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Gastroprotective and Antioxidant Effects of Opipramol on Indomethacin-induced Ulcers in Rats

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Tricyclic antidepressants are particularly useful in the treatment of endogenous depression. Since the 1950s, tricyclic antidepressants (TCAs) have also been used for the treatment of gastric ulcer disease. Many TCAs have been evaluated for their antiulcer effects, but there are presently no data in the literature specifically concerning the antidepressant opipramol. This study aimed to investigate the antiulcer effects of opipramol and to determine its potential relationship with oxidant and antioxidant systems. The antiulcer activities of 25, 50 and 100 mg/kg opipramol have been investigated on indomethacin-induced ulcers in rats. Compared with a control group (indomethacin alone), opipramol decreased indomethacin-induced ulcers significantly at all doses used (52%, 71% and 76% respectively). Opipramol also significantly increased the glutathione (GSH), superoxide dismutase (SOD) and nitric oxide (NO) levels in the stomach tissue, all of which were decreased in the control group given only indomethacin. All doses of opipramol also significantly decreased myeloperoxidase (MPO), malondialdehyde (MDA) and catalase (CAT) levels in stomach tissue compared to the control. In conclusion, the activation of enzymatic and non-enzymatic antioxidant mechanisms, as well as the inhibition of some toxic oxidant mechanisms, appear to play a role in the antiulcer effect of opipramol. This new indication for opipramol prompts a rethinking about the possible clinical application of opipramol, particularly for peptic ulcer patients also presenting depression.

Key words——opipramol; ulcer; antioxidant; indomethacin; rat

INTRODUCTION

Since the 1950s, antidepressants have been used for a variety of non-psychiatric indications, including a variety of uses in the field of gastroenterology. The earliest reported use of antidepressants for gastrointestinal (GI) illness was the use of tricyclic antidepressants (TCAs) for the treatment of gastric ulcer disease.[1] Tricyclic antidepressants are particularly useful in the treatment of endogenous depression, but certain antidepressants also possess definite antimuscarinic actions, thus reducing gastric secretion. This property has formed the basis of the use of doxepin and trimipramine in the management of gastric ulceration. Studies have shown that a significant number of patients known to suffer from gastrointestinal ulceration also possess both psychic and somatic symptoms, and that a majority of peptic ulcer patients also have symptoms of depression.[2] Imipramine and amitryptiline, two TCAs, have been reported to prevent gastric ulcers in a dose-dependent manner in several ulcer models.[3,4] Desimipramine, an active metabolite of imipramine, has also potentially inhibited gastric acid secretion and produced gastroprotective effects in other ulcer models.[5–7]

Opipramol is a tricyclic compound with the nucleus of the anticonvulsant carbamazepine and the side chain of the neuroleptics, fluphenazine and perphenazine, but which lacks the reuptake inhibiting properties for serotonin (5-HT) or noradrenaline. The blocking potential for H1, 5-HT2 and D2 receptors places opipramol somewhere between classical antidepressants, atypical neuroleptics and anxiolytics. Recent basic research has also characterized opipramol as strong sigma ligand[8,9] with complex interactions on the dopaminergic system[10] and the NMDA receptor complex. It also induces increased levels of cGMP and possesses anti-ischemic effects.[11]

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Clinical studies suggest that many antidepressant drugs have antiulcer activities.[12,13] However, there is no information in the literature about the antiulcer effects of opipramol specifically.

It is known that stress, alcohol and steroidal and non-steroidal anti-inflammatory drugs are some of the factors that increase ulcer risk.[14] The role of reactive oxygen species (ROS) in the pathogenesis of stress and in indomethacin-induced stomach damage has been shown.[15] Bilici *et al*. have also determined the role of oxidant and antioxidant mechanisms in the antiulcer effect mechanism of mirtazapine, a newly developed antidepressant drug.[16] ROS, which cause tissue damage, are decreased by antioxidant enzymes such as endogenous glutathione (GSH), superoxide dismutase (SOD), and catalase (CAT). This study aimed to investigate the antiulcer effects of opipramol and determine its possible relationship with oxidant and antioxidant systems.

