit monoamines reuptakes as norepinephrine and serotonins in central nervous system(1,5,6) in result it can inhibit descending pathways of pain in brain and spinal cord (7,8). In some studies it was revealed that tramadol in usual doses can inhibit seizures in low degree but in high dose, it was shown to enhance seizures(6).Also some other experimental studies indicated that inhibitory Gabaergic pathways associated with activating of opioids receptor is important for pre-seizure properties of tramadol(6,7). In a study ,it was demonstrated that L-NAME ,a NOS inhibitor could have reduced the seizure intensity according to Tramadol(13). Also in some studies it has found that opioids analgesics can have seizure or anti-seizure properties(14) which these effects depends on doses or seizure models(14).Although there are some reports about seizures with tramadol but animal studies indicated that Tramadol can have seizuric effects only in high and toxic doses(6,14). Also ,it was demonstrated that anti-seizure effect of tramadol in some studies is related to expression of opioids receptors (15).In some reports some unexpected anti-seizure effects for tramadol have been observed in high doses by kindling or electroshock model in rat(14,16). Based on current study ,Tramadol in mild to moderate doses can increase seizures in kindling model of PTZ in rat and as one of the special mechanisms for seizure effects of PTZ resulted of its' inhibitory effect against gabaergic system(14) and as based on some studies tramadol can inhibit GABA receptors(15) so inhibition of these receptors can be considered for seizure synergic effects of tramadol with PTZ also these results are different from those studies which shown anti-seizure properties of tramadol in low doses. It was understood that GABA is an inhibitory neurotransmiter in brain and spinal cord(1) and any chemical which activate GABA receptor as benzodiazepines(for example: dazepam) can have inhibitory effect as (sedative,hypnotic or relaxation and anti-seizure activities)(1)

Tramadol is an non-typical opioid agonist which contracts with opioids receptors weakly (17,18).and many of pharmacologic effect of tramadol is mediated through non-opioids mechanisms which inhibited with Naloxone(a pure opioid antagonist) partially(19).

Finally according to recent study's results, synergism interaction of tramadol with PTZ and activating of seizure properties of PTZ ,evenly in mild to moderate doses is better explained with anti-GABAergic properties of tramadol and its' ability to decrease seizure threshold of PTZ in high dose may be explained by its' serotonergic or opioid toxicity .

Conclusions

In recent study tramadol could have enhanced the seizure activity of pentylen tetrazol (PTZ) and decreased its' minimum and maximum seizure threshold and as one of the mechanisms for seizure effect of PTZ is inhibition of gabaergic system ;so it can be concluded that tramadol's exciting activity on seizure is its' synergism with inhibition of gabaergic system in CNS;Besides other mechanisms of tramadol as serotonergic or opioid activity can also be considered for tramadol's neural toxicity in high doses. Also we suggest more precise studies to reveal better the pharmacologic mechanisms for tramadol seizure effects.

Acknowledgements

We appreciate Dr. Makloogh ,the supervisor of lab animals collections of Mazandaran University of Medical Ssciences for her close and nice collaborations in this study.

References

1-Brunton Laurence L.,Lazo John S.,Parker Keith L.Goodman and Gilman's manual of pharmacology and therapeutics,2006;Eleventh edition.MacGrow and Hill Publication:566-578.

2- MEHRPOUR O. ADDICTION AND SEIZURE ABILITY OF TRAMADOL IN HIGH-RISK PATIENTS INDIAN J ANAESTH. 2013 JAN-FEB; 57(1): 86–7.

3-Haggag BS, Hasanin AH, Raafat MH, Abdel Kawy HS. Lamotrigine decreased hippocampal damage and improved vascular risk markers in a rat model of pentylenetetrazole induced kindling seizure. Korean J Physiol Pharmacol.2014 ;18:269-78.

4-Meng XJ, Wang F, Li CK. Resveratrol is Neuroprotective and Improves Cognition in Pentylenetetrazole-kindling Model of Epilepsy in Rats.Indian J Pharm Sci. 2014 ;76:125-31.

