

Oxygen-Derived Free Radical Scavengers: A New Approach to the Problem of Refractory Peptic Ulceration

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Summary

Refractory peptic ulceration refers to ulcers which are slow to heal despite active treatment for at least three months. Oxygen-derived free radicals are cytotoxic and promote tissue injury. Twelve consecutive patients with refractory peptic ulceration (eight with duodenal ulcers and four with solitary pre-pyloric gastric ulcers) were treated using the radical scavengers allopurinol or dimethyl sulphoxide. This treatment was well tolerated by all patients and produced no adverse effects. Endoscopic examination four weeks later demonstrated complete healing (an intact gastric or duodenal mucosa without any breaches) in all patients. The results suggest that oxygen-derived free radicals perpetuate the process of peptic ulceration and exert an adverse effect on healing. Scavengers of these radicals stimulate the healing of refractory gastric and duodenal ulceration.

Key words: Oxygen radicals, Gastric and duodenal ulceration.

Introduction

Oxygen-derived free radicals formed during metabolic activities may readily initiate chain reactions that can damage cellular membranes and release intracellular components, e.g. lysosomal enzymes, leading to further tissue injury, in addition to degradation of hyaluronic acid (the principal component of the epithelial basement membrane) and cross-linking proteins, lipids and nucleic acids¹⁻³. These radicals were shown in experimental animals and in man to be implicated in the mechanism of peptic ulceration, and removing them stimulates ulcer healing⁴⁻⁷.

The term refractory peptic ulceration can be applied to ulcers which fail to heal after three months of cimetidine treatment⁸. Based on initial healing rates alone⁹, some 10% of duodenal ulceration is refractory. The present study was designed to examine the influence of oxygen-derived free radical scavengers on the healing rate of refractory peptic ulceration.

Patients and Methods

The patients studied were 12 consecutive cases of gastric or duodenal ulceration refractory to standard treatment, who were managed by the author at the