DMSO

A NEW APPROACH TO THE TREATMENT OF NONSTEROIDAL ANTI-INFLAMMATORY DRUGS INDUCED GASTRIC BLEEDING BY FREE RADICAL SCAVENGERS

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The effect of the free radical scavengers allopurinol (50 milligrams) and dimethyl sulfoxide (DMSO) (500 milligrams), taken orally four times a day, on the clinical outcome of hematemesis resulting from nonsteroidal anti-inflammatory drugs (NSAID) induced erosive gastritis was examined in a prospective randomized double-blinded controlled trial. In 180 fully evaluable patients with osteoarthritis or rheumatoid arthritis, administration of allopurinol (n=63) or DMSO (n=58) enabled significantly ($p<0.01$) larger numbers of patients to remain hemodynamically stable with no rebleed relative to those in the control group (n=59). The results of endoscopic examination 48 hours after admission demonstrated that gastric erosions were still present in significantly more patients in the control group ($p<0.01$; n=20; 50 percent) than in the allopurinol (n=5; 9 percent) or DMSO (n=4; 7 percent) groups. The radical scavengers also reduced the number of patients requiring blood transfusion because of a rebleed or continued bleeding and emergency operation relative to control values. It is, thus, construed that oxygen derived free radicals mediate the mechanism of NSAID induced erosive gastritis. Scavenging these radicals impairs the gastritis, stimulates healing and protects against the complications of its hemorrhagic episodes. *Surg. Gynecol. Obstet.*, 1992, 175: 484-490.

SEVERAL NONSTEROIDAL anti-inflammatory drugs (NSAID), such as aspirin or indomethacin, are known to irritate the mucosa of the gastrointestinal tract of humans and animals, resulting in bleeding or ulceration, or both (1–5). The irritation ranges in severity from a few small acute ulcers to a situation in which the entire gastric mucosa is inflamed and studded with erosions—erosive gastritis. This gastritis may produce life-threatening bleeding that requires surgical intervention. The mortality rate of the intervention is at least 30 percent (3, 4).

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Oxygen derived free radicals are cytotoxic and promote tissue damage (6–10). These radicals injure cellular membranes, crosslink proteins, lipids and nucleic acids and produce degradation of hyaluronic acid, the principal component of epithelial basement membranes (6, 7). Administration of NSAID inhibits prostaglandin synthesis, an action that may reduce gastric mucosal blood flow (11–13), thereby generating oxygen derived free radicals by converting the native xanthine dehydrogenase to an oxidase (6, 7, 14). The latter enzyme forms superoxide radicals (6, 7, 14). The fact that oxyradicals are directly implicated in the mechanism of tissue injury (6–10, 14) proposes that they may have a role in mediating the gastric mucosal injury produced by NSAID. Therefore, scavengers of oxygen derived free radicals might be beneficial in the treatment of NSAID induced erosive gastritis and in protecting against its complications. The present study was carried out to address this issue.

PATIENTS AND METHODS

Drugs. A 1 percent solution of allopurinol (Burroughs Wellcome Co.) was prepared by dissolving the powder in double distilled water containing the molar equivalent of 0.1 molar of sodium hydroxide. A 10 percent solution of dimethyl sulfoxide (DMSO)—pharmaceutical grade B.P. (Sigma) was prepared by diluting the stock solution with double distilled water. The vehicle solution of allopurinol was given to those patients in the control group. Solutions were placed in identical dark colored glass bottles containing 300 milliliters.

Ethical considerations. The current investigation was approved by the Ethical Committee on Human Experimentation at the hospital and every patient gave written informed consent.

Study design. The present study was a prospective randomized double blinded controlled trial con-

ducted on consecutive patients with rheumatoid arthritis or osteoarthritis who presented to the Medical City in Iraq between March 1979 and October 1981 with hematemesis caused by NSAID induced gastric erosions. Randomization was effected by selecting sealed envelopes. Treatment was begun immediately after the diagnosis was made.

A patient was judged suitable for the study when there was hematemesis within two hours of presentation, no treatment of any form had been received and no clinical signs of shock or any apparent hemodynamic disturbance (pulse rate <100 per minute, systolic blood pressure >100 millimeters of mercury, hemoglobin level >10 grams per deciliter and packed cell volume in men >0.4 and in women, >0.37).

