ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

The Study of the Analgesic Activity of Fluoxetine and its Interactions with Morphine, Naltrexone and Ondansetron in Mice.

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ABSTRACT

Present study is conducted to evaluate analgesic activity of fluoxetine and to study its interactions with morphine, naltrexone and ondansetron in albino mice.The analgesic activity of fluoxetine (2, 5 & 10mg/kg) and its interactions with morphine (0.5mg/kg), naltrexone (5mg/kg) & ondansetron (1mg/kg) were studied by tail flick method. Fluoxetine at 2mg/kg did not produce significant analgesic effect but at doses 5 & 10 mg/kg produced significant dose dependent analgesia. Morphine in subanalgesic dose (0.5mg/kg) with fluoxetine 2mg/kg did not produce significant analgesia but produced highly significant analgesia with fluoxetine 5mg/kg. Naltrexone (5mg/kg) given as pretreatment with fluoxetine 5 & 10mg/kg significantly reduced the analgesic effect of fluoxetine. Ondansetron 1mg/kg pretreatment reduced analgesia produced by fluoxetine 5mg/kg significantly, but not that produced by 10mg/kg fluoxetine. Therefore it is concluded thatfluoxetine produced dose dependent analgesic effect. As fluoxetine potentiates morphine analgesia,it is suggested that opioid analgesics may be given in low doses with fluoxetine in chronic pain management. Fluoxetine may be producing analgesic effect by acting through 'μ' opioid receptors as naltrexone blocked it completely. Serotonergic system may be also involved, as ondansetron blocked analgesic effect partially.

Keyword: Fluoxetine, Morphine, Naltrexone, Ondansetron, Tail flick, Analgesia

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ISSN: 0975-8585

INTRODUCTION

Pain is very common phenomenon. It is an unpleasant sensation, though it acts as warning signal for many diseases. When it becomes chronic, it not only affects physical activity but also affects psychology of patient. This also lowers quality of life and thus social well-being is also affected [1].

The principle objective is to remove cause of pain. But many times pain is multifactorial and associated with undiagnosed underlying diseases. These reasons become barriers for the treatment of pain. Because of this delay in treatment, pain may become chronic condition and many times accompany with depression [2-4].

Currently non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for the treatment of pain. But they cause adverse effects like gastritis, peptic ulcer, nephropathy etc. also they increased risk of cardiovascular accidents on chronic use [5].

Opioid analgesics are also prescribed for treatment but because of their potential to cause dependence and other adverse effects like vomiting and constipation their use is limited.[6]

Recent studies on persistent pain model like nerve injury model which has relevance to chronic pain in human being, have demonstrated consistent analgesic effects with antidepressants [7, 8]. Tricyclic antidepressants have proven efficacy in chronic pain conditions [9]. Their side effects like dry mouth, constipation, orthostatic hypotension and urinary retention limit their use.

Therefore considerable interest has been developed in the use of selective serotonin reuptake inhibitors (SSRI) for management of chronic pain.We want to study that actually at which doses fluoxetine produces analgesic effect. There are few previous reports suggest that fluoxetine acts as analgesic through opioid receptors [10, 11]. As fluoxetine is SSRI, we thought it worthwhile to study whether serotonergic system is also involved in its analgesic activity. Therefore we studied interactions of morphine naltrexone and ondansetron with fluoxetine in our study.

All experiments were conducted in accordance with the guidelines from committee for the purpose of control and supervision of experiments on animals (CPCSEA). The study design was evaluated and were approved by Institutional Animal Ethics Committee of KIMSDU, Karad.

MATERIALS AND METHODS

Animals

Study was conducted in laboratory of pharmacology department of KIMSDU. Albino mice of either sex weighing 20-40 gms bred in central animal house were used.

Animals were housed under standard conditions i.e. with 12 hr light and dark cycle. Temperature was maintained at 25 ±3^{0}C. They had free access to food and water up to the time of experimentation.

Drugs

Fluoxetine (Sun Pharmaceutical), Morphine (Modi Mundipharma), Naltrxone (Intas Pharmaceutical), Ondasetron (Cipla) are used.

Instruments used

Analgesic effect was tested by analgesiometer by tail flick method using radiant heat from electric sources.

Animals were divided into 10 equal groups, 5 animals in each group.

