



International Journal of Research in Pharmacology & Pharmacotherapeutics



ISSN Print: 2278-2648
ISSN Online: 2278-2656

IJRPP |Vol.4 | Issue 1 |Jan-Mar-2015
Journal Home page: www.ijrpp.com

Research article

Open Access

A comparative study of efficacy and safety of tramadol in male versus female patients suffering from pain.

Kiranpreet Kaur, Harinder Singh, Hardeep Singh Mann, Anjleen Kaur, Prabhsimran Singh
Department of Pharmacology and Department of Orthopedics, Govt Medical College and Hospital,
Patiala, Punjab, India.

*Corresponding author: Kiranpreet Kaur
E-mail id: drkiranpreetmalhotra@gmail.com

ABSTRACT

Background : Gender difference exists both in pharmacokinetics and pharmacodynamics of various drugs. So this study was designed to evaluate efficacy and safety of Tramadol in males versus female patients suffering from pain.

Material and Methods : An open randomized parallel group study was conducted . 100 patients enrolled were 50 males and 50 females coming to Department of Orthopedics, in a tertiary care hospital. All patients were divided into four groups of 25 each. Tramadol was prescribed in two doses of 50mg or 100mg BD for 7 to 14 days depending on severity (based on Visual Analogue Scale) and then patients were monitored and adverse drug reactions were noted in males and females. The data was analyzed statistically using T- test for efficacy and descriptive stats for assessing the safety.

Results : Efficacy was assessed by comparing difference in mean score and mean percentage change in mean score. Comparing males and females taking 50 mg tramadol percentage improvement was not statistically significant ($p > 0.05$). While comparing 50 mg and 100 mg percentage improvement in groups was statistically significant ($p < 0.05$). Comparing groups males and females, percentage of adverse drug reaction in females was higher on each dose of tramadol. Percentage of adverse drug reaction in group taking 100mg was higher compared to group taking 50mg tramadol.

Conclusion: There was no significant difference in efficacy of tramadol between males and females on same dose. Females experience more adverse drug reactions than males on same dose of tramadol and ADR increases with increase in dose.

Keywords: Tramadol, gender difference, VAS, severe pain

INTRODUCTION

Pain is one of the most common reasons to consult a physician. Better pain relief is now main motive of health care professionals. Pain management involves

combination of various treatment modalities and a comprehensive assessment leading to an individualized treatment approach.^[1] Opioids are among the most effective and potent analgesics used

to treat moderate to severe pain. Among opioids tramadol has become the most commonly used analgesic worldwide. Tramadol is synthetic 4-phenyl-piperidine analogue of codeine. Tramadol is a centrally-acting analgesic, used for treating moderate to severe pain. Tramadol exhibits some opioid like characteristics though not an opioid. Tramadol has complimentary mechanisms other than binding to μ receptors are weak inhibition of reuptake of norepinephrine and serotonin.^[2] Tramadol is a successful candidate among opioids mainly because of its favourable side effect profile, which differs significantly from that of other opioids.^[3]

Gender difference exists both in pharmacokinetics and pharmacodynamics of various drugs.^[4] In some studies, many drugs metabolised by CYP3A4 like alfentanil, tramadol have demonstrated 50- 70% higher clearance in young females compared with males.^[5] It has also been shown that females are more sensitive to analgesic effect of pentazocine than males.^[6] There are gender-related differences in the pharmacokinetics of the enantiomers of tramadol trans-T and M1 which may be due to the greater body weights for men and/or the higher CYP2D6 activity in women.^[7] so, present study has been done to compare efficacy and safety of tramadol in male versus female patients of moderate to severe pain.

MATERIAL AND METHODS

An open, randomized, parallel group study was conducted after obtaining written informed consent from the patients. The study was done in accordance with the principles laid in the Declaration of Helsinki and was approved by Institutional ethics committee.^[8] Visual analogue scale was explained during first and subsequent visits. Patients included in the study were males and females aged above 20 years suffering from moderate to severe pain as evaluated from visual analogue scale. Patients with known hypersensitivity to tramadol, Children, history of epilepsy, those taking centrally acting drugs, other analgesic, and history of renal and liver dysfunction were excluded from the study.

Conduct of Study

A total of 100 patients were enrolled and divided into four groups (Group A, Group B, Group C, Group D)

of 25 each. Patients of group A included 25 males and they were given 50mg tramadol. Patients of group B included 25 females and were given 50mg tramadol. Patients of group C included 25 males and were given 100mg tramadol. Patients in group D included 25 females and were given 100mg tramadol. All subjects were randomly assigned into one of the four treatment groups.