MATERIALS AND METHODS

Animals A total of 36 male albino Wistar rats, obtained from the Medical Experimental Research Centre, Atatürk University, weighing between 190 and 210 g, were used for this study. The animals were fed under normal conditions (22℃) in separate groups. Animal experiments were performed in accordance with the national guidelines for the use and care of laboratory animals and were approved by the local animal care committee of Atatürk University.

Chemicals All chemicals for laboratory experimentation were purchased from Sigma Chemical Co. (Germany). Indomethacin, opipramol, ranitidine and thiopental sodium were obtained from Deva Holding-Turkey, Novartis-Turkey, Fako-Turkey and IE Ulagay-Turkey respectively.

Effect of Opipramol on Indomethacin-induced Gastric Ulcer in Rats The antiulcer activities of different doses of opipramol were investigated in an indomethacin-induced ulcer model in rats.[17] Opipramol at doses of 25, 50 and 100 mg/kg and a 25 mg/kg dose of ranitidine were administered to 24-hour fasted rat groups by oral gavage. An equal volume of distilled water was administered to the control group as a vehicle. Five minutes after drug administration, all groups received 25 mg/kg indomethacin, also by oral gavage. Six hours after indomethacin administration, all rat groups were killed with a high dose of thiopental sodium (50 mg/kg). The stomachs of all the rats were excised, and ulcer areas on the surface of the stomachs were examined macroscopically and measured on square millimeter paper. The results obtained from opipramol groups were evaluated by comparing them with those of the control and ranitidine groups.

Biochemical Analyses

Biochemical investigation of stomach tissues All biochemical analyses were performed in whole stomach tissue. Each tissue for all assays, except MDA level, MPO activity and tGSH level, was homogenized in 0.9% NaCl solution (10% w/v) with an OMNI TH International homogenizer. Tissue homogenates were centrifuged for 15 min at 18000 g, and the supernatants were removed for analysis.

tGSH levels To determine the total GSH level, the tissues were homogenized on ice by the homogenizer in a 1 : 10 (w/v) dilution of ice-cold 0.5 N perchloric acid. The tGSH level in the supernatant was measured spectrophotometrically at 412 nm by a glutathione disulfide reductase recycling method at room temperature. Tissue concentrations were estimated by linear regressions from the standard curve.[18] Results were expressed as nmol/g protein.

SOD Activity Cu-Zn SOD activity was measured by the reduction of nitroblue tetrazolium by the xanthine-xanthine oxidase system, a superoxide generator. Enzymatic activity leading to 50% inhibition of the xanthine oxidase activity was accepted as one SOD unit.[19] Results were expressed as U/g protein.

NO Levels Tissue NO levels were measured as total nitrite + nitrate levels with the use of the Griess reagent.[20] The Griess reagent consists of sulfanilamide and N-(1-napthyl)-ethylenediamine and the method is based on a two-step process. The first step is the conversion of nitrate into nitrite using nitrate reductase. The second step is the addition of the Griess reagent, which converts nitrite into a deep purple azo compound. Photometric measurement of absorbance at 540 nm of the azo chromophore accurately determines nitrite concentration. NO levels were expressed as nmol/g protein.

MPO Activity MPO activity in tissues was measured by a procedure similar to that described by Hillegass *et al*.[21] Tissue samples were homogenized in 50 mM potassium phosphate buffer (PB), with pH 6.0, and centrifuged at 41400 g for 10 min. The pellets were then suspended in 50 mM PB containing 0.5%

hexadecyltrimethylammonium bromide (HETAB). Aliquots (0.3 ml) were added to 2.3 ml of a reaction mixture containing 50 mM PB, o-dianisidine and 20 mM H_2O_2 solution. One unit of enzyme activity was defined as the amount of MPO that caused a change in absorbance, measured at 460 nm, over 3 min. MPO activity was expressed as U/g protein.

MDA Levels For the MDA assay, tissue samples were homogenized so that each gram of tissue contained 9 ml of a 1.15% KCl solution. MDA was determined by spectrophotometry of the pink-colored product of the thiobarbituric acid-reactive substances complex.[22] Total thiobarbituric acid-reactive substances (TBARS) were expressed as MDA. Results were expressed as μmol/g protein.

