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Full Length Research Paper

Comparative effectiveness of *Glycyrrhiza glabra* vs. omeprazole and misoprostol for the treatment of aspirin-induced gastric ulcers

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The aim of the study was to evaluate the comparative effectiveness of *Glycyrrhiza glabra* (liquorice) root decoction vs. omeprazole and misoprostol for the treatment of aspirin-induced gastric ulcers in rats. Animals were randomly assigned first to the "prophylaxis" and "treatment" groups and then to the test and the control groups. Liquorice decoction (25 ml/kg; i.g.); omeprazole (2.3 mg/kg; i.p.) and misoprostol (50 µg/kg; i.g.) were administered for 3 consecutive days 30 min before aspirin (200 mg/kg, i.g.) administration, in the prophylaxis group. In the treatment group, aspirin (200 mg/kg, i.g.) was administered for 3 consecutive days, and then other drugs were administered at the same doses as the prophylaxis group daily for 4 weeks. According to histopathologic evaluation, misoprostol showed significant protection; however, liquorice decoction and omeprazole failed to protect. In the treatment group histopathological examinations showed no significant difference among liquorice decoction, misoprostol and omeprazole regarding aspirin-induced ulcer treatment; ulcers in all treatment groups were completely cured. The results of this study suggest that Glycyrrhiza glabra can be used for the treatment of NSAID-induced ulcers as an inexpensive alternative to misoprostol and omeprazole.

Key words: Aspirin, liquorice, misoprostol, nonsteroidal antiinflammatory drugs induced ulcers, omeprazole.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) possess excellent analgesic, antipyretic and anti-inflammatory effects, and are widely accepted in daily practice for the treatment of arthritis (Dehpour et al., 1994), headache (Wiklund, 1999), joint and muscle discomfort associated with various disorders (Lacy, 2002). Despite their good efficacy, NSAIDs are associated with gastrointestinal (GI) toxicity and gastroduodenal ulcer formation (Saggioro et al., 1991; Wiklund, 1999), which may be accompanied by anemia from the resultant blood loss (Dehpour, 1995). NSAIDs are considered the most important class of drugs which may affect the GI tract; these GI side effects may be seen in 2 - 30% of patients (Handerson et al., 2000). Daily use of NSAIDs significantly increases the risk of ulcer disease 10 - 20 fold (Graham, 1989). 60 - 100% of patients on NSAID therapy for only 1 - 2 weeks develop mucosal hemorrhage and superficial erosions (Raskin et al., 1999). Currently misoprostol is an accepted agent indicated for preventing NSAID-induced gastric ulceration (Handerson et al., 2000). On the basis of efficacy, safety and costs prescription of a proton pump inhibitor appears to be a good alternative to prostaglandin analogue (Handerson et al., 2002). In general, the superiority of the proton pump inhibitor omeprazole over ranitidine and misoprostol, in preventing and healing NSAID-associated peptic ulcers was documented (Raskin, 1999; Wiklund, 1999). In traditional medicine, extracts of *Glycyrrhiza glabra* (liquorice, family: Leguminosa) have been used in the treatment of peptic ulcer for many years; also it is used as the basis of antiulcer therapy in tradition medicine (Fukai et al., 2002; Dhingra et al., 2004). Glycyrrhetic acid (enoxolone), account for its antiulcer activity by inhibiting 15-hydroxyprostaglandin dehydro-

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genase and Δ13- prostaglandin (PG) reductase. Inhibitions of these two enzymes stimulate an increase in the concentration of prostaglandins E and F2α in the stomach which thus promotes the healing of peptic ulcers (WHO, 2002).

Carbenoxolone, which is a semisynthetic ester of glycyrrhetic acid (Doyle et al., 2001) has been used clinically for years in the treatment of gastric and duodenal ulcers (WHO, 2002); it is considered to have a PG-like cytoprotective effect on gastric mucosa (Dehpour et al., 1995). It acts by increasing the life span of gastric epithelial cells, increasing mucus production, decreasing hydrogen ion back-diffusion, inhibiting peptic activity, and stimulating immunoreactive secretin production (Garnett et al., 1993; Dehpour et al., 1994). Carbenoxolone, which has been shown to inhibit prostaglandin inactivation, at the same concentration only slightly, inhibited (about 20%) prostaglandin synthesis (Peskar et al., 1977).

