W J Med Sci ISSN: 1817-3055

© International Digital Organization for Scientific Information **Online Open Access**
Volume 1 Number (1) : 40-43, Jan-Jun, 2006

Tramadol Dependence Rate as Compared with Morphine in Rats

Ali Rafati, Sayed Mojtaba Yasini, Mohammad Hossein Dashti-Rahmatabadi,
Saeed Pakdel and Foroogh Norani
Department of Physiology, Medical School, Shahid Sadoughi Medical University, Yazd, Iran

Abstract: Tramadol is a codeine synthetic analogue that has an affinity to opioid μ receptors, also some evidence show that tramadol has a potency to induce drug dependence, so we conducted to study and compare tramadol dependence with morphine in rats. In this study 30 wistar male rats were randomly divided in to 5 groups: Sham (normal saline), control (increasing doses of morphine), test 1 (fixed dose of tramadol), test 2 (increasing doses of tramadol) and test 3 (first morphine and then tramadol). Two milliliter of each planed administrating regimen were injected intraperitoneally for 10 days, 3.5 h after last injection 5 mg kg^{-1} of naloxane was injected and withdrawal symptoms were recorded in all groups and analyzed as a criterion for dependence. Results showed that both fixed and increasing doses of tramadol induce drug dependence as compared with sham ($p<0.05$ and $p<0.001$, respectively). Furthermore the dependence rate in test 1 and test 2 groups was significantly less than control ($p<0.05$). Although there was a significant dependence rate in test 3 group as compared with sham ($p<0.05$), but there wasn't a significant difference between test 3 and control groups. According to our findings and data reported in similar studies tramadol has a relative potency to induce drug dependence, so it is suggested to be more careful in prescribing it as an analgesic.

Key words: Tramadol · Drug dependence · morphine

INTRODUCTION

Nowadays addiction is an ever-increasing problem in the world and despite all efforts to prevent and control it, it continues to be a tremendous public health issue. Analgesics are among the most popular drugs which are being abused.

Choosing appropriate analgesics with Minimum side effects is one of the main parts of pain management. The most important side effects of many analgesics are drug dependence and abuse potential. Tramadol, a centrally acting analgesic, available in Europe since 1977 [1], has pharmacological mechanisms of analgesia that include μ opioid receptor agonist activity and /or inhibition of serotonin and norepinephrine reuptake [1, 2]. Although possessing considerably less abuse potential than morphine [3], tramadol is not without dependence liability [4] and has been reported to produce dependence and withdrawal [5]. Various clinical and pharmacological studies have indicated a potential for tolerance [6], physical dependence [6] and abuse [4] whereas other studies have failed to show significant effects [7]. In order to evaluate tramadol dependence potential, this experimental study was carried out to compare dependence rate of tramadol and morphine in rats.

MATERIALS AND METHODS

Thirty adult, male wistar rats weighing 200-250 g were selected randomly and divided in to 5 groups. All animals were given free access to food and drinking water. Housing was maintained at a constant temperature of 21-22 degree of centigrade and a 12 h/12 h light-dark cycle. Drugs were tramadol HCI (100 mg/Amp product by German grunenthal company), morphine sulfate (Powder, prepared from Iranian Temad factory) and Naloxan HCI (0.4 mg/Amp from Iranian Toliddaroo factory). A specific box was design to observe withdrawal symptoms. Study groups include:

- Sham group (injection of normal saline for 10 days)
- Control group (injection of increasing doses of morphine. First dose was 40 mg kg^{-1}, 60 mg kg^{-1} in 2nd and 3rd days, 80 mg kg^{-1} in 4th and 5th day and 100 mg kg^{-1} from 6th to 10th day)
- Test 1 group (fixed dose of tramadol : 40 mg kg^{-1} for 10 days)
- Test 2 group (increasing doses of tramadol : similar to control group)

Corresponding Author: Dr. Ali Rafati, No. 83 Talash St., Atlasi Sq., Safaeyeh, Yazd, Iran

- Test 3 group (at first increasing doses of morphine similar to control and then injection of 40 mg kg^{-1} of tramadol 3 h after the last dose of morphine)

All injections were done at the same time as far as possible. Two milliliter of each substance was injected intra peritonealy (I.P) for 10 days. Finally, 2 mg kg^{-1} of Naloxan HCI was injected to all rats 4.5 h after last injection to induce withdrawal syndrome in order to observe withdrawal symptoms such as standing, tooth grinding, jumping, wet dog shaking and diarrhea. These symptoms were recorded during 30 min. It should be noted that observer was blind to the method of study. Then the results were analyzed by SPSS software version 11.5, one way ANOVA and T-student test. For behavioral testing permission of the animal ethics committee of Yazd medical sciences university (Yazd, Iran) in accordance with the internationally accepted principles for laboratory animal used and care mentioned by the European community guidelines were obtained.