CAT Activity Catalase (CAT) activity was determined by measuring the rate of decay of H_2O_2 absorbance at 240 nm.[23] CAT activity was expressed as k/g protein. The supernatant protein concentration was measured by the Bradford method.[24]

***In Vitro* Linoleic Acid Peroxidation Assay** The antioxidative activity of opipramol assayed by using thiobarbituric acid (TBA) method based on inhibition of linoleic acid peroxidation by the extract. Linoleic acid was chosen as the source of unsaturated fatty acid.[25] The TBA method was used for measurement of lipid peroxidation[26] and Fe-ascorbate system was used for the catalysis of oxidation.[27] 2 mg opipramol was dissolved in 2 ml distilled water. 100 μl of linoleic acid was emulsified with 0.2 ml of Tween 20 and 19.7 ml of distilled water. Phosphate buffer solution (0.02 M, pH 7.4) was mixed with 1 ml of linoleic acid emulsion, 0.2 ml of FeSO4 (0.01%), 0.2 ml of ascorbate (0.01%) and 0.4 or 0.8 ml of drug solution and incubated at 37℃. Distilled water was substituted for the extract in the blank sample. After 3 h of incubation, 2 ml of the reaction solution was mixed with 0.2 ml of TCA (4%), 2 ml of TBA (0.8%), 0.2 ml of butylated hydroxyl toluene (BHT, 0.4%) and incubated at 100℃ for 30 min and cooled. The absorbance was measured at 532 nm. The percent inhibition of linoleic acid peroxidation was defined as:

% inhibition = [1-(absorbance of sample at 532 nm /absorbance of control at 532 nm)] × 100.

Statistical Analyses Data for enzyme activity and ulcer score were subjected to one-way ANOVA, with the presence of negative and positive controls, using SPSS 11.0 software. Differences among groups were obtained using the LSD option, and significance was declared at $p<0.05$.

RESULTS

Effect of Opipramol on Indomethacin-induced Gastric Ulcer in Rats Macroscopic analyses showed that there was ulcer formation in all stomachs of all of the rat groups. In damaged stomachs, the lesions had been dispersed to all stomach surfaces, but with different forms and sizes. There was remarkable hyperemia in the ulcerative stomachs, which was more evident in the control group (given indomethacin only) than in the others (given ranitidine and opipramol). As seen in Table 1, the mean ulcer area was 32.0 ± 5.8 mm^2 in the control group that received only indomethacin. While there was 15.0 ± 3.5 mm^2, 9.3 ± 2.0 mm^2, and 7.7 ± 1.5 mm^2 ulcer area in the stomachs of 25, 50 and 100 mg/kg opipramol groups respectively, the mean ulcer area was in the 25 mg/kg ranitidine group was 15.8 ± 2.3 mm^2 (Fig. 1).

Effects of Opipramol and Ranitidine on GSH, SOD and NO Levels in Indomethacin-given Rat Stomach Tissue As seen in Figs. 2, 3 and 4, tGSH, SOD and NO levels were, respectively, 1.1 ± 0.12 nmol/gprotein, 19.6 ± 3.4 U/gprotein and 1358 ± 199 nmol/gprotein in the stomach tissue of rats given only indomethacin. These levels were measured at 7.9 ± 0.15

Table 1. Effect of Opipramol and Ranitidine on Indomethacin Induced Gastric Ulcer in Rats

Drugs	Dose (mg/kg)	Number of Animals	Ulcer area mm^2	Antiulcer effect%	p
Opipramol	25	6	15.0 ± 3.5	52	<0.001
Opipramol	50	6	9.3 ± 2.0	71	<0.001
Opipramol	100	6	7.7 ± 1.5	76	<0.001
Ranitidine	25	6	15.8 ± 2.3	50	<0.001
Control (Indomethacin)	25	6	32 ± 5.8	—	<0.001