Although the anti-ulcer effect of liquorice extract is well-established, there are no studies evaluating this effectiveness in comparison with omeprazole or misoprostol. Therefore, for the possibility of identifying an effective, inexpensive agent with few side effects in order to prevent and treat NSAID-induced ulcers, this study was conducted to compare the effect of *G. glabra* root decoction with those of omeprazole and misoprostol in rats.

MATERIALS AND METHODS

Animals

Wistar albino rats of both genders, approximately of the same age and weighing 200 - 300 g were obtained from Marmara University, Experimental Research and Animal Laboratory. The experimental animals were maintained under standard laboratory conditions with alternating light and dark cycles of 12 h each. During the study they were allowed to take standard laboratory pellets and tap water ad libitum and were housed in suitable and adequate conditions that fulfill the animal house instructions. The experimental protocol was approved by Marmara University, Faculty of Medicine Experimental Research Ethics Committee (Reg. No. 03.2004.mar).

Drugs

Liquorice (*G. glabra*) root was purchased from a local herbal store. The plant was identified by a pharmacognosy professor. The voucher specimens are stored at Marmara University Pharmacognosy Laboratory. Aspirin (Atabay Drug Company, Turkey), misoprostol (Ali Raif Drug Company, Turkey) and omeprazole (Astra Drug Company, Turkey) were used as comparative agents.

Preparation of liquorice decoction

The dose of liquorice root was chosen depending on the literature. Morgan et al. showed that deglycyrrhizinized extract of the dried liquorice root, administered by gastric intubation to rats at a dose of 2.0 g/kg was active against aspirin-and bile-induced ulcers (Morgan et al., 1983). Deglycyrrhinized liquorice and liquorice with 15% glycyrrhizinic acid added showed the same effect (Ross 1999). On the other hand, hot water extract of the dried root administered by gastric intubation to mice at a dose of 1.589 g/kg was found to be inactive on stress-induced ulcers (Yamazaki and Shirota, 1981). So, we chose a similar dose (2.5 g/kg) and prepared our decocotion in the appropriate concentration needed to reach this dose. Five grams of finely chopped dried liquorice root was soaked in 100 mL of distilled water and boiled for about 30 min to 50 mL. After boiling, the preparation was let steep for 10 min and then filtered into a clean container.

The concentration of the final solution was 100 mg/mL. The decoction was prepared using a relatively longer extraction time (30 min) and a cooling time of 10 min, as recommended by the Soviet pharmacopoeia (USSR State Pharmacopoeia 1987). The freshly prepared (Hanrahan, 2001) decoction of liquorice root (100 mg/mL) was given to the rats in aliquots of 25 mL/kg by intragastric route, corresponding to a dose of 2.5 g/kg.

Vehicle

The liquorice decoction was prepared with distilled water. Aspirin was dissolved in 0.2 M HCl (1.5 mL for each 100 mg of drug). Omeprazole was dissolved in its specific solvent solution ready for injection (Stewart et al., 1987; Kastrup et al., 1998). Misoprostol was dissolved in a sufficient amount of distilled water.

Aspirin-induced gastric ulcer formation

Gastric ulcerations were induced according to the method of Asano et al. (1990) by intragastric (i.g.) aspirin (200 mg/kg) administration for 3 consecutive days. Experiments were initiated following a 24 h fasting with water *ad libitum*.

Experimental groups: Animals were randomly assigned to the “prophylaxis” and “treatment” groups. Then the rats were assigned to the test and the control groups by a second randomization. The study was carried on the following groups:

Prophylaxis groups:

Pro-A (n = 5): Saline [0.9%NaCl] (0.5 ml; i.g.) was administered for 3 consecutive days 30 minutes before aspirin administration.

Pro-AL (n = 5): Liquorice decoction (2.5 g/kg; i.g.) was administered for 3 consecutive days 30 minutes before aspirin administration.

Pro-AO (n = 5): Omeprazole (2.3 mg/kg; i.p.) was injected for 3 consecutive days 30 minutes before aspirin administration.