RESULTS

Some withdrawal symptoms such as jumping and standing were more related to dependence. The mean of all withdrawal symptoms rate in test I group was grater than sham group which was significant in jumping, tooth grinding and wet dog shaking ($p<0.05$) but was not significant for standing. In other hand all withdrawal symptoms in test I group were significantly less than control group ($p=0.000$ Table 1). Also there was a significant difference between test II and sham groups in all withdrawal symptoms ($p=0.000$). Although there was no significant difference between the tooth grinding and wet dog shaking in test II and control groups, test 2 group showed significantly less standing and jumping signs ($p<0.05$ Table 2). Our data showed that all withdrawal syndrome signs in test I were significantly less than test II group ($p<0.05$ Table 3). Although, some signs such as standing and wet dog shaking in test III were less than control group but they were not significant (Table 4).

Table 1: Means of withdrawal symptoms in test 1 (fixed doses of tramadol) as compared with sham and control groups (N=6)

	Symptoms ($\overline{X} \pm SEM$)				
Groups	Jumping	Standing	Wet dog shaking	Tooth grinding	Diarrhea
Sham	0.66±0.333	4.66±0.76	0.16±0.166	2.33±0.557	-
Control	11.00±0.856	20.16±0.60	6.16±0.60	10.16±0.542	+++
Test 1	3.83±0.401	7.66±0.494	2.5±0.562	5.00±0.577	+
Test1 V sham (P value)	0.018	0.058	0.035	0.038	
Test1 V control (P value)	0.000	0.000	0.000	0.000	

Table 2: Means of withdrawal symptoms in test 2 (increasing doses of tramadol) as compared with sham and control groups (N=6)

	Symptoms ($\overline{X} \pm SEM$)				
Groups	Jumping	Standing	Wet dog shaking	Tooth grinding	Diarrhea
Sham	0.66±0.333	4.66±0.76	0.16±0.166	2.33±0.557	-
Control	11.00±0.856	20.16±0.60	6.16±0.600	10.16±0.542	+++
Test 1	6.83±0.703	11.16±0.60	4.83±0.477	7.83±0.477	++
Test1 V sham (P value)	0.000	0.000	0.000	0.000	
Test1 V control (P value)	0.000	0.000	0.426	0.084	

Table 3: Means of withdrawal symptoms in test 1 as compared with test group 2 (N=6)

	Symptoms ($\overline{X} \pm SEM$)				
Groups	Jumping	Standing	Wet dog shaking	Tooth grinding	Diarrhea
Test 1	3.83±0.401	7.66±0.494	2.50±0.562	5.00±0.577	+++
Test 2	6.83±0.703	11.16±0.60	4.83±0.477	7.83±0.477	+++
Test1 V test 2 (P value)	0.028	0.016	0.035	0.024	

Table 4: Mean of withdrawal symptoms in test 3 (increasing doses of morphine and single dose of tramadol) as compared with sham and control groups (N=6)

	Symptoms ($\overline{X} \pm SEM$)				
Groups	Jumping	Standing	Wet dog shaking	Tooth grinding	Diarrhea
Sham	0.66±0.333	4.66±0.76	0.16±0.166	2.33±0.557	-
Control	11.00±0.856	20.16±0.60	6.16±0.60	10.16±0.542	+++
Test 3	11.16±0.477	18.66±0.714	5.33±0.421	11.5±0.562	+++
Test3 V sham (P value)	0.018	0.058	0.035	0.038	
Test3 V control (P value)	1.000	0.61	0.813	0.56	

DISCUSSION

Analgesics are the most commonly consumed over- the-counter preparation all over the world. It should be tried to choose appropriate analgesic with minimum tolerance and dependence. Tramadol, a synthetic analogue of codeine, is a centrally acting analgesic drug with a dual mechanism of action. Binding to μ- opioid receptors and inhibition of norepinephrine and serotonin reuptake. It is rapidly and extensively absorbed after oral doses and is metabolized in the liver. Analgesia begins within one hour and starts to peak in two hours [8]. Evidence suggests different ideas about tramadol abuse and dependency. For example Huber [9], Richter [10], Preston [11] and Cami [12] suggest low drug dependence rate for tramadol, in other hand Brink *et al*., [13], Mcdiarmid [14], Patt setal [15] suggest abuse, dependence and withdrawal associated with tramadol misuse the abuse potential of tramadol was investigated using *in vivo* micro dialysis measures of dopamine release within the nucleus accumbens shell in rats [16] as a criterion for dependence which is proved by single cell recording of dopaminergic neuron in nucleolus accumbens by Rafati *et al*., [17]. In the present study, the fixed dose of the tramadol lead to dependence to some extent, but not significant in comparison with morphine. Our results are in agreement with some other studies. We should accept that tramadol especially long- term administration and increasing doses has significant drug dependence potency, although this potency is less than morphine. Finally, although, there were decreases in some signs of withdrawal symptoms in test 3 group, but tramadol administration did not decrease withdrawal symptoms in morphine dependent rats significantly. In a similar study which was done by Ren *et al*., [18], it was shown that tramadol administration to morphine dependent rats decrease withdrawals symptoms severely. Probably, the difference between our results and Ren's could be related to doses of injected morphine and tramadol. They were injected 4 mg kg^{-1} morphine to induce dependence and their return doses were higher than 39 mg kg^{-1} tramadol, which resulted in decreasing of withdrawal symptoms. In other words, we injected 100 mg kg^{-1} of morphine for 10 days to rats to cause dependence, so we ought to administer higher doses of tramadol (more than 40 mg kg^{-1}) to have similar results. In addition, it may be better to inject tramadol later (more that 3 h) after last dose of morphine too let opioid receptors be accessible to tramadol and its metabolites. In Conclusion According to our findings, fixed dose of tramadol (40 mg kg^{-1}) leads to the expression of some withdrawal syndrome signs and increasing doses of tramadol significantly induced dependency, so physicians should be careful in administering tramadol to patients due to its abuse potency.