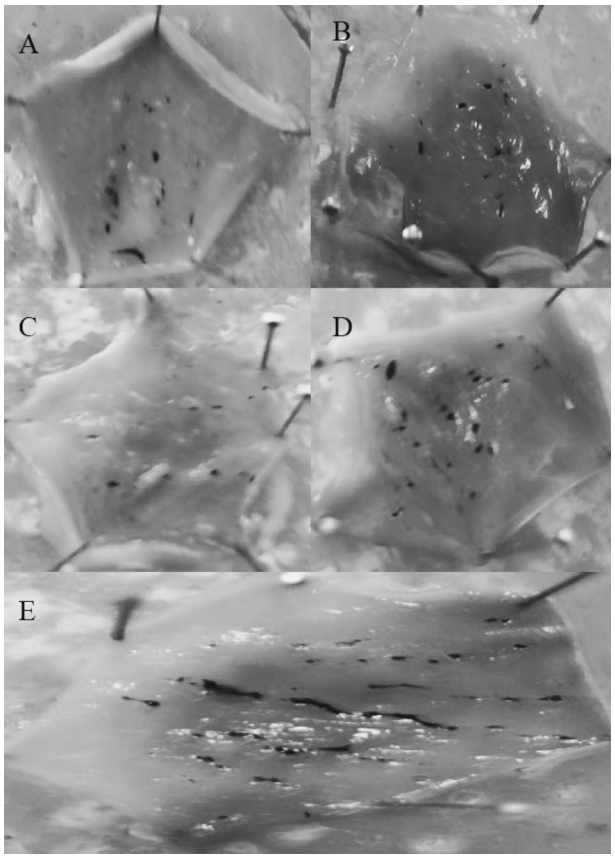

Fig. 1. Stomach of the rat which received opipramol (25, 50 and 100 mg/kg) + indomethacin (A, B, C), ranitidine (25 mg/kg) + indomethacin (D) and (E) only-indomethacin

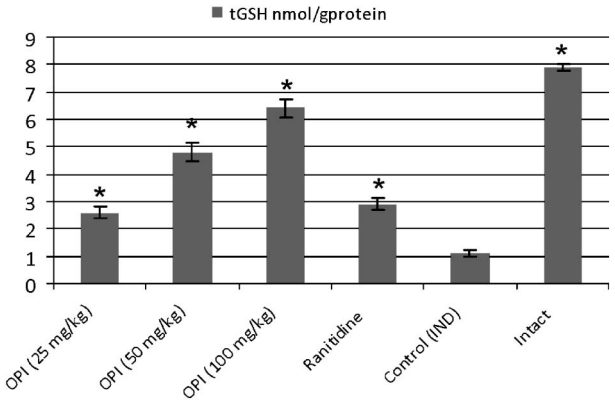

Fig. 2. Effects of Opipramol and Ranitidine on Total GSH Levels in the Stomach Tissues of Rats Given Indomethacin

*Significant at $p<0.05$. Opipramol (25, 50 and 100 mg/kg) and ranitidine (25 mg/kg) were administered to 24-h fasted rat groups by oral gavage. Five minutes after drug administration, all groups received 25 mg/kg indomethacin. Six hours after indomethacin administration, all rat groups were killed and the stomachs of all the rats were removed. Then total GSH content was determined in each stomach tissue. $n=6$ for each group.

nmol/gprotein, 92.3±7.0 U/gprotein and 5504±274 nmol/gprotein, respectively, in healthy intact rat stomach tissue. In rats given 25 mg/kg opipramol,

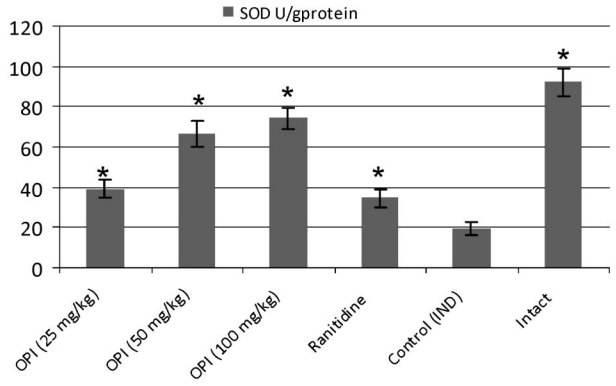

Fig. 3. Effects of Opipramol and Ranitidine on SOD Levels in the Stomach Tissues of Rats Given Indomethacin

*Significant at $p<0.05$. 25, 50 and 100 mg/kg doses of opipramol and a 25 mg/kg dose of ranitidine were administered to rat groups, which were fasted for 24 h. All rat groups received 25 mg/kg indomethacin, five minutes after drug administration. Six hours later, all rat groups were killed and the stomachs of all the rats were excised. The rat stomachs were transferred to biochemistry laboratory for determination of SOD content. $n=6$ for each group.