NSAID induced acute gastric mucosal injury (erosive gastritis) was diagnosed when, at endoscopy under sedation, most of the gastric mucosa showed hemorrhagic inflammation (a red colored, deeply congested mucosa) studded with erosions (breaches of the mucosa, regardless of the shape, size, site or number). Patients with hematemesis judged suitable for the study had the history recorded and were physically examined. They were then put on a complete fast, admitted to the hospital and hydrated intravenously. Endoscopy was undertaken within six hours after admission. Once erosive gastritis had been diagnosed, patients were randomized to one of the study groups and allowed fluids and milk (the intravenous line was disconnected soon after these were taken). Standard hematologic and biochemistry measurements and urine examination were performed and repeated daily until the patients were discharged or complications developed. Roentgenologic examination with plain abdominal films was always undertaken to exclude visceral perforation. Patients remaining stable with no further hematemesis underwent endoscopy again 48 hours after commencing treatment (preceded by a complete fast for three hours) to study the integrity of the gastric mucosa. These patients were then allowed to eat solid food. If this food was well tolerated for 24 hours, the treatment ceased and the patients were discharged from the hospital. The return to NSAID was not permitted until a week later. All the endoscopic examinations of the current study were performed by the author.

A central venous line was inserted into patients having clinical signs of shock or hemodynamic disturbance, or both (pulse rate >100 per minute, systolic blood pressure <100 millimeters of mercury, hemoglobin <10 grams per deciliter, packed cell volume <0.4 in men and <0.37 in women and oliguria) and into those having a rebleed. Restoration of the circulating blood volume was attained by blood transfusion and the effectiveness of resuscitation was determined by clinical observations and central venous pressure monitoring.

TABLE I.—EVALUABILITY OF PATIENTS

	Control	*Allopurinol*	*Dimethyl sulfoxide*
Total entered	71	73	72
Fully evaluable	59	63	58
Not evaluable because			
Intolerance	2	2	3
Adverse events	—	2	2
Prohibited drugs used	2	1	3
Noncompliant	8	5	6
Total not evaluable	12	10	14

The decision to abandon conservative management and to undertake emergency operation—vagotomy and antrectomy with under running by suture of any obviously bleeding points—was based on criteria that were exactly applied to control and test patients and included for patients more than 60 years of age: 4 units of blood required within 24 hours to correct acute loss of blood or one rebleed; and for patients less than 60 years of age: 8 units of blood required in 24 hours to correct acute loss of blood or two rebleeds during the same admission. The compliance of patients with the regimen and any adverse reactions to it were carefully monitored on special charts. The end point for the current study when the treatment code was broken was when patients were discharged or when they required insertion of a central venous line.

Recruiting criteria. Patients were not recruited if one or more of the following situations were identified: erosions extending beyond the stomach into the esophagus or duodenum, or both; previous hemorrhage in the upper part of the gastrointestinal tract; previous history of dyspepsia; bleeding diathesis or any hematologic disorders; well-established causes for the development of stress induced acute gastric mucosal injury (trauma, surgical treatment, burns, shock or sepsis); treatment with any form of healing agents for gastrointestinal ulcers during the four weeks before presentation; hiatal herniation; esophageal erosions or ulcers; coexistent or previously noted gastric or duodenal ulceration; visible vessel; spurting vessel or a clot adherent to a vessel seen during endoscopy; previous operation for peptic ulceration; the use, during the month pre-

TABLE II.—PATIENT CHARACTERISTICS

	Control	*Allopurinol*	*Dimethyl sulfoxide*
n	59	63	58
Age, yrs.			
Range	25 to 71	29 to 74	24 to 71
Mean	57	59	56
Males	22	29	25
Females	37	34	33
Smokers	21	25	22
Social drinkers	20	21	24
NSAID indication			
Rheumatoid arthritis	34	34	31
Osteoarthritis	25	29	27
Duration of NSAID therapy			
<3 mos.	45	48	43
3 to 12 mos.	8	7	9
>12 mos.	6	8	6
NSAID used			
Diclofenac	18	19	16
Piroxicam	17	14	13
Mefenamic acid	9	10	12
Naproxen	8	7	5
Ibuprofen	4	6	7
Others	3	7	5

NSAID, Nonsteroidal anti-inflammatory drugs.

ceding the bleeding episode, of corticosteroids, antineoplastic agents, antimalarial agents, gold preparations, multiple NSAID, anticholinergics, phenothiazines or tetracyclines; presence of significant symptoms from other disorders of the gastrointestinal tract that would make it difficult to evaluate efficacy and safety of the trial drugs—for example, severe irritable bowel syndrome; cardiorespiratory problems; hepatic (including cirrhosis) or renal disorders; pregnancy or alcoholism.