Group I : received distilled water 10ml/kg i.e. vehicle
Group II : received Fluoxetine2mg/ kg
Group III : received Fluoxetine 5mg/ kg
Group IV : received Fluoxetine 10mg/ kg
Group V : received Morphine 0.5mg/kg + Fluoxetine 2mg/ kg
Group VI : received Morphine 0.5mg/kg + Fluoxetine 5mg/ kg
Group VII : received Naltrexone 5mg/kg + Fluoxetine 5mg/ kg
Group VIII : received Naltrexone 5mg/kg + Fluoxetine 10 mg/ kg
Group IX : received Ondansetron1mg/kg + Fluoxetine 5mg/ kg
Group X : received Ondansetron1mg/kg + Fluoxetine 10mg/ kg

In all groups the analgesic activity was tested before giving drugs i.e. 0 and after giving drugs at 15, 30, 60 and 120 min. after administration of drugs or vehicle.

Morphine and fluoxetine given simultaneously and same schedule for testing analgesic activity was followed as above. Naltrexone and ondansetron were given 30 min before giving fluoxetine. After giving fluoxetine analgesic activity was tested after 15, 30, 60, and 120 min.

In order to prevent injury 10 seconds exposure to radiant heat was taken as cut off points.

Statistical Analysis

All results were analyzed by repeated ANOVA followed by Tukey's posttest. To compare between two groups unpaired 't' test is used.

ISSN: 0975-8585

RESULTS

Effect of vehicle i.e. distilled water (Table 1)

In vehicle treated mice there was no significant change in the tail flick latency during the entire test period of 120 min.

Effects of Fluoxetine (Flu) at doses 2, 5 and 10 mg/kg:(Table 1)

Flu at dose of 2 mg/kg did not produce significant analgesic effect. Flu at dose of 5 mg/kg produced significant analgesic effect with onset and maximum analgesic activity at 30 min ($p < 0.05$) as compared with basal (before) readings.

Flu at dose 10 mg/kg produced significant analgesic effect ($p< 0.0002$) at all time intervals. With onset at 30 min ($p< 0.01$) and maximum at 60 min ($p< 0.001$) and maintaining the effect till 120 min.

Table 1: Effect of Fluoxetine 2, 5 and 10mg/kg

TIME INTERVALS		CONTROL	FLUOXETINE 2	FLUOXETINE 5	FLUOXETINE 10
BEFORE		2.24±0.172	2.4±0.4313	1.4±0.1871	2±0.4472
AFTER	15 MIN	3.66±0.5653	4.42±0.9846	5.4±1.271	5.12±1.235
	30 MIN	3.58±0.656	3.82±0.7172	6.78±1.037*	7.72±1.485**
	60 MIN	3.56±0.3881	3.84±0.8542	6.4±1.479	8.56±1.017***
	120 MIN	3.32±0.8393	4.04±0.6005	6.18±1.363	8.54±0.9537***
ANOVA *P* VALUE		0.1732	0.3751	**0.0379**	**0.0002**

Data is analyzed by using repeated measures one way analysis of variance (ANOVA) followed by Tukey's test . Values are expressed as mean ± standard error of mean (n=5) in each group. *$P < 0.05$, ** $P< 0.01$, *** $P < 0.001$ when compared with basal readings.

Effect of Morphine (Mor) and Fluoxetine (Flu) combined treatment (Table 2)

Table 2: Effect of Morphine (0.5mg/kg) and Fluoxetine (2,5mg/kg) combined treatment

TIME INTERVALS		CONTROL	MORPHINE + FLUOXETINE 2	MORPHINE + FLUOXETINE 5
BEFORE		2.24±0.172	4.18±0.6837	2.4±0.470
AFTER	15 MIN	3.66±0.5653	7.14±0.7698	8.94±0.665***
	30 MIN	3.58±0.656	7.64±0.99	9.56±0.277***
	60 MIN	3.56±0.3881	6.98±1.351	9.88±0.12***
	120 MIN	3.32±0.8393	6.9±1.045	9.46±0.34***
ANOVA *P* VALUE		0.1732	0.0558	**<0.0001**

Data is analyzed by using repeated measures one way analysis of variance (ANOVA) followed by Tukey's test . Values are expressed as mean ± standard error of mean (n=5) in each group. *$P < 0.05$, ** $P< 0.01$, *** $P < 0.001$ when compared with basal readings.