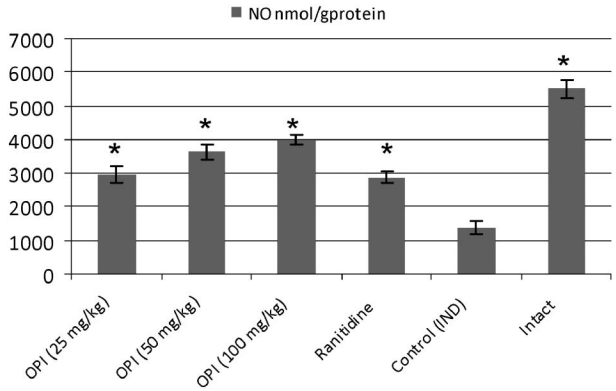

Fig. 4. Effects of Opipramol and Ranitidine on NO Levels in the Stomach Tissues of Rats Given Indomethacin

*Significant at $p<0.05$. Three doses of opipramol (25, 50 and 100 mg/kg) and a dose of ranitidine (25 mg/kg) were administered to 24-h fasted rat groups. 25 mg/kg dose of indomethacin was administered to all rat groups received as ulcerative agent. Six hours after indomethacin administration, all rat groups were killed *via* high dose general anesthetic. The stomachs of all the rats were then removed. Then biochemical investigation was performed for determination of NO content. $n=6$ for each group.

tGSH, SOD and NO levels were 2.6±0.21 nmol/gprotein, 39.2±4.4 U/gprotein, 2950±257 nmol/gprotein, respectively. When the opipramol dosage was increased to 50 mg/kg, these values became 4.8±0.33 nmol/gprotein, 66.3±6.6 U/gprotein and 3642±216 nmol/gprotein, respectively. For a dosage of 100 mg/kg, the values were 6.4±0.36 nmol/gprotein, 74.3±5.1 U/gprotein and 3997±167 nmol/gprotein, while for rats treated with 25 mg/kg ranitidine, the values were 2.9±0.23 nmol/gprotein, 34.5±4.2 U/gprotein and 2875±165 nmol/gprotein, respectively.

Effects of Opipramol and Ranitidine on CAT, MDA and MPO Levels in Indomethacin-given Rat Stomach Tissue While MPO, MDA and CAT levels in stomach tissues were 39.4±1.9 U/gprotein, 196±17.9 μmol/gprotein and 6872±247 k/gprotein, respectively, in the control group given indomethacin only, they were 15.9±1.2 U/gprotein, 42.2±6.2 μmol/gprotein and 3207±162 k/gprotein, respectively, in the untreated control group. MPO, MDA and CAT levels were 29.8±1.8 U/gprotein, 95.2±9.6 μmol/gprotein and 4743±107 k/gprotein for an opipramol dose of 25 mg/kg; 23.5±1.4 U/gprotein, 86.7±5.7 μmol/gprotein and 4059±120 k/gprotein for a 50 mg/kg dose; and 20.4±1.3 U/gprotein, 78.6±5.0 μmol/gprotein and 3968±98 k/gprotein for a 100 mg/kg dosage. These respective values were 28.1±2.6 U/gprotein, 101±3.4 μmol/gprotein and 4922±137 k/gprotein, respectively, in rats given ranitidine (Figs. 5, 6 and 7). When we calculated the dose of opipramol that decreased oxidant parameters by 50% (IC_{50}), we determined that a dose of 100.2 mg/kg opipramol is necessary for 50% inhibition of MPO, while 148 mg/kg is necessary for CAT and 6 mg/kg for MDA (Fig. 8).