Tramadol was prescribed in two doses of 50 mg or 100mg BD for 7 to 14 days depending on severity and then patients were monitored and adverse drug reactions were noted in males and females. Based on visual analogue scale, patients were divided into mild, moderate and severe pain.^[9] No other drugs that interfere with metabolism of tramadol were allowed during the study. Patients already taking other analgesic drugs were included in the study after washout period of 1 week.

Diagnosis of pain was confirmed by clinical examination and required investigations. Patients were assessed at visit one i.e. 0 day (baseline visit) then visit 2 (at 1 week) and visit 3 (after 2 weeks) and for carry - over effect of drugs. Patients were asked to report for assessment for pain (VAS). Data was collected on patient's demographic characteristics, functional status involving different parameters like pain intensity and safety. The pain Intensity was measured by Visual Analogue Scale. The classic version of the VAS was used; 10 centimetre line, horizontal. VAS on present pain ranged from "no pain" to "the worst pain possible" and VAS on pain relief ranged from "no pain relief" to "the maximum pain relief". Scores ranged from 0 to 10.^[9]

Statistical Analysis

Data was statistically analysed using student's 't' test.^[10] For adverse drug reaction evaluation Descriptive Statistics was used. A difference between the treated and control group which would have arisen by chance is 'p' value. If it is less than 0.05, it is considered significant (S), 'p' value less than 0.001 is considered highly significant (HS). If it is more than 0.05, it is considered non-significant (NS).

RESULTS

Hundred patients were analyzed in groups of 50 males and 50 females. The two groups of patients were comparable with baseline

characteristics with respect to age, sex, weight (Table 1). Table 2 shows comparison of pain intensity scores between the two groups A & B at baseline (visit 1) and improvement at subsequent visits (visit 2 and visit 3). By taking inter-group comparison, it was observed that $p > 0.05$ at all the three visits i.e. difference in group A and group B was not statistically significant at baseline as well as final visit. It shows there is no difference in efficacy with respect to dose 50mg in males and females. Similarly it was found that there is no difference in efficacy with 100 mg dose of tramadol in males and females.

Table 3 shows comparison of pain intensity scores between groups A and B (males and females given 50mg tramadol) and group C and D (males and females given 100mg tramadol) at different visits. By taking inter-group comparison, it was observed that $p < 0.05$ at all the visits i.e. difference in groups A and B and groups C and D was statistically significant at final visit. This comparison proves that reduction in pain intensity with 100mg was more as compared with 50mg tramadol.

Safety

Safety of study drugs was assessed by recording adverse events as reported by patients on subsequent visits. In Graph 1 it was observed that in the patients of (Group A) males given 50mg tramadol, incidence of dizziness/ vertigo was 3(12%), nausea was 4 (16%), constipation was 2 (8%) and headache was 1(4%). somnolence 1(4%), vomiting was 2(8%), while dyspepsia was reported in 1(4%) patients. In female patients taking 50mg tramadol

incidence of dizziness/vertigo was 6(24%), nausea was 4(16%), constipation was 3(12%), headache was 2(8%), somnolence was 1(4%), vomiting was 2(8%), dyspepsia was 2(8%), dry mouth was 1(4%), while diarrhea was reported in 1(4%) patients. It was observed that adverse drug reactions were more in females than males on same dose i.e either 50mg or 100mg.

Graph 2 shows comparison of adverse events between group A and B (males and females given 50mg tramadol) and group C and D (males and females given 100 mg tramadol). It was observed that in the patients of (groups A and B) males and females given 50 mg tramadol, incidence of dizziness/vertigo was 9(18%), nausea was 8 (16%), constipation was 5(10%) and headache was 3(6%). somnolence 2(4%), vomiting was 4(8%), dyspepsia was 3(6%), dry mouth was 1(2%) while diarrhoea was reported in 1(2%) patients. In males and female patients taking 100mg tramadol incidence of dizziness/vertigo was 13(28%), nausea was 8(16%), constipation was 7(14%), headache was 5(10%), somnolence was 5(10%), vomiting was 6(12%), pruritis was 1(4%), dyspepsia was 3(6%), dry mouth was 1(2%), while diarrhea was reported in 2(4%) patients. By comparing it was found that adverse drug reaction increases with increase in dose. Females and males experience more adverse drug reaction with 100mg as compared to 50mg tramadol and females experience more ADRs with higher dose as compared to 50 mg tramadol.