Pro-AM (n = 5): Misoprostol (50 µg/kg; i.g.) was administered for 3 consecutive days 30 min before aspirin administration.

Treatment groups:

Tre-A (n = 5): Saline [0.9%NaCl] (0.5 ml; i.g.) was administered for 4 weeks after 3-days aspirin administration.

Tre-AL (n = 5): Liquorice decoction (2.5 g/kg; i.g.) was administered for 4 weeks after 3-days aspirin administration.

Tre-AO (n = 5): Omeprazole (2.3 mg/kg; i.p.) was injected for 4 weeks after 3-days aspirin administration.

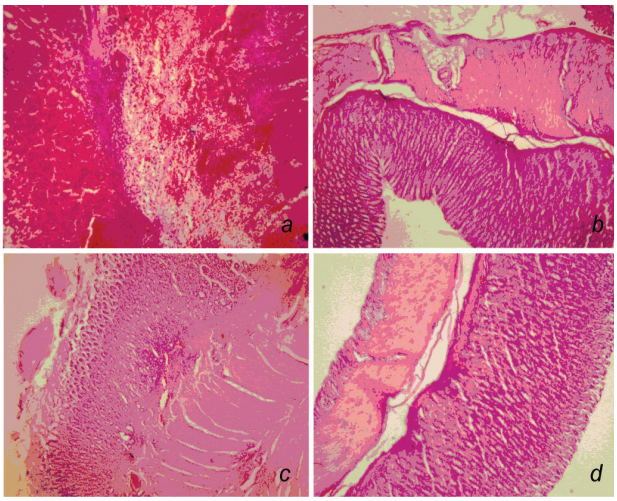

Figure 1. (a) Severe gastric ulcer formation observed in aspirin (200 mg/kg; i.g.) administered rats. (b) Minimal changes observed at the gastric mucose of the misoprostol-treated (50 µg/kg; i.g.) rats in the prophylaxis group. (c) Example of moderate gastric ulcerations observed in the liquorice decoction (25 mL/kg; i.g.) and omeprazole (2.3 mg/kg; i.p.) treated rats in the prophylaxis group. (d) Gastric mucosal view representative of the misoprostol (50 µg/kg; i.g.), liquorice decoction (25 mL/kg; i.g.) and omeprazole (2.3 mg/kg; i.p.) treated rats in the treatment group. Hematoxylin - Eosin staining; original magnifications: x125.

Tre-AM (n = 5): Misoprostol (50 µg/kg; i.g.) was administered for 4 weeks after 3-days aspirin administration.

Tre-L (n = 5): Liquorice decoction (2.5 g/kg; i.g.) was administered for 4 weeks.

Measurement of biochemical parameters

Pre- and post-treatment hematocrit levels were measured for both the prophylaxis and the treatment groups; while serum creatinine, uric acid, potassium, blood urea nitrogen (BUN) and total protein levels were only measured for the treatment groups. All assays were conducted on blood samples obtained from the animals' tail veins.

Histopathological examination

Animals in the prophylaxis group were sacrificed on the 4th and animals in the treatment group were sacrificed on the 30th day of the experiment by lethal dose of ketamine. To assess the gastric lesions produced by aspirin, stomachs of the animals including part of the duodenum were removed by laporatomy (Eastwood et al., 1982). The stomach of each animal was opened along the greater curvature, emptied of its contents, washed with stream water and stored in 10% formalin solution (Bauer et al., 1986; Kuwayama et al., 1991; Segmai et al., 1996). For light microscopic evaluation skin tissue samples were fixed in 10% formaldehyde and processed routinely for embedding in paraffin. Paraffin sections were stained with Hematoxylin and Eosin to indicate histological degeneration (Wang et al., 1989; Kuwayamo et al., 1991). The size of lesions was measured using a light microscope and graded according to the scoring system as described by Schmassmann et al. (1998).