***In Vitro* Linoleic Acid Peroxidation Assay** While the absorbance of the blank sample was 1.255±0.003, that was 0.265±0.005 and 0.557±0.036 in 0.8 and 0.4 ml opipramol solution samples. Antioxidant activity was 78.8% and 55.7% for 0.8 and 0.4 ml opipramol solutions respectively. In this

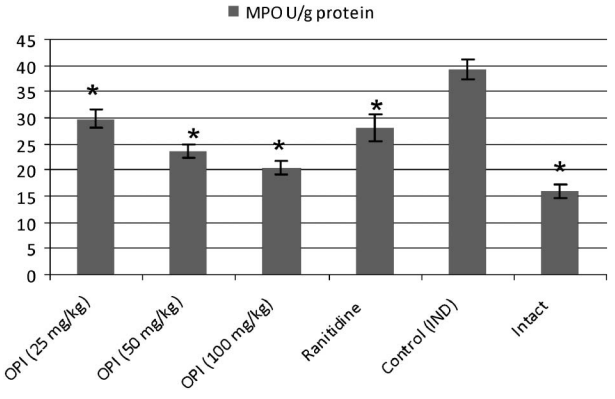

Fig. 5. Effects of Opipramol and Ranitidine on MPO Levels in the Stomach Tissues of Rats Given Indomethacin

*Significant at $p<0.05$. 25, 50 and 100 mg/kg doses of opipramol and a 25 mg/kg dose of ranitidine were administered to 24-hour fasted rat groups by oral gavage. Five minutes after drug administration, all groups received 25 mg/kg indomethacin. Six hours after indomethacin administration, all rat groups were killed and the stomachs of all the rats were then evaluated biochemically for determination of MPO content. $n=6$ for each group.

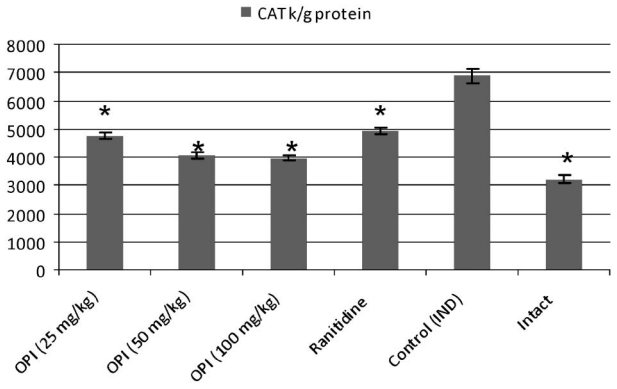

Fig. 6. Effects of Opipramol and Ranitidine on CAT Levels in the Stomach Tissues of Rats Given Indomethacin

*Significant at $p<0.05$. 25, 50 and 100 mg/kg doses of opipramol and a 25 mg/kg dose of ranitidine were administered to 24-h fasted rat groups by oral gavage. 25 mg/kg dose of indomethacin was administered to all rat groups received as ulcerative agent. Stomachs of rats were excised six hours after indomethacin administration. The rat stomachs were evaluated biochemically for determination of CAT content. $n=6$ for each group.

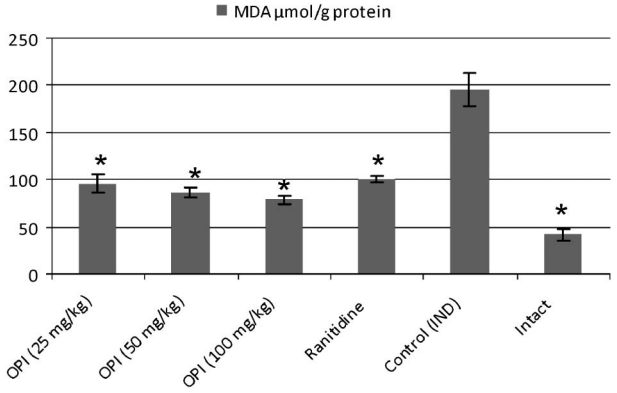

Fig. 7. Effects of Opipramol and Ranitidine on MDA Levels in the Stomach Tissues of Rats Given Indomethacin

*Significant at $p<0.05$. 25, 50 and 100 mg/kg doses of opipramol and a 25 mg/kg dose of ranitidine were administered to 24-h fasted rat groups by oral gavage. Five minutes after drug administration, all groups received 25 mg/kg indomethacin. Six hours after indomethacin administration, all rat groups were killed and the stomachs of all the rats were then evaluated biochemically for determination of MDA content. $n=6$ for each group.