Exclusion of patients from efficacy analysis. The exclusion was based on rules that were rigidly applied, including adverse events to the therapeutic regimen, intolerance of this regimen, failure to comply accurately with the regimen and the use of any form of medication, other than the trial regimen, to avoid therapeutic activities of unknown origin. The decision to regard patients nonevaluable for efficacy analysis was made before breaking the treatment code. Additional analyses of intention to treat were performed, including such patients and using various theoretically possible outcomes to examine what influence the exclusion had on the conclusions reached.

The study groups. Two hundred and sixteen consecutive patients presenting with hematemesis caused by NSAID induced erosive gastritis were divided into three groups. In the first group, patients were orally treated with 5 milliliters of the vehicle solution of allopurinol every six hours. In the second group, patients were orally treated with 5 milliliters of 1 percent allopurinol (50 milligrams) every six hours. In the third group, patients were orally treated with 5 milliliters of 10 percent DMSO (500 milligrams) every six hours. All patients were given the same volumes of solutions and were treated for three days unless their conditions deteriorated, as previously stated.

Statistical analysis. A sample size of 150 patients with 50 patients in each group was initially chosen. Based on a two tailed test, such a size will detect a significant difference of 30 percent between active and placebo therapy ($p<0.05$) with a probability rate of 80 percent for the overall sample. Because of the anticipated problems of nonevaluability of some patients, which could weaken any conclusion, the goal was to enter approximately 70 patients in each group. The differences detectable within any subgroup are considerably larger than 30 percent.

The chi-square test with Yates' correction was used to determine the statistical significance ($p< 0.05$) of observed differences in the percentage incidence between the groups and the Mann-Whitney U test for nonparametric data was used to establish the statistical significance of observed differences in mean values among the study groups. Life table analyses with Mantel-Cox (log rank) and Breslow generalized Wilcoxon's statistics were used to evaluate the statistical differences in the results of treatment among the groups. Pairwise comparisons were made between groups, with or without radical scavengers. Cox proportional hazards models were then used to investigate the effect of the radical scavengers on the outcome of treatment, when taking into account the other patient factors as covariates.

RESULTS

Patient characteristics. Seventy-one patients (46 women and 25 men with an age range of 25 to 74 years; mean of 59 years) were randomized to the control group. Seventy-three patients (41 women and 32 men with an age range of 28 to 76 years; mean of 57 years) were randomized to the allopurinol group. Seventy-two patients (40 women and 32 men with an age range of 24 to 71 years; mean of 55 years) were randomized to the DMSoh group. These patients were randomized from 423 patients seen during the study that was conducted during a period of two years and seven months. Twelve patients in the control group, ten patients in the allopurinol group and 14 patients in the DMSO group were excluded

from evaluability (Table I). The characteristics of the remaining patients are presented in Table II and they appear similar among the groups in terms of numbers, age ranges, sex ratio and number of smokers and social drinkers (having no more than 14 units per week—a unit equals one-half a pint of beer, a glass of wine or a standard measure of spirits). None of the patients studied indulged heavily in alcohol consumption, but all drank coffee every day. Both the daily coffee intake and amount of smoking (all cigarettes) were comparable among the groups. Fifteen women in the control group, 11 women in the allopurinol group and 14 women in the DMSO group had taken contraceptive pills during some time period.

Comparison between the groups. No significant differences were noted among the study groups regarding the indication for NSAID, the type of NSAID used or the duration of therapy (Table II). Approximately 10 percent of patients in each of the study groups experienced adverse events—mostly headache, nausea, dyspepsia and abdominal pain. They were sufficiently troublesome, however, and led to withdrawal in two patients given allopurinol and in another two given DMSO. Two patients in the control group, two patients given allopurinol and three patients given DMSO did not tolerate the regimen (Table I). There were no obvious treatment related changes in hematologic or biochemistry values, including hepatic and renal function tests.