ISSN: 0975-8585

Subanalgesic dose of Mor (0.5 mg/kg) produced significant analgesia when combined with Flu 5mg/kg (p<0. 0001), with onset and maximum effect at 15 min and maintained the effect till 120 min.

Comparison of effect of Mor (0.5 mg/kg) andFlu (5 mg/kg) combined treatment with Flu 5 mg/kg (Table 3)

Statistically significant higher analgesia is produced by combination of Mor (0.5mg/kg) and Flu (5mg/kg) at all time intervals.

Table 3: Comparison of effect of Morphine (0.5 mg/kg) and Fluoxetine (5 mg/kg) combined treatment with Fluoxetine 5 mg/kg

TIME INTERVALS		FLUOXETINE 5	MORPHINE + FLUOXETINE 5	UNPAIRED 't' TEST
BEFORE		1.4±0.1871	2.4±0.470	0.0835
AFTER	15 MIN	5.4±1.271	8.94±0.665***	**0.0388**
	30 MIN	6.78±1.037*	9.56±0.277***	**0.0322**
	60 MIN	6.4±1.479	9.88±0.12***	**0.0471**
	120 MIN	6.18±1.363	9.46±0.34***	**0.0478**
ANOVA *P* VALUE		**0.0379**	**<0.0001**	

Data is analyzed by unpaired 't' test. Values are expressed as mean ± standard error of mean (n=5) in each group. *$P < 0.05$, ** $P< 0.01$, *** $P < 0.001$ when compared with basal readings.

Effect of Naltrexone (Nal) pretreatment (Table 4)

Pretreatment of Nal (5 mg/kg) significantly reduced analgesic effect of Flu (5mg/kg) (p=0.1468) and 10 mg/ kg (p=0. 1789).

Table 4: Effect of Naltrexone (5mg/kg) pretreatment

TIME INTERVALS		CONTROL	NALTREXONE + FLUOXETINE 5	NALTREXONE + FLUOXETINE 10
BEFORE		2.24±0.172	3.42±0.6391	2.82±0.477
AFTER	15 MIN	3.66±0.5653	6.62±1.47	3.28±0.56
	30 MIN	3.58±0.656	4.5±0.6557	6.16±1.662
	60 MIN	3.56±0.3881	3.64±1.658	5.48±1.894
	120 MIN	3.32±0.8393	3.74±0.8376	4.34±1.571
ANOVA *P* VALUE		0.1732	0.1468	0.1789

Data is analyzed by using repeated measures one way analysis of variance (ANOVA) followed by Tukey's test . Values are expressed as mean ± standard error of mean (n=5) in each group. *$P < 0.05$, ** $P< 0.01$, *** $P < 0.001$ when compared with basal readings.

ISSN: 0975-8585

Effect of Ondansetron (Ond) pretreatment (Table 5)

Pretreatment of Ond (5mg/kg) significantly reduced analgesic effect of Flu (5mg/kg), (p=0.0873), but not that of Flu (10 mg/kg)(p = 0.0005).

Table 5: Effect of Ondansetron (0.1mg/kg) pretreatment

TIME INTERVALS		CONTROL	ONDANSETRON + FLUOXETINE 5	ONDANSETRON + FLUOXETINE 10
BEFORE		2.24±0.172	2.4±0.3271	1.5±0.2191
AFTER	15 MIN	3.66±0.5653	3.12±0.4398	4.6±0.7887
	30 MIN	3.58±0.656	3.62±0.27	6.94±1.38**
	60 MIN	3.56±0.3881	4.04±0.2421	7.66±1.194***
	120 MIN	3.32±0.8393	3.82±0.5809	5.44±1.344*
ANOVA *P* VALUE		0.1732	0.0873	**0.0005**

Data is analyzed by using repeated measures one way analysis of variance (ANOVA) followed by Tukey's test . Values are expressed as mean ± standard error of mean (n=5) in each group. *$P < 0.05$, ** $P< 0.01$, *** $P < 0.001$ when compared with basal readings.

DISCUSSION

Pain is an unpleasant feeling at any age. Though it is sensory in nature, to some extent emotional phenomenon is also present. Therefore it is both sensory and emotional experience. Many times removal of cause of pain is not possible, symptomatic treatment is a mainstay of the treatment.

The present study is conducted to evaluate analgesic activity of fluoxetine which is SSRI and being widely used as antidepressant.