TABLE 1

Variable	Male	Female
sex	50	50
Age	47.36±12.77	45.28±13.34
Weight	66.84 ± 7.92	16 (32%)
Mean±SD	66.84 ± 7.92	65.12 ± 7.41
p value	0.125 (NS)	

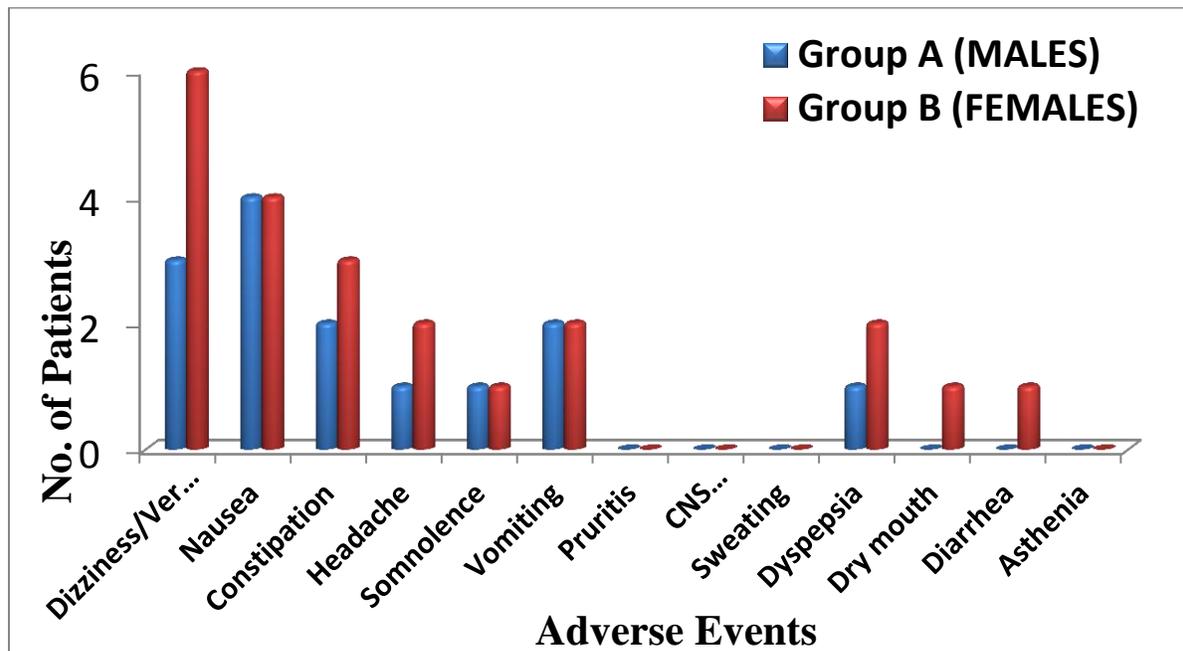
Table 2: Comparison of mean pain intensity scores between group a (males given 50mg tramadol) and group b (females given 50mg tramadol) at different visits

Visit (Duration)	Group A vs B (Male vs Female)					t	p	sig.
	Group	Mean	SD	Mean %age change				
Visit 1 (0 Week)	A	7.60	0.91	-		1.347	0.1842	NS
	B	7.92	0.76	-				
Visit 2 (1 Week)	A	4.48	0.92	41.05		0.191	0.8497	NS
	B	4.52	0.51	42.93				
Visit 3 (2 Weeks)	A	1.36	0.70	69.64		1.017	0.0181	NS
	B	1.56	0.69	65.49				