5- Santos JG Jr, Do Monte FH, Russi M, Agustine PE, Lanziotti VM.Braz .Proconvulsant effects of high doses of venlafaxine in pentylenetetrazole-convulsive rats. J Med Biol Res. 2002; 35:469-72.

6-Potschka H, Friderichs E, Löscher W .Anticonvulsant and proconvulsant effects of tramadol, its enantiomers and its M1 metabolite in the rat kindling model of epilepsy. Br J Pharmacol . 2000; 131:203–12.

7-Raffa RB, Friderichs E, Reimann W, Shank RP, Codd EE, Vaught JL . Opioid and non-opioid components independently contribute to the mechanism of action of tramadol, an 'atypical'opioid analgesic. J Pharmacol Exp Ther .1992;260:275–85.

8-Miranda HF, Pinardi G .Antinociception, tolerance, and physical dependence comparison between morphine and tramadol. Pharmacol Biochem Behav .1998; 61:357–60.

9-Rehni AK, Singh I, Kumar M .Tramadol induced seizurogenic effect: a possible role of opioid-dependent GABA inhibitory pathway. Basic Clin Pharmacol Toxicol .2008; 103:262–66.

10- Barke KE, Hough LB .Simultaneous measurement of opiateinduced histamine release in the periaqueductal gray and opiate antinociception: an in vivo microdialysis study. J Pharmacol ExpTher .1993; 266:934–942.

11- Rehni AK., Singh T G , Singh N., Arora S. 19Tramadol-induced seizurogenic effect: a possible role of opioid-dependent histamine (H1) receptor activation-linked mechanism. Naunyn-Schmied Arch Pharmacol .2010; 381:11–12.

12-Zhu-Ge ZB, Zhu YY, Wu DC, Jin CL, Chen Z .Involvement of endogenous histamine in modulatory effect of morphine on seizure susceptibility in mice. Zhejiang Da Xue Xue Bao Yi Xue Ban . 2007; 36:130–33.

13-Lesani A, Javadi-Paydar M, Kabiri Khodadad T, Asghari-Roodsari A, Shirkhodaei M, Norouzi A, Dehpour AR. Involvement of the nitric oxide pathway in the anticonvulsant effect of tramadol on pentylenetetrazole-induced seizures in mice.Epilepsy & Behavior . 2010; 19; 290–95.

14- Potschka H, Friderichs E, Löscher W. Anticonvulsant and proconvulsant effets of tramadol, its enantiomers and its M1 metabolite in the rat kindling model of epilepsy. Br J Pharmacol 2000;131:203–12.

15-Rehni AK, Singh I, Kumar M. Tramadol-induced seizurogenic effect: a possible role of opioid dependent γ-aminobutyric acid inhibitory pathway. Basic Clin Pharmacol Toxicol 2008;103:262–6.

16-Manocha A, Harman KS, Mediratta PK. On the mechanism of anticonvulsant effect of tramadol in mice. Pharmacol Biochem Behav 2005;82:74–81.

17- Scott LJ, Perry CM. Tramadol: a review of its use in perioperative pain. Drugs 2000;60:139–76.

18- Raffa RB, Friderichs E, Reimann W, Shank RP, Codd EE, Vaught JL. Opioid and nonopioid components independently contribute to the mechanism of action of tramadol, an 'atypical' opioid analgesic. J Pharmacol Exp Ther 1992;260: 275–85.

19-Rojas-Corrales MO, Berrocoso E. Mico JA. Role of 5-HT1A and 5-HT1B receptors in the antinociceptive effect of tramadol. Eur J Pharmacol 2005;511:21–6.

LEGENDS OF FIGURES:

Graph1:Number of seizured animals with increasing doses of PTZ (5mg/kg-60mg/kg)
Graph2:Number of seizured animals with increasing dose of tramadol before minimum seizure treshold of PTZ(30mg/kg)
Graph3:Number of seizured animals with increasing dose of tramadol before minimum seizure treshold of PTZ(50mg/kg)
Table1,A),B):The results of Chi-Squre and Fisher exact tests for treatment with different doses of tramadole before PTZ(30mg/kg)
Table2,A),B):The results of Chi-Squre and Fisher exact tests for treatment with different doses of tramadole before PTZ(50mg/kg)