Though opioid analgesics are mainly used for relieving pain, their use is associated with many serious and nonserious adverse effect, therefore we evaluated fluoxetine which may be able to treat pain as well as emotional component associated with it.

In the present study Flu has produced dose-dependent analgesic effect. Fluoxetine as well as other SSRI have been reported to produce analgesia[11], thus our results are in agreement with others.[7,8] Fluoxetine has also reported clinically useful in diabetic neuropathy and migraine[12] as well as in rheumatic pain conditions.[13]

Further it was observed that subanalgesic doses of Morphine (0.5 mg/kg) and that of fluoxetine (5mg/kg) has produced significant analgesic effect as compared to Fluoxetine alone. Our results coincides with results of Sikka et al.[10] In the study of Kurlekar et al.,[11] fluoxetine (2mg/kg) in combination with morphine (0.5mg/kg) has produced significant analgesia, but in our study we did not get significant analgesic effect for this combination.

This suggests that, low doses of morphine and fluoxetine together will reduce adverse effects of both the drugs. The clinical study by Erjavec et al [14]. supports this finding. They found that fluoxetine augmented analgesic effect of morphine and reduced morphine-associated nausea and drowsiness. Therefore combined treatment with both the drugs can minimize dose requirement and adverse effect of opioid analgesics.

In our study Nal has blocked analgesic effect of Flu completely, which suggest that Flu might be producing analgesic effect through μ opioid receptors. Our findings are in agreement with Sikka et al [10]. and Kurlekar et al [11].

It is also observed that 5HT3 antagonist Ond partially blocked analgesic effect of Flu. Thus serotonergic system may be partially involved in analgesic effect fluoxetine.

CONCLUSION

Fluoxetine showed dose dependent analgesic effect, as it produces this effect at 5 & 10mg/kg dose. Subanalgesic dose of morphine 0.5mg/kg & fluoxetine 5mg/kg produced significant analgesia. It suggests that fluoxetine potentiates morphine analgesia. Therefore opioid analgesics can be given in low doses with fluoxetine in chronic pain management. As naltrexone blocked analgesic effect of fluoxetine completely, it may be producing analgesia by acting through 'μ' opioid receptors. Serotonergic system may also be partly involved in analgesic effect of fluoxetine, as ondansetron partially blocked analgesic effect of fluoxetine.

ACKNOWLEDGEMENT

Authors are grateful to management KIMSDU for providing facilities for research work. Sun Pharmaceutical, Modi Mundipharma, Cipla and Intas pharmaceutical for procuring drugs. We are also thankful to statistician Dr. S.V.Kakade and techniqual staff for their help.

REFERENCES

[1] Atkinson JH, Slater MA, Patterson TL, Grant I, Garfin SR. Pain 1991;45(2):111-21.
[2] Magni G, Marchetti M, Moreschi C, Merskey H, Luchini SR. Pain 1993;53(2):163-8.
[3] Elliott TE, Renier CM, Palcher JA. Pain Med 2003;4(4):331-9.
[4] Fishbain DA, Cutler R, Rosomoff HL, Rosomoff RS. The Clin J Pain 1997;13(2):116-37.
[5] Ong C, Lirk P, Tan C, Seymour R. Clin Med Res 2007;5(1):19-34.
[6] Holdgate A, Pollock T. BMJ 2004;328(7453):1401.
[7] Butler SH, Weil-Fugazza J, Godefroy F, Besson J-M. Pain 1985;23(2):159-75.
[8] Jett M-F, McGuirk J, Waligora D, Hunter JC. Pain 1997;69(1):161-9.
[9] Max MB, Lynch SA, Muir J, Shoaf SE, Smoller B, Dubner R. New England J Med 1992;326(19):1250-6.
[10] Sikka P, Kaushik S, Kumar G, Kapoor S, Bindra V, Saxena K. J Pharm Bioallied Sci 2011;3(3):412-6.
[11] Kurlekar P, Bhatt JD. Indian J Pharmacol 2004;36(6):369-72.

[12] Jung AC, Staiger T, Sullivan M. J Gen Int Med 1997;12(6):384-9.
[13] Rani PU, Naidu M, Prasad V, Rao TRK, Shobha J. Anesthesia Analgesia. 1996;83(2):371-5.
[14] Erjavec MK, Coda BA, Nguyen Q, Donaldson G, Risler L, Shen DD. The J Clin Pharmacol 2000;40(11):1286-95.