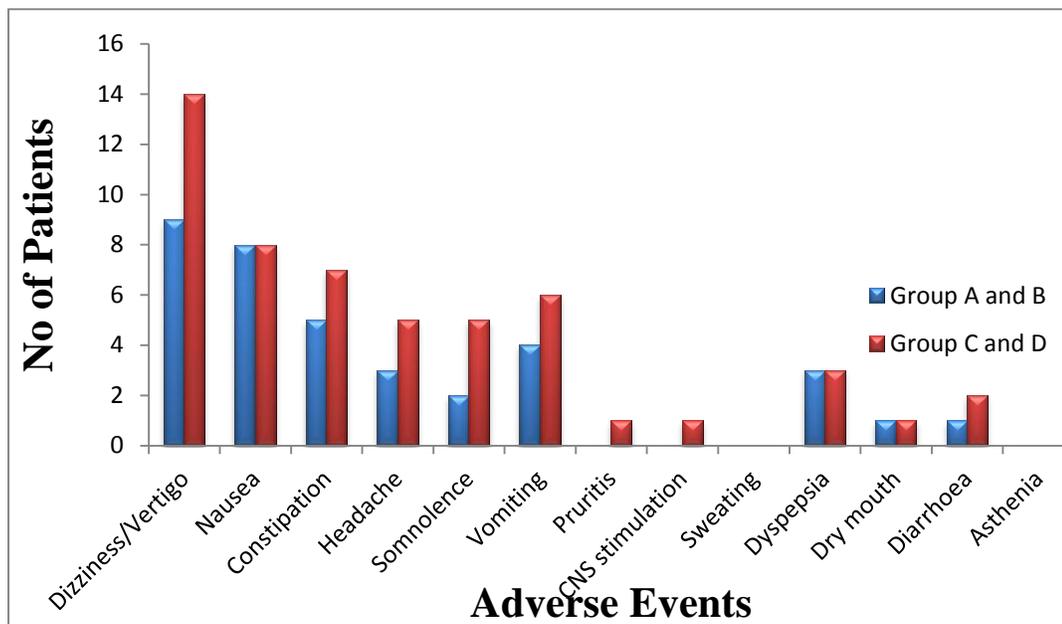
TABLE 3 Comparison of mean pain intensity scores between groups a and b (males and females given 50mg tramadol) and group c and d (males and females given 100mg tramadol) at different visits

Visit (Duration)	Group A and B vs C and D					t	p	sig.
	Group	Mean	SD	Mean %age Change				
Visit 1 (0 Week)	AB	7.76	0.85	-		0.53	0.59	NS
	CD	7.77	0.65	-				
Visit 2 (1 Week)	AB	4.50	0.74	42.01		2.09*	0.05	HS
	CD	4.82	0.79	37.97				
Visit 3 (2 Weeks)	AB	1.60	0.73	64.44		2.94**	0.01	HS
	CD	1.16	0.77	75.93				

Graph 1 Comparison of adverse events between group a (males given 50mg tramadol) and group b (females given 50mg tramadol)



Graph 2 Comparison of adverse events between group a and b (males and females given 50mg tramadol) and group c and d (males and females given 100 mg tramadol)



DISCUSSION

The use of opioids to treat moderate to severe pain is widely accepted. The effect of various opioids in pain management was studied and it was found that opioids are our most powerful analgesics.^[11] In one study it was stated that various opioid members act on opioid receptors have different analgesic efficiencies and different side effect profile because of unique affinities for different opioid receptor.^[12] Tramadol is a centrally acting analgesic used to treat moderate to severe pain. A randomized, double blind, placebo controlled trial was conducted to evaluate efficacy and safety of tramadol in treatment of fibromyalgia and significant improvement in VAS pain score was found in both groups.^[13]

Our Study confirms the analgesic efficacy of tramadol in males and females and compares the safety profile of tramadol in males and females. We observed that analgesic effect of tramadol in males and females is same there is no significant difference in the analgesic effect on same dose. In concern with the dose it was found that analgesic effect is more with 100mg of tramadol as compared with 50mg of

tramadol. In various studies it was observed that other members of opioid family show different analgesic effect in males and females. One study done on buprenorphine & morphine suggested that in females analgesic efficacy is increased compared to males.^[14] Our results do not correspond to previously reported data in different studies and it was found that there is no significant difference in efficacy related to gender.

Safety profile of tramadol was also observed in males and females. According to literature common ADR with tramadol are nausea, vomiting, vertigo, dizziness, constipation.^[15] My study results comply with the literature. In our study it was observed that females experience more adverse drug reaction with tramadol compared to males on same dose. Possible mechanism responsible for difference in safety profile of tramadol in males and females shown by studies was apparent cytochrome P450 activity. It is observed that cytochrome P450 activity higher in females than in males.^[16] Sex difference in drug metabolism was responsible for higher incidence of drug reaction in women compared to men.

In one study it was reported that there are significant differences in pharmacokinetics of enantiomers of

trans –tramadol and its active metabolite (M1) both in males and females. This gender related differences in pharmacokinetics of enantiomers is may be due to greater body weight for men and higher CYP2D6 activity in women.^[7] Cytochrome P450 is highly polymorphic liver enzyme.^[17] Some are fast metabolizers while other are poor metabolizers. Tramadol is metabolized by CYP2D6 enzyme and active metabolite M1 which is formed is more potent which is the considered to be responsible for higher ADR in females^[18].