ACKNOWLEDGMENTS

The authors give thanks to all people who have help and to the research deputy of Yazd medical university as the sponsor of this research.

REFERENCES

1. Gibson, I.P., 1995. Pharmacokinetics, efficacy and safety analgesia with a focus on tramadol Hcl. Am. J. Med. 101: 475-535.
2. Radbruchl, Ground S. and K.A. Lehmann, 1996. A risk-benefits assessment of tramadol in the management of pain. Drug saf, 15: 8-29.
3. Budd, K., 1994. Chronic pain- challenge and response Drugs, 47: 33-38.
4. Liu, Z.M., W.H. Zhou, Z. Lian, Z.H. Muy Ren, J.Q. Cao and Z.J. Cai, 1999. Drug dependence and abuse potential of tramadol. Acta pharmcol Sinica, 20: 52-54.
5. Ehrenreich, H. and W. Poser, 1993. Dependence on tramadol. Clin Invest, 72: 76.
6. Murano, T., H. Yamamoto, N. Endo, Y. Kud, N. Okada, Y. Masuda and I. Yano, 1978. Studies of dependence on tramadol in rats. Arzneimittel - forschung/ Drug Res, 28: 152-168.
7. Miranda, H.F. and C. Pinardi, 1998. Antinociception, tolerance and physical dependence comparison between morphine and tramadol. Pharmacol. Biochem. Behav., 61: 357-360.
8. Lewis, K.S. and N.H. Han, 1997. Tramadol: A new centrally acting analgesic Am. J. Health Syst. Pharm. Mar. 15, 54: 643-52.
9. Huber, H.P., 1978. Examination of psychic effects of a new analgesic agent of the cyclohexanols sevies. A contribution to a possible psychic dependence potential of tramadol. Arzneimittel - forschung, 28: 189-91.
10. Richter, W., H. Barth, L. Flohe and H. Giertz, 1985. Clinical investigations on the development of dependence during oral therapy with tramadol. Arzneimittel - Forschung, 35: 1742-1744.
11. Preston, K.L., D.R. Jasinski and M. Testa, 1991. Abuse potential and pharmacological comparison of tramadol and morphine. Drug Alcohol Depend Jan., 27: 7-17.
12. Cami, J., X. Lamas and M. Farre, 1994. Acute effects of tramadol in methadone - maintained volunteers. Drugs, 47: 43.
13. Brinker, A., R.A. Bonnel and J. Betiz, 2002. Abuse, dependence or withdrawal associated with tramadol. Am. J. Psychiatry, 159: 881-882.

14. Mcdiarmid, T., L. Mackler and D.M. Schneider, 2005. Clinical inquiries. What is the addiction risk associated with tramadol? J. Farm. Pract. Jan., 54: 72-73.
15. Datt, S. and T. Mcdiarmid, 2005. Tramadol addiction. J. Farm. Pract. Apr., 54: 356.
16. Spraguese, Leifhit M., J. Selken, M.M. Milks, D.H. Kinder and D.E. Nichols, 2002. *In vivo* microdialysis and conditioned place preference studies in rats are consistent with abuse potential of tramadol. Synapse, Feb., 43: 118-21.
17. Rafati, A., A.A. Pourshanazari and H. Alaei, 2003. Electrical stimulation of Nucleus accumbens changes basal firing rate of dopaminergic neurons as a criterion for dependence to morphine in rat. Proceedings of the Sixth IBRO World congress of Neuroscience, Prague.
18. Ren, Y.H. and J.W. Zheng, 2000. Influence of tramadol on morphine discriminative behavior in rats. Acta Pharamacol., Oct., 21: 924-926.