Clinical progress. Forty patients in the control group remained stable 48 hours after admission and had no further hematemesis or signs of continued blood loss. The number of patients in the allopurinol group (59) and DMSO group (54) achieving the same outcome was significantly higher ($p<0.01$). The results of the second endoscopic examination demonstrated signs of hemorrhagic inflammation (deeply congested red colored mucosa) in every stomach inspected. However, erosions (multiple breaches in the gastric mucosa) were present in significantly ($p<0.01$) more patients in the control group (20) relative to the allopurinol (five) and DMSO (four) groups. The clinical progress of these patients continued and they were all discharged after three days of hospitalization. Therefore, the number of patients tolerating solid food and then discharged was significantly ($p<0.01$) larger in the allopurinol and DMSoh groups, relative to the control group (Table III).

Nineteen patients in the control group required blood transfusion because of continued blood loss in ten patients and because of a rebleed in nine patients. Two patients given allopurinol required blood transfusion because of continued hemorrhage and another two required transfusion because of a rebleed. In the DMSO group, three patients required blood transfusion for continued bleeding and one patient was given blood because of rebleeding. Emergency operation was necessary in seven patients in the control group who continued to lose blood, in six patients in the control group who had a rebleed, in one patient from each of the allopurinol and DMSO groups who continued to bleed and in one of the patients in the allopurinol group who had rebleeding (Table III). Four patients in the control group died during the immediate postoperative period (two of cardiac arrest, one patient of respiratory failure and one patient of bronchopneumonia), giving an operative mortality rate of 31 percent and an overall group mortality rate of 7 percent.

TABLE III.—CLINICAL PROGRESS

	Control	*Allopurinol*	*Dimethyl sulfoxide*
Number studied	59	63	58
Stable after 48 hours	40 (68)	59 (94)*	54 (93)*
Second endoscopy			
Hemorrhagic inflammation	40	59	54
Erosions	20 (50)	5 (9)*	4 (7)*
Blood transfusion because			
Continued blood loss	10 (17)	2 (3)	3 (5)
Rebleed	9 (15)	2 (3)	1 (2)
Surgical treatment because			
Continued blood loss	7 (12)	1 (2)	1 (2)
Rebleed	6 (10)	1 (2)	—
Return to solid food after 48 hours	40 (68)	59 (94)*	54 (93)*
Discharge from hospital after 3 days	40	59	54

*P<0.01 comparing with the control group.
Numbers in parentheses are percentages.

A series of Cox proportional hazards models was fitted using, as covariates, all factors other than treatment with the radical scavengers to obtain a group of patients and conditions that independently and significantly influence recovery from the hemorrhagic episode. Treatment with allopurinol and DMSO was then added as separate covariates. Age of more than 60 years, a rebleed during the same admission, receipt of blood, continued bleeding after hospitalization and shock had a significantly ($p<0.001$) detrimental effect upon the recovery rate at the 5

percent level. When these and all the other nonsignificant variables were allowed for, treatment with allopurinol or DMSO continued to exert a significantly beneficial effect upon recovery from the hemorrhagic episode ($p<0.01$).

The influence of method of analysis on the clinical progress and recovery from the hemorrhagic episode was studied. Analyses of intention to treat were performed to determine what might have happened if all patients had been evaluable. This required assuming that some patients would have remained stable and experienced no rebleed or continued blood loss while others would have had a further rebleed or continued to lose blood at various time periods.

When all the excluded patients were assumed to have remained stable after admission to the hospital and had no further blood loss or a rebleed or when they were assumed to have deteriorated, treatment with allopurinol and DMSO continued to afford a significant therapeutic advantage ($p<0.01$) in terms of the numbers of patients remaining stable and the recovery from the hemorrhagic episode. This advantage, however, was lost when only the patients excluded from the control group were assumed to have remained stable and to have made a full recovery, whereas all those excluded from the other groups deteriorated because of rebleeding or continued blood loss.

DISCUSSION

The gastrointestinal tract is particularly vulnerable to the adverse effects of NSAID, which can produce damage ranging from acute gastric mucosal injury to a perforating peptic ulcer (1–3). The incidence of the mucosal injury is approximately 30 percent and may increase to 51 percent in patients taking multiple NSAID (2). Inhibition of cyclo-oxygenase by NSAID prevents prostaglandin synthesis, an action that initiates acute gastric mucosal injury (11). Prevention of this synthesis depresses gastric mucosal blood flow and bicarbonate secretion, reduces mucus production and causes atrophy of the gastric epithelium (12). The mucosal defensive properties are thereby impaired, allowing gastric acid to attack the mucosa and to injure it (12, 13).