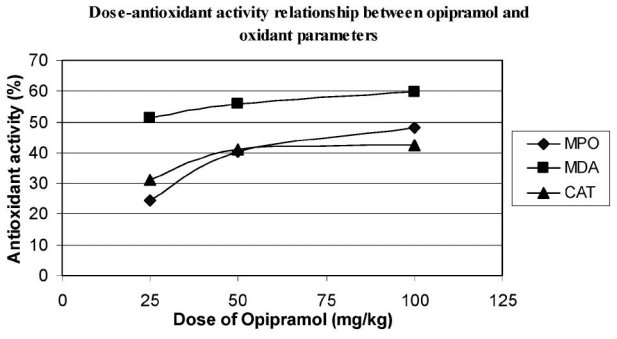

Fig. 8. Dose-antioxidant Activity Relationship between Opipramol and Oxidant Parameters

Antioxidant IC50 values of opipramol MPO, CAT and MDA were determined as 100.2 mg/kg, 148 mg/kg and 6 mg/kg, respectively.

experiment IC_{50} value of opipramol has been determined as 38.6 mM.

DISCUSSION

In this study, the antiulcer activity of opipramol was investigated in rats, using an indomethacin-induced ulcer model, and the effect of opipramol on oxidant and antioxidant parameters in rat stomach tissue was evaluated. Our experimental results showed that opipramol decreased the indomethacin-induced ulcers significantly at all doses, and in a dose-dependent manner. Ranitidine, a strong H_2 receptor antagonist, also inhibited the indomethacin-induced ulcers significantly. For this reason, we used ranitidine as a positive control group in this study and also compared the effectiveness of opipramol with ranitidine as an antiulcer agent. Our results show that 25 mg/kg opipramol was as effective as ranitidine in decreasing stomach ulcers and that 50 and 100 mg/kg doses of opipramol were more effective than ranitidine.

Non-steroidal anti-inflammatory drugs (NSAIDs) are known to produce gastric damage.[28] Indomethacin was shown to produce higher gastric damage in rats when compared to other NSAIDs.[29] It is thought that the ulcerative effect of indomethacin on GIS results from the inhibition of prostaglandin (PG) synthesis.[30]

In many studies, antidepressant drugs, particularly tricyclic antidepressants, have been used to decrease gastric acid secretion and as an ulcer treatment[16,31–33] Eicosanoids have been reported to play an important role in ulcerogenesis in various ulcer models (*e.g.*, indomethacin, ethanol, and cold stress).[32] Inhibition of the cyclooxygenase (COX) enzyme causes excessive production of lypooxygenase (LoAZ) products.[34] Sen *et al*. suggested that amitriptyline's antiulcer effect might be attributable to LoAZ inhibition in indomethacin-induced ulcers, leucotriene (LT) blockade and 5-LoAZ inhibition in ethanol-induced ulcers, and central and peripheral anti-LT activity in cold-stress-induced ulcers.[32] Many experimental studies have shown that antidepressant drugs elicit antiulcer effects by reducing histamine secretion from mast cells, inhibiting gastric acid secretion, and blocking LT (LTC_4, D_4, and E_4) receptors.[32,35] Apart form these factors and mechanisms, other studies have shown that the important primary factor in indomethacin-induced gastric damage is the reactive oxygen species (ROS) mediated lipid peroxidation.[36] Also several antidepressants such as tricyclic antidepressants, tiyaneptine and mirtazapine have been reported to exert antioxidative effect.[16,37,38] The atypical anxiolytic and antidepressive drug, opipramol, is a tricyclic compound with no reuptake-inhibiting properties. However, it has pronounced D2-, 5-HT2-, and H1-blocking potential and a high affinity for sigma receptors (sigma-1 and sigma-2).[39] In early controlled trials, both anxiolytic and antiischemic effects were revealed.[11,39]