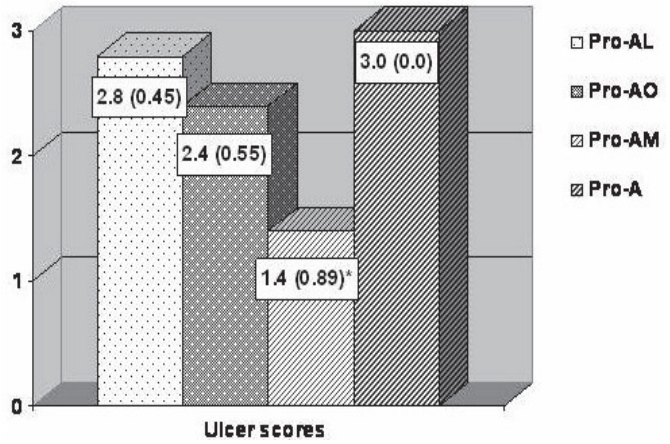

Figure 2. Ulcer scores of different groups in prophylaxis study. Pro-A: aspirin+saline; Pro-AL: aspirin+liquorice; Pro-AM: aspirin+misoprostol; Pro-AO: aspirin+omeprazole; values are expressed as mean (standard deviation); $^{*}p < 0.05$ when compared with controls.

Statistical analysis

The study was conducted on a total of nine groups, each consisting of 5 animals. All results were expressed as mean ± standard deviation (SD). Differences between ulcer scores among groups were analyzed using one-way ANOVA followed by Dunnett's multiple comparison tests as a post-hoc test. A p value <0.05 was considered as statistically significant. The significance of the difference between the pre- and post-treatment values of the hematocrit, serum creatinine, uric acid, potassium, BUN and total protein levels was tested using independent t-test.

RESULTS

Aspirin-induced gastric ulcer formation

Aspirin-induced gastric ulcer formation was confirmed by histopathological examination (Figure 1a).

Prophylaxis group

Control animals received saline [0.9%NaCl] (0.5 ml; i.g.) for 3 consecutive days 30 min before aspirin (200 mg/kg; i.g.) administration. Other groups were compared against the control group. At histopathological examinations, control group had a mean ulcer score of 3.0 ± 00. Rats receiving misoprostol showed a statistically significant protection (ulcer score: 1.4 ± 0.89) when compared with the controls ($p = 0.001$), but liquorice decoction (ulcer score: 2.8 ± 0.45) and omeprazole (ulcer score: 2.4 ± 0.55) did not show a similar significant protection ($p > 0.05$) (Figure 2). Minimal changes were observed at the gastric mucosa of the misoprostol-treated rats in the prophylaxis group (Figure 1b). However, rats in the liquorice decoction and omeprazole groups revealed similar histopathological properties characterized by

Table 1. The pre- and post-treatment hematocrit values of different groups in the prophylaxis study.

Groups	Pre-treatment	Post-treatment
Pro-A (n = 5)	47.16 ± 1.28	45.30 ± 2.33
Pro-AL (n = 5)	48.16 ± 1.32	46.80 ± 1.96
Pro-AO (n = 5)	48.42 ± 2.73	45.72 ± 1.75
Pro-AM (n = 5)	47.04 ± 0.85	46.70 ± 1.03*

Pro-A: aspirin+saline; Pro-AL: aspirin+liquorice; Pro-AM: aspirin+misoprostol; Pro-AO: aspirin + omeprazole; values are expressed as mean ± standard deviation; *p < 0.05 when compared with the pre-treatment value.

moderate gastric ulcerations (Figure 1c).

The pre-treatment hematocrit values were similar for all groups. When the pre-treatment hematocrit values were compared with the post-treatment values, the reduction was found to be statistically significant for the control, omeprazole and liquorice groups (p < 0.05 for all) while it was insignificant for the misoprostol group (p > 0.05) (Table 1).