DMSO and allopurinol scavenge hydroxyl radicals (14, 15) and the latter also inhibits the enzyme xanthine oxidase, which is responsible for the formation of superoxide radicals (14). The use of two radical scavengers instead of just one has several advantages. Results similarly achieved by two different agents are more convincing and attributable to an actual pharmacologic mechanism rather than to a nonspecific action or to an experimental error. Moreover, such similarity at a time when the only action shared between the agents used is scavenging oxygen derived free radicals implicates this action rather than any other one in the mechanism of the effects achieved. The results of the present investigation demonstrate that the radical scavengers used were equally effective in stimulating the healing of acute gastric mucosal injury produced by NSAID and in protecting against the complications associated with the hemorrhagic episodes (Table III). Continued bleeding and a rebleed are among such complications and are particularly serious because they may demand emergency operation, with a mortality rate as high as 30 percent. The similarity in efficacy between allopurinol and DMSoh suggests, on the basis of the aforementioned explanation, that scavenging oxygen derived free radicals was the mechanism by which these agents produced their actions. Therefore, from the results and the knowledge that free radicals are cytotoxic and mediate tissue damage (6–10, 14), it is construed that these radicals are directly implicated in the mechanism of NSAID induced acute gastric mucosal injury and that removing them prevents injury progress and stimulates healing. This last effect is probably achieved by scavenging the deleterious agents causing tissue injury and, thus, providing a more suitable environment for healing. The bleeding produced by erosive gastritis represents the magnitude of mucosal damage and the disruption of its vasculature. By scavenging the agents that seem to cause these adverse mucosal effects, the potential for continued bleeding or for initiating a fresh bleed are minimized because the process of tissue damage is impaired and the natural tendency for repair and healing is, therefore, being enhanced.

The acute inflammatory reaction generated in the gastric mucosa by NSAID is associated with infiltration by neutrophils, which produce oxidative bursts that yield free radicals. DMSO inhibits the function of these cells (16), suggesting that its action on free radicals could have been achieved through prevention of inflammatory cell functions.

The knowledge that allopurinol and DMSO have no known antibiotic effects capable of affecting *Helicobacter pylori*, excludes any actions against this bacterium from being responsible for

the results noted in the present investigation. It might be argued that the criteria for abandoning conservative management and undertaking emergency operation may have been responsible for the high operative rate noted in the present study, in that they were too tight and might have, therefore, denied some patients a successful outcome with conservative management, were it to be continued for a longer period. Although these criteria aimed at striking a balance between earlier intervention before the patient becomes a poor risk for operation when conservative management is unlikely to succeed and a chance for this management to achieve a successful outcome, it must be stressed that they applied to patients who required blood transfusion because of continued hemorrhage or a rebleed. These events may well reflect a more aggressive degree of NSAID induced acute gastric mucosal injury that may prove to be refractory to conservative management and that may, therefore, benefit from earlier operation.

The doses of allopurinol and DMSO were the same as those of another trial (17) in which they had been extracted on the basis of dose response experiments in animals and therapeutic ranges in humans. Among the well-known side effects are that allopurinol may induce hepatic injuries and skin reactions and DMSO may cause hemolysis, dermatitis, neuropathy and encephalopathy. Adverse events, whether or not mild or sufficiently troublesome to lead to withdrawal, occurred in a few patients in each of the active therapy groups (Table I). Furthermore, there were no obvious treatment related changes in hematologic or biochemistry values, including hepatic and renal function tests. These findings illustrate the safety of the radical removing agents when used within the range of their elected doses. It would be, however, an advantage if the daily doses could be reduced, without compromising efficacy.

The compliance of patients with the various regimens was carefully monitored and any infringements led to exclusion (Table I). This compliance was similar among the groups. Therefore, the results cannot be ascribed to differences in patient compliance or to an unintended bias in favor of a particular group, which may influence compliance.

Although DMSO can be detected in the breath, it was never mentioned by any patient as a significant source of inconvenience. Furthermore, it could not be seen as a source of bias in favor of any of the study groups, because the primary parameters of assessment were objective ones (Table III).

The results suggest that oxygen derived free radicals are directly implicated in the mechanism of NSAID induced acute gastric mucosal injury. Scavenging the radicals prevents injury progress, stimulates healing and protects against the complications of its hemorrhagic episodes.

SUMMARY

The current prospective randomized double blinded controlled study investigated the effect of the free radical scavengers allopurinol (50 milligrams taken orally, four times a day) and dimethyl sulfoxide (DMSO, 500 milligrams taken orally, four times a day) on the clinical outcome of hematemesis resulting from NSAID induced erosive gastritis.

