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Evaluation of anti-inflammatory activity, effect on blood pressure & gastric tolerability of antidepressants

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***Background & objectives*: Antidepressants are being used as analgesics for various pain related disorders like neuropathic and non neuropathic pain. Although their analgesic activity is well recognized but anti-inflammatory potential of antidepressants is still inconclusive. Since the antidepressants are used for longer duration, it becomes important to elucidate effect of anti-depressants on blood pressure and gastric mucosa. This study was undertaken to evaluate the anti-inflammatory potential of various antidepressant drugs as well as their effect on blood pressure and gastric tolerability on chronic administration in rats.**

***Methods*: Rat paw oedema model was used for studying anti-inflammatory activity, single dose of test drug (venlafaxine 20 and 40 mg/kg, amitryptline 25 mg/kg, fluoxetine 20 mg/kg) was administered intraperitoneally 45 min prior to administration of 0.1 ml of 1 per cent carrageenan in sub-planter region. Oedema induced in test group was compared with normal saline treated control group. For studying effect on blood pressure and gastric tolerability, test drugs were administered for 14 days. Blood pressure was recorded on days 0, 7 and 14 using tail cuff method. On day 14, 4 h after drug administration, rats were sacrificed and stomach mucosa was examined for ulcerations.**

***Results*: Pretreatment of rats with venlafaxine (40 mg/kg) resulted in a significant decrease in paw oedema as compared to control (2.4 ± 0.15 to 1.1 ± 0.16 ml, $P<0.01$). Similarly, in the group pretreated with fluoxetine, significant decrease in paw oedema was observed in comparison to control ($P<0.05$). Significant change in mean blood pressure was seen in rats pretreated with venlafaxine 40 mg/kg (126.7 ± 4.2 to 155.2 ± 9.7, $P<0.05$) and fluoxetine (143.5 ± 2.6 to 158.3 ± 1.2, $P<0.05$) on day 7. No significant difference with regard to gastric tolerability was observed among groups.**

***Interpretation & conclusions*: Our findings showed significant anti-inflammatory activity of venlafaxine (40 mg/kg) and fluoxetine but these drugs were also associated with an increase in blood pressure. No significant change in mean ulcer index was observed among groups.**

Key words Anti-depressants - anti inflammatory - paw oedema - venlafaxine

Antidepressants have been used for the treatment of neuropathic and non neuropathic chronic pain[1,2]. Several antidepressants are known to possess intrinsic antinociceptive activity. Antidepressants by inhibiting the uptake of monoamines lead to increased amount of noradrenaline and serotonin in the synaptic cleft at both spinal and supraspinal levels causing reinforcement of descending pain inhibitory pathways[1]. There is a

paucity of literature comparing antinociceptive/anti inflammatory efficacy among the three different classes of antidepressants namely tricyclic antidepressants (TCA), selective serotonin reuptake inhibitors (SSRI) and atypical antidepressants.

In experimental models of inflammation, fluoxetine, imipramine and cloimipramine have been shown to have some anti-inflammatory activity[3]. Since this group of drugs is to be used for longer durations, it becomes important to elucidate effect of antidepressants on blood pressure and gastric mucosa. Moreover, it has been observed that patients of chronic pain disorder are often associated with depression affecting their day to day routine[2]. Antidepressants may benefit these patients having depression along with inflammatory pain disorder.

Antidepressants often have to be taken for a long period. Cardiovascular side effects from anti-depressant drugs, including clinically significant blood pressure changes may complicate long term therapy. It has been suggested that though depression is associated with a decrease in blood pressure, the use of antidepressants increases the risk of hypertension[4]. In a study, venlafaxine and imipramine were found to be associated with small, but significant increase in supine diastolic blood pressure during acute phase therapy[5]. The effects on blood pressure may be due to noradrenergic potentiation by the antidepressants[6]. Chronic fluoxetine intake has been shown to cause a 2 per cent increase in supine systolic blood pressure in depressed patients[7].