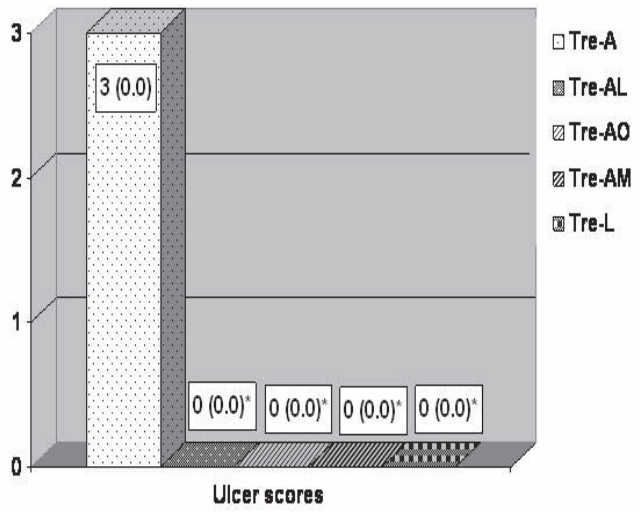

Figure 3. Ulcer scores of different groups at the end of (day 30) treatment. Tre-A: aspirin+saline; Tre-AL: aspirin+liquorice; Tre-AM: aspirin+misoprostol; Tre-AO: aspirin+omeprazole; Tre-L: liquorice; values are expressed as mean (standard deviation); *p < 0.05 when compared with controls.

Treatment group

Control animals received saline [0.9%NaCl] (0.5 ml; i.g.) for 4 weeks after 3 days aspirin (200 mg/kg; i.g.) Administration. At histopathological examinations, control group had a mean ulcer score of 3.0 ± 00. The ulcer scores of other groups (0.00 ± 0.00, for all) were all significantly lower than the score of the control group (p < 0.05) (Figure 3). A gastric mucosal view representative of the misoprostol, liquorice decoction and omeprazole groups was as presented in Figure 1d.

None of the administered agents produced any change in biochemical values, as presented in Table 2.

DISCUSSION

The use of NSAIDs still represents a serious problem due to their side effects, particularly those affecting the GI tract. Despite this fact, NSAIDs are widely accepted in daily practice worldwide. The risks of gastropathy and related death are increased 3 - 10 times in patients who consume NSAIDs (Hawkey et al., 1998). The present study aiming to compare the anti-ulcer effect of liquorice in comparison with omeprazole or misoprostol revealed that *Glycyrrhiza glabra* can be used as an alternative to omeprazole and misoprostol in NSAID-induced ulcer treatment.

The prophylaxis part of this study showed that treatment with liquorice decoction (2.5 g/kg) 30 min before aspirin administration did not prevent aspirin-induced gastric ulcer development. Similar to the present study, Morgan et al. (1983), in their animal study indicated that prior exposure of liquorice component to gastric mucosa did not demonstrate significant protection against gastric defect produced by aspirin administration. They suggest that this result was related to the delay in absorption and distribution of liquorice or its rapid passage through the stomach. This was supported by pharmacokinetic studies showing that the time required for a maximum concentration (Tmax) in plasma after oral administration of aqueous solution of licorice root extract (at a glycyrrhizin-based dose of 6276 mg/kg) to rats was 12 h (Cantelli-Forti et al., 1994). Ozaki et al. (1990) reported a similar Tmax (8 hr) in rats after administration of liquorice extract (Ozaki et al. 1990).

Dehpour et al. (1994), in their animal study examined and evaluated the ability of liquorice and its derivates to protect gastric mucosa against aspirin-induced gastric lesions. Aspirin was coated with liquorice or its derivates and given orally to the animals; the findings showed that liquorice successfully reduced the ratio of gastric ulcer from 96 - 46% and from 96% to 62 - 76% when coated with derivates (Dehpour et al., 1994).

The treatment part of this study showed that aspirin-induced gastric ulcers treated by intragastric liquorice for 4 weeks, were completely cured. Similar effects were seen when treatment was performed with misoprostol and omeprazole. The present results were supported by results of similar studies in the literature. In a study by Bianch et al. (1985) 66 patients with gastric ulcer were admitted to the study to receive pirenzepine 50 mg three times a day (tid) for 6 weeks, carbenoxolone (a component of liquorice) 100 mg/day for 1 week followed by 50 mg tid for the remaining 5 weeks. At the end of the study finally they found that 59% of patients receiving pirenzepine treatment and 52% of patients receiving

Table 2. The pre- and post-treatment values of biochemical values of different groups in the treatment study.