In 180 patients with osteoarthritis or rheumatoid arthritis, administration of allopurinol (n= 63) or DMSO (n=58) enabled significantly ($p< 0.01$; chi-square test with Yates' correction) more patients to remain hemodynamically stable with no rebleed relative to controls (n=59). The results of endoscopic examination 48 hours after admission demonstrated that gastric erosions were still present in significantly more patients in the control group ($p<0.01$; n=20; 50 percent) than in the allopurinol (n=5; 9 percent) or DMSO (n=4; 7 percent) groups.

Nineteen controls required blood transfusion because of a rebleed or continued bleeding relative to only four patients in each of the allopurinol and DMSO groups who required the same transfusion ($p<0.01$). Emergency operation was necessary in 13 patients in the control group, in two of the patients in the allopurinol group and in one patient in the DMSO group who were given blood. Four patients in the control group died postoperatively (operative mortality rate of 31 percent; overall group mortality rate of 7 percent).

The results suggest that oxygen derived free radicals are directly implicated in the mechanism of NSAID induced erosive gastritis. Scavenging these radicals impairs the gastritis, stimulates healing and protects against the complications of its hemorrhagic episodes.

REFERENCES

1. Pemberton, R. E., and Strand, L. J. A review of upper gastrointestinal effects of the newer nonsteroidal anti-inflammatory agents. Dig. Dis. Sci., 1979, 24: 53-64.
2. Bijlsma, J. W. J. Treatment of NSAID-induced gastro-

intestinal lesions with cimetidine: an international multicentre collaborative study. Aliment. Pharmacol. Ther., 1988, 2: 85-96.
3. Raimes, S. A., and Venables, C. W. Acute upper gastrointestinal bleeding. Hosp. Update, 1987, 13: 669-684.
4. Snyman, J. H., Wheatley, K. E., and Keighley, M. R. B. Management of non-variceal upper gastrointestinal bleeding. Hosp. Update, 1990, 16: 402-417.
5. Langman, M. J. S. Non-steroidal drug-induced gastric damage. In: Key Developments in Gastroenterology. Edited by P. R. Salmon. Pp. 145-149. New York: John Wiley & Sons Inc., 1988.
6. Butterfield, J. D., and McGraw, C. P. Free radical pathology. Stroke, 1978, 9: 443-445.
7. Del Maestro, R. F., Thaw, H. H., Bjork, J., and others. Free radicals as mediators of tissue injury. Acta Physiol. Scand., 1980, 492: 43-57.
8. Salim, A. S. Role of oxygen-derived free radicals in the mechanism of chronic gastric ulceration in the rat. Implications for cytoprotection. Digestion, 1989, 43: 113-119.
9. Idem. Role of oxygen-derived free radicals in mechanism of acute and chronic duodenal ulceration in the rat. Dig. Dis. Sci., 1990, 35: 73-79.
10. Idem. The significance of removing oxygen-derived free radicals in the treatment of acute and chronic duodenal ulceration in the rat. J. Pharm. Pharmacol., 1990, 42: 64-67.
11. Hogan, D., Thomas, F., and Isenberg, J. A single dose of cimetidine prevents aspirin-induced gastric damage in man. Dig. Dis. Sci., 1986, 31: 481S.
12. Hawkey, C. J., Ramptom, D. S. Prostaglandins and the gastrointestinal mucosa: are they important in its function, disease, or treatment? Gastroenterology, 1985, 89: 1162-1188.
13. Bennett, A., Collins, P., and Tavares, I. Human gastric mucosal damage by anti-inflammatory drugs. Dig. Dis. Sci., 1986, 31: 483S.
14. Itoh, M., and Guth, P. H. Role of oxygen-derived free radicals in hemorrhagic shock-induced gastric lesions in the rat. Gastroenterology, 1985, 88: 1162-1167.
15. Moorhouse, P. C., Grootveld, M., Halliwell, B., and others. Allopurinol and oxypurinol are hydroxyl radical scavengers. FEBS Lett., 1987, 213: 23-28.
16. Beilke, M. A., Collins-Lech, C., and Solnle, P. G. Effects of dimethyl sulfoxide on the oxidative function of human neutrophils. J. Lab. Clin. Med., 1987, 110: 91-96.
17. Salim, A. S. Oxygen-derived free radicals and the prevention of duodenal ulcer relapse: a new approach. Am. J. Med. Sci., 1990, 300: 1-6.