Antidepressants are often taken by the elderly, and in whom the intake of other medications, especially non steroidal anti inflammatory drugs (NSAIDs), is seen for the treatment of different medical conditions. NSAIDs are known to cause gastric intolerance and ulceration[8]. SSRIs have been shown to increase the risk of upper gastrointestinal (GI) bleeding and more so with the concurrent use of NSAIDs in a population based case-control study[9]. However, animal studies have not been conducted comparing the effect of various antidepressants on gastric tolerability. Hence, this study was designed to evaluate anti-inflammatory activity of different classes of antidepressants along with their effect on blood pressure and gastric tolerability in a rat model.

Material & Methods

This study was conducted in the department of Pharmacology, Maulana Azad Medical College, New Delhi, India. The study protocol was approved by institutional animal ethical committee.

Wistar rats weighing 150-200 g body weight were used. Animals were procured from central animal house and were housed in airconditioned environment. A gap of one week was given for acclimatization of animals. They were provided with normal rat food pellet diet with water *ad libitum*. Rats were divided into 10 groups with eight rats in each group. All animals received drugs through intraperitoneal (ip) route in various dosage (Table I). Drugs were dissolved in normal saline. Prazosin, an alpha 1 adrenoceptor antagonist was additionally added to drugs to elicit mechanism of action.

Anti-inflammatory activity: Paw oedema model: On the morning of experiment, rats were weighed and baseline paw volume was measured with the aid of plethysmometer[10]. To ensure uniformity, lateral malleolus of left hind limb was marked in all animals so that the same length of paw is dipped in fluid each time. This was followed by administration of drugs. After 45 min of drugs administration, animals were injected with 0.1 ml of 1 per cent carrageenan in sub-planter region for inducing inflammation. Paw volume was again measured after 3 h of sub-planter injection of 1 per cent carrageenan. The paw volume and per cent decrease in paw oedema was compared between control group and drug-treated groups.

Effect on blood pressure: For measuring blood pressure non invasive rat tail cuff-BP measuring device by Biopac (India) was used. The animals were administered with drugs (groups 1 to 6) once daily. The blood pressure

Table I. Dose and duration of antidepressants in various groups of rats (n=8)

Group	Drug	Dose (ip)
1	Normal saline	0.1 ml/10 g
2	Prazosin	1 mg/kg
3	Fluoxetine	20 mg/kg
4	Amitryptline	25 mg/kg
5	Velnafaxine	20 mg/kg
6	Velnafaxine	40 mg/kg
7	Fluoxetine + Prazosin	20 mg/kg +1 mg/kg
8	Imipramine + Prazosin	25 mg/kg + 1 mg/kg
9	Velnafaxine + Prazosin	20 mg/kg + 1 mg/kg
10	Velnafaxine + Prazosin	40 mg/kg + 1 mg/kg

i.p. intraperitoneal

was measured on days 0, 7 and 14. Digital readings of blood pressure were obtained using computerized software.

Gastric tolerability: Animals who were being administered drugs intraperitoneally once daily for a period of 14 days to check out the effect on blood pressure were used for evaluating gastric tolerability. In the control group, rats received normal saline for 14 days. On day 14, 4 h after drug administration animals were sacrificed. Each rat was subjected to midline abdominal incision, abdomen was opened and stomach was removed after ligating both oesophageal and pylorus ends. Incision was given in the stomach along greater curvature; mucosal surface was exposed and washed with normal saline[10]. It was then stretched and pinned on cork board. Mucosal surface was examined for erosions and ulcerations. Severity of lesions was recorded according to following scale[11]. 0=normal gray-coloured mucosal surface. 0.5=pink to red colouration of mucosal surface. 1=spot ulcer.1.5=haemorrhagic streak. 2=number of ulcers less than five. 3=number of ulcers more than five. 4=ulcers with bleeding. Ulcer index was calculated by adding the total number of ulcers plus the severity score. Ulcer index were recorded and compared among drug-treated and control groups.

Statistical analysis: Results of paw oedema model, blood pressure and ulcer index are expressed as mean ± standard error of mean. One way ANOVA followed by post-hoc analysis with Dunnett test were applied for paw oedema test. Student's t test was used for blood pressure comparisons among groups. Mann-Whitney test was used for analysis of ulcer index outcomes.