Serum parameters	Time	Tre-A (n = 5)	Tre-AO (n = 5)	Tre-AM (n = 5)	Tre-AL (n = 5)	Tre-L (n = 5)
Creatinine	pre-	0.40 ± 0.00	0.45 ± 0.07	0.40 ± 0.00	0.43 ± 0.05	0.42 ± 0.08
	post-	0.53 ± 0.06	0.50 ± 0.00	0.55 ± 0.07	0.55 ± 0.06	0.52 ± 0.04
Uric acid	pre-	3.40 ± 0.50	3.40 ± 0.57	2.20 ± 0.00	2.48 ± 0.50	2.23 ± 0.42
	post-	2.60 ± 0.61	1.95 ± 0.07	2.25 ± 0.78	2.00 ± 0.37	1.82 ± 0.20
Potassium	pre-	4.43 ± 0.15	4.85 ± 0.50	4.00 ± 0.00	4.30 ± 0.45	5.01 ± 0.97
	post-	4.00 ± 0.44	4.10 ± 0.14	3.45 ± 0.21	3.65 ± 0.26	4.22 ± 0.16
BUN	pre-	12.3 ± 1.2	14.0 ± 2.8	15.0 ± 0.0	16.5 ± 3.3	14.0 ± 1.6
	post-	15.7 ± 1.2	14.5 ± 0.7	14.0 ± 1.4	13.8 ± 2.2	13.2 ± 1.0
Total protein	pre-	6.40 ± 0.20	6.05 ± 0.64	6.30 ± 0.28	6.60 ± 0.39	7.05 ± 0.33
	post-	7.30 ± 0.36	7.85 ± 0.35	7.35 ± 0.21	7.25 ± 0.13	7.28 ± 0.25

BUN: blood urea nitrogen; post-: post-treatment; pre-: pre-treatment; Tre-A: aspirin+saline; Tre-AL: aspirin+liquorice; Tre-AM: aspirin+misoprostol; Tre-AO: aspirin+omeprazole; Tre-L: liquorice; values are expressed as mean±standard deviation.

carbenoxolone were healed. No significant difference was found in healing rates for duodenal ulcers between carbenoxolone and cimetidine when used for short term treatment (Schenk et al., 1980). Similarly, no significant difference was found in ulcer recurrence rates after one year maintenance treatment between Caved-S ® (a commercial preparation contains deglycyrrhizinated liquorice) when compared with cimetidine to treat 100 patients with gastric ulcer (Glick, 1982).

The gastric ulcer healing effects of misoprostol and omeprazole observed in the present study correlated with results of other studies. In the study of Saggioro et al. (1991) the effect of misoprostol was evaluated in patients with osteoarthritis or rheumatoid arthritis consuming NSAIDs. The results showed that misoprostol provided gastroduodenal protection when used in that patient group without interfering with the anti-rheumatic activity of NSAIDs and the treatment was well tolerated by the patients (Saggioro et al. 1991). In an animal study by Okabe et al. (1986) the efficacy of misoprostol in preventing gastroduodenal lesion caused by different noxious agents was evaluated. Their results showed that misoprostol 30 - 100 µg/kg significantly inhibited the development of gastric and duodenal lesions.

Hawkey et al. (1998) studied at 935 patients with ulcers on more than 10 erosions in the stomach or duodenum or both who required continuous treatment with NSAIDs. The patients received omeprazole 20 mg or 40 mg/day and misoprostol 200 µg four times a day. At the end of the study, the results obtained after 8 weeks of treatment showed a healing rate of 76% with omeprazole 20 mg and 75% with omeprazole 40 mg and 71% with misoprostol. A drawback of this study is the lack of dose-response experiments. If the experiment was repeated with different doses, changes in response could have been observed. Another drawback is the lack of experiments on administration of longer and/or more frequent dosing regimens that could have yielded positive results in the prophylaxis part of the study.

Conclusion

As a conclusion, misoprostol was effective in prevention and treatment of aspirin-induced gastric ulcer and was found to be more beneficial than omeprazole and liquorice. Liquorice decoction in the doses used in this study showed a poor protective effect in aspirin-induced gastric ulcers. However, it was significantly effective in the treatment of aspirin-induced gastric ulcers. The results of this study suggest that Glycyrrhiza glabra can be used for the treatment of NSAID-induced ulcers as an inexpensive alternative to misoprostol and omeprazole.

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