In the present study it was found that adverse drug reaction increases with increase in dose. Females and males experience more adverse drug reaction with 100 mg as compared to 50 mg tramadol.

REFERENCES

- [1] Gureje O, Simon GE, Von Korff M. A cross-national study of the course of persistent pain in primary care. *Pain*. 2001;92(1-2):195-200.
- [2] 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(1):275-85.
- [3] Preston KL, Jasinski DR, Testa M. Abuse potential and pharmacological comparison of tramadol and morphine. *Drug and Alcohol Dependence*. 1991;27(1):7-17.
- [4] Rademaker M. Do women have more adverse drug reactions? *Am J Clin Dermatol*. 2001;2(6):349-51.
- [5] Pinto N, Dolan ME. Clinically relevant genetic variations in drug metabolizing enzymes. *Curr Drug Metab* 2011;12(5):487-97.
- [6] Gear RW, Gordon NC, Heller PH, Paul S, Miaskowski C, Levine JD. Gender difference in analgesic response to the kappa-opioid pentazocine. *Neurosci Lett*. 1996;205(3):207-9.
- [7] Hui-Chen L, Yang Y, Na W, Ming D, Jian-Fang L, Hong-Yuan X. Pharmacokinetic of enantiomers of Trans- Tramadol and its active metabolite, Trans-O-desmethyl Tramadol, in healthy male and female Chinese volunteers. *Chirality* 2004;(2):112-8.
- [8] Spilker B. Drug development and approval process. In : Speight TM, Holford NHG, Editors. *Avery's Drug Treatment*. (4th edn.) Auckland Adis International; 1997:423-49. 11.10.
- [9] Beaulieu AD, Peloso P, Bensen W, Clark AJ, Watson CP, Gardner-Nix J et al. A randomized double-blind, 8- week crossover study of once-daily controlled-release tramadol versus immediate-release tramadol taken as needed for chronic noncancer pain. *Clin Ther*. 2007;29(1):49-60.
- [10] Mahajan BK, *Methods in Biostatistics for Medical Students and Research Workers* (7th ed). New Delhi; Jaypee; 2010.
- [11] McQuay H. Opioids in Pain Management. In: *Lancet* 1999;353 (9171):2229-32.
- [12] Maher TJ, Chaiyakul P. Opioids (Bench). In: Smith HS, editor. *Drugs for pain*. Philadelphia: Hanley and Belfus; 2003;83-96.
- [13] Russell J, Kamin M, Bennett RM, Schnitzer TJ, Green JA, Katz WA. Efficacy of tramadol in treatment of pain in fibromyalgia. *JCR: Journal of Clinical Rheumatology*. 2000;6(5):250-257.
- [14] Prakash S, Tyagi R, Gogia AR, Singh R, Prakash S, Efficacy of three doses of Tramadol with bupivacaine for caudal analgesia in Paediatric inguinal herniotomy. *Br J Anaesth*. 2006;97(3):385-8.

CONCLUSION

It was concluded from the study that there was no significant difference in efficacy of tramadol between males and females on same dose. There were more adverse drug reactions with increase in dose. Females experience more adverse drug reactions than males on same dose of tramadol. To prove this effect further studies with larger sample size are required.

ACKNOWLEDGEMENT

I would like to acknowledge Dr Prabhsimran Singh and Dr Harinder Singh for their fruitful discussion which initiated this article.

- [15] Mongin G, Yakusevich V, Köpe A, Shostak N, Pikhlak E, Popdán L et al. Efficacy and Safety Assessment of a Novel Once-Daily Tablet Formulation of Tramadol : A Randomised, Controlled Study versus Twice-Daily Tramadol in Patients with Osteoarthritis of the Knee. *Clin Drug Investig.* 2004;24(9):545-58.
- [16] Harris RZ, Benet LZ, Schwartz JB. Gender effects in pharmacokinetics and pharmacodynamics. *Drugs.* 1995;50(2):222-39.
- [17] Zhou SF. Polymorphism of human cytochrome P450 2D6 and its clinical significance: Part I. *Clin Pharmacokinet Naunyn Schmiedebergs Arch Pharmacol* 2009;48(11):689-723.
- [18] Liu HC, Jin SM, Wang YL. Gender-related differences in pharmacokinetics of enantiomers of trans-tramadol and its active metabolite, trans-O-demethyltramadol, in rats. *Acta Pharmacol Sinn* 2003;24(12):1265-9.