Results

Marked paw oedema was produced in rats with sub-planter injection of 0.1 ml of 1 per cent carrageenan. Mean paw oedema in the control rats was 2.4±0.15 ml (Table II). Venlafaxine (40 mg/kg) and fluoxetine showed significant reduction (P<0.05) in paw oedema compared to control group. However, in the groups treated with amitryptyline and venlafaxine 20 mg/kg, no significant decrease in oedema was observed as compared to control group (Table II). Pretreatment of rats with prazosin alone resulted in mean paw oedema of 2.7±0.20 ml. Addition of prazosin to fluoxetine, venlafaxine (20 and 40 mg/kg) and amitryptline groups did not influence oedema significantly in comparison to control.

Mean BP was recorded on days 0, 7 and 14 (Table III). Mean BP was 126.7±4.2 mmHg on day 0 in group administered with venlafaxine (40 mg/kg), on day 7 recorded mean BP was 155.2±9.7 mmHg. The change in mean BP was significant (P<0.05). Mean BP on day 14 (145.7±7.5 mmHg) was significantly different as compared to mean BP of day 7 (P<0.05).Similarly, in the group administered with fluoxetine, significant change in mean BP (143.5±2.6 to 158.3±1.2 mmHg) was observed on day 7 (P<0.05) and day 14 (P<0.05). In groups administered with venlafaxine (20 mg/kg) and amitryptline, no significant difference in mean BP was observed.

Mean ulcer index in control rats was 0.18±0.09. Rats pretreated with fluxoteine (0.37±0.08), amitryptline (0.25±0.09) and two doses of venlafaxine (0.56±0.2, 0.37±0.08) did not show significant difference in mean ulcer index as compared to control group.

Table II. Effect of various drugs on paw oedema in rats

Group	Drugs	Paw oedema
		Mean paw oedema (ml)
1	Control (normal saline)	2.4±0.15
2	Prazosin	2.7±0.20
3	Fluoxetine	0.9±0.30*
4	Amitryptline	1.6±0.26
5	Velnafaxine 20 mg	1.9±0.17
6	Velnafaxine 40 mg	1.1±0.17**
7	Fluoxetine+Prazosin	2.0±0.28
8	Amitryptline+Prazosin	1.6±0.33
9	Velnafaxine 20+Prazosin	1.8±0.20
10	Velnafaxine 40+Prazosin	1.7±0.10

Values are mean±SEM (n=8), P *<0.05, **<0.01 compared to control

Table III. Effect of drug treatment on mean blood pressure (mm Hg)

Drugs	Day 0	Day 7	Day 14
Venlafaxine (40 mg/kg)	126.7 ± 4.2	155.2 ± 9.7*	145.7 ± 7.5+
Venlafaxine (20 mg/kg)	148.7 ± 1.8	146.9 ± 2.1	147.5 ± 1.3
Amitryptline	136.0 ± 4.8	144.5 ± 8.4	141.7 ± 5.7
Fluoxetine	143.5 ± 2.6	158.3 ± 1.2*	153.3 ± 0.8+

Values are mean ± SEM (n=8), *P<0.05 compared to day 0, +P<0.05 compared to day 7

Discussion

Antidepressants are prescribed worldwide and chronic treatment often lasts several months. The observation that these classes of drugs have anti-inflammatory potential might led to important clinical implication. Moreover, it has been observed that patients with chronic inflammatory disorders have high prevalence of depression[12-14]. Earlier studies have demonstrated analgesic activity of antidepressants but there is scanty information on anti-inflammatory activity of various groups of antidepressants.

In our study, a significant anti-inflammatory activity of fluoxetine and venlafaxine 40 mg/kg was observed in rat paw oedema model but this activity was blunted, when prazosin was added to venlafaxine and fluoxetine. Addition of prazosin resulting in loss of anti-inflammatory activity of fluoxetine and venlafaxine is indicative of probable role of noradrenergic/ serotonergic pathway in inflammation.

Fluoxetine dose-dependently inhibited the release of tumour necrosis factor-α (TNF-α) from lipopolysaccharide (LPS)-treated monocytes and anti-oedema effect of fluoxetine was partially suppressed by the opioid antagonist naloxone[15,16]. Other hypothesis was brought up that serotonin/ noradrenaline transporters are expressed in peripheral leucocytes and amines released from these cells have immunomodulatory role on interacting with receptors present on immune cells[17-19]. In our study, a significant anti-inflammatory activity of venlafaxine at a dose of 40 mg/kg and fluoxetine was observed but amitryptline did not show significant anti-inflammatory potential which is in contrast to earlier published studies[20-22]. This could be due to low dose of amitryptline used in our study.

In our study, we observed significant increase in blood pressure with venlafaxine 40mg/kg and fluoxetine when administered for 14 days, which is in concordance with earlier published studies[4,5]. Increase in blood pressure with venlafaxine is documented but data for association of fluoxetine with increase in BP are lacking. In a meta-analysis with 3744 patients, dose-dependent increase in supine diastolic blood pressure with venlafaxine was observed[5]. One study documents increase in blood pressure with intracerebral administration of fluoxetine mainly attributed to increase in sympathetic tone and vasopressin release[23]. In two studies, low rate of sustained hypertension with fluoxetine was observed[24,25]. Whether hypertension is a class effect of antidepressants or is associated with all classes of antidepressants is still not clear.

We did not observe increased risk of gastric ulceration with any of the test drugs used in our study whereas literature shows increased propensity of gastric ulcerations with selective serotonin reuptake inhibitors as these block the uptake of serotonin into platelets, leading to an impairment in the platelet haemostatic response[26]. Also, concurrent use of NSAIDs, anticoagulants, and antiplatelet agents with SSRIs leads to increase risk of GI bleeding[6]. In a nested case control study, risk of gastric bleeding with venlafaxine was found to be significantly higher than matched controls[27]. These findings were in contrast to our observations; which could be attributed to short duration (14 days) of drug administration.

In conclusion, venlafaxine in high dose and fluoxetine showed potent anti-inflammatory activity in rats. This effect was associated with an increase in blood pressure on chronic therapy but did not have adverse gastric tolerability when administered as monotherapy. Limitations of our study were that ED_{50} was not elucidated of various test drugs and gastric tolerability was not studied in combination with NSAIDs.

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References

1. Maizels M, McCarberg B Antidepressants and antiepileptic drugs for chronic non-cancer pain. *Am Fam Physician* 2005; *71* : 483-90.
2. McQuay HJ, Tramèr M, Nye BA, Carroll D, Wiffen PJ, Moore RA. A systematic review of antidepressants in neuropathic pain. *Pain* 1996; *68* : 217-27.
3. Abdel-Salam OM, Nofal SM, El-Shenawy SM. Evaluation of the anti-inflammatory and anti-nociceptive effects of different antidepressants in the rat. *Pharmacol Res* 2003; *48* : 157-65.
4. Licht CM, de Geus EJ, Seldenrijk A, van Hout HP, Zitman FG, van Dyck, *et al.* Depression is associated with decreased blood pressure, but antidepressant use increases the risk for hypertension. *Hypertension* 2009; *53* : 631-8.
5. Thase ME. Effects of venlafaxine on blood pressure: a meta-analysis of original data from 3744 depressed patients. *J Clin Psychiatry* 1998; *59* : 502-8.
6. Sawynok J, Esser MJ, Reid AR. Antidepressants as analgesics: an overview of central and peripheral mechanisms of action. *J Psychiatry Neurosci* 2001; *26* : 21-9.