Oxidative stress mediated by reactive oxygen species (ROS) has been shown to be the important primary factor in indomethacin-induced gastric damage.[36] Many antioxidant agents, vitamin C, melotonin, montelukast, vegetable oils and alpha-tocopherol etc., have been reported to protect gastric mucosa against indomathacin ulcers.[40–43] Also ranitidine, an antiulcer agent, has been reported to decrease oxidant parameters and increase antioxidant parameters in gastric mucosa.[41,44] Therefore, we investigated the effects of opipramol on GSH, SOD, NO, MPO, MDA and CAT levels in the indomethacin-induced ulcerous stomach tissue of rats, in order to at least partially explain the antiulcer effect of opipramol.

We showed that GSH, SOD and NO levels in the stomach tissue of rats given opipramol prior to indomethacin were statistically higher than were those of the control group that received indomethacin only. In stomach tissue, while decreasing tGSH levels cause gastric damage, increasing tGSH levels produce a gastroprotective effect.[45,46] There was also a parallel between the dose and the opipramol antiulcer effect. Similar results in ulcer studies also appear in the literature.[16,41,44] It is known that GSH is an endogenous antioxidant component. Previous studies have also reported that decreased SOD activity and ROS produce gastric damage in stomach tissue,[47,48] and SOD and other antioxidants are known to be protective against indomethacin-induced damage.[49] The relation between SOD activity and prostaglandin synthesis may be a possible mechanism to explain indomethacin-induced ulcers.[49–51] NO at low concentrations also plays roles in the modulation of the gastric system,[52] protecting the integrity of epithelial tissues by improving mucosal blood flow in the gastrointestinal system (GIS).[53] This protective effect on gastric mucosa is predominantly based on its anti-inflammatory effect, because NO inhibits the activation, ad-

hesion and migration of leucocytes in the inflammatory area.[54] In this study, all of these protective factors were decreased by indomethacin treatment and all doses of opipramol and ranitidine (25 mg/kg) reversed the negative effects of indomethacin. We also studied the *in vitro* antioxidant activity of opipramol in lipid peroxidation assay and found significant antioxidant activity. This result supports the data obtained from stomach tissues.

As reported here, the levels of MPO, MDA and CAT, parameters that are indicators of oxidative stress, were all increased by indomethacin administration. It has been determined that MPO activity increases in NSAID-damaged stomach tissue.[55] MPO is highly concentrated in PMN leucocytes; the activation of neutrophils causes excessive release of radicals such as O_2^-, H_2O_2 and OH^-. As a result of the reaction between these radicals and MPO, products such as hypochlorous acid and N-chloramines are generated, which cause tissue damage.[56,57] All doses of opipramol we used decreased the MPO activity significantly when compared to the control group. It is also known that tissues exposed to oxidative stress, including large amounts of toxic oxygen radicals, induce lipid peroxidation that causes MDA formation.[58,59] Previous studies have also shown that MDA levels increase in damaged gastric tissue.[60] All the doses of opipramol that we used significantly decreased the MDA level when compared to the control group. In our study there was also a significant decrease in the CAT levels of the stomach tissue of rats given opipramol. Many experimental studies have shown CAT activity increases where there is indomethacin-induced stomach damage[15,61] though in some of literatures reported decreased CAT activity in indomethacin administered rats.[47] The difference should be a result of different experimental conditions (day, season, and environment etc.). The CAT enzyme catalyzes the conversion of H_2O_2 to H_2O[62] and as such, an increase in CAT activity in damaged stomach tissue is important in terms of secondarily aiding in gastric protection. Our results and literature reports[47] demonstrate that SOD GSH and MDA would play more important roles for indomethacin treatment.

Although current therapeutic use of tricyclic antidepressants in antiulcer therapy has not been widespread, when compared to the use of classic antiulcer drugs like H_2 blockers and proton pump inhibitors, the results of the present study are indeed thought provoking. The current finding about the possible interaction of opipramol with oxidant and antioxidant parameters prompts a rethinking about the possible clinical application of opipramol, particularly for peptic ulcer patients with depression.

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