7. Roose SP, Glassman AH, Attia E, Woodring S, Giardina EG, Bigger JT Jr. Cardiovascular effects of fluoxetine in depressed patients with heart disease. *Am J Psychiatry* 1998; *155* : 660-5.
8. Armstrong CP, Blower AL. Non-steroidal anti-inflammatory drugs and life threatening complications of peptic ulceration. *Gut* 1987; *28* : 527-32.
9. de Abajo FJ, Rodríguez LA, Montero D. Association between selective serotonin reuptake inhibitors and upper gastrointestinal bleeding: population based case control study. *BMJ* 1999; *319* : 1106-9.
10. Sharma JN, Samud AM, Asmauei MZ. Comparison between plethysmometer and micrometer methods to measure acute paw oedema for screening anti-inflammatory activity in mice. *Inflammopharmacology* 2004; *12* : 89-94.
11. Kunchandy J, Khanna S, Kulkarni SK. Effect of alpha 2 agonists clonidine, guanfacine and B-HT 920 on gastric acid secretion and ulcers in rats. *Arch Int Pharmacodyn Ther* 1984; *275* : 123-38.
12. Hurwitz EL, Morgenstern H. Cross-sectional associations of asthma, hay fever, and other allergies with major depression and low-back pain among adults aged 20-39 years in the United States. *Am J Epidemiol* 1999; *150* : 1107-16.
13. Kozora E, Ellison MC, West S. Depression, fatigue, and pain in systemic lupus erythematosus (SLE): relationship to the American College of Rheumatology SLE neuropsychological battery. *Arthritis Rheum* 2006; *55* : 628-35.
14. Zielinski TA, Brown ES, Nejtek VA, Khan DA, Moore JJ, Rush AJ. Depression in asthma: Prevalence and clinical implications. *Prim Care Companion J Clin Psychiatry* 2000; *2* : 153-8.
15. Roumestan C, Michel A, Bichon F, Portet K, Detoc M, Henriquet C, *et al*. Anti-inflammatory properties of desipramine and fluoxetine. *Respir Res* 2007; *8* : 35.
16. Abdel-Salam OM, Baiuomy AR, Arbid MS. Studies on the anti-inflammatory effect of fluoxetine in the rat. *Pharmacol Res* 2004; *49* : 119-31.
17. Faraj BA, Olkowski ZL, Jackson RT. Expression of a high-affinity serotonin transporter in human lymphocytes. *Int J Immunopharmacol* 1994; *16* : 561-7.
18. Marino F, Cosentino M, Bombelli R, Ferrari M, Lecchini S, Frigo G. Endogenous catecholamine synthesis, metabolism storage, and uptake in human peripheral blood mononuclear cells. *Exp Hematol* 1999; *27* : 489-95.
19. Elenkov IJ, Wilder RL, Chrousos GP, Vizi ES. The sympathetic nerve-an integrative interface between two supersystems: the brain and the immune system. *Pharmacol Rev* 2000; *52* : 595-638.
20. Abdelmawla AH, Langley RW, Szabadi E, Bradshaw CM.Comparison of the effects of venlafaxine, desipramine, and paroxetine on noradrenaline- and methoxamine-evoked constriction of the dorsal hand vein. *Br J Clin Pharmacol* 1999; *48* : 345-54.
21. Hajhashemi V, Sadeghi H, Minaiyan M, Movahedian A, Talebi A. The role of central mechanisms in the anti-inflammatory effect of amitriptyline on carrageenan-induced paw edema in rats. *Clinics (Sao Paulo)* 2010; *65* : 1183-7.
22. Vismari L, Alves GJ, Palermo-Neto J. Amitriptyline and acute inflammation: a study using intravital microscopy and the carrageenan-induced paw edema model. *Pharmacology* 2010; *86* : 231-9.
23. Lazartigues E, Brefel-Courbon C, Bagheri H, Costes S, Gharib C, Tran MA, *et al*. Fluoxetine-induced pressor response in freely moving rats: a role for vasopressin and sympathetic tone. *Fundam Clin Pharmacol* 2000; *14* : 443-51.
24. Amsterdam JD, Garcia-Espana F, Fawcett J, Quitkin FM, Reimherr FW, Rosenbaum JF, *et al*. Blood pressure changes during short-term fluoxetine treatment. *J Clin Psychopharmacol* 1999; *19* : 9-14.
25. Volkers AC, Tulen JH, van den Broek WW, Bruyn JA, Passchier J, Pepplinkhuizen L. Effects of imipramine, fluvoxamine and depressive mood on autonomic cardiac functioning in major depressive disorder. *Pharmacopsychiatry* 2004; *37* : 18-25.
26. Andrade C, Sandarsh S, Chethan KB, Nagesh KS. Serotonin reuptake inhibitor antidepressants and abnormal bleeding: a review for clinicians and a reconsideration of mechanisms. *J Clin Psychiatry* 2010; *71* : 1565-75.
27. de Abajo FJ, García-Rodríguez LA. Risk of upper gastrointestinal tract bleeding associated with selective serotonin reuptake inhibitors and venlafaxine therapy: interaction with nonsteroidal anti-inflammatory drugs and effect of acid-suppressing agents. *Arch Gen Psychiatry* 2008; *65* : 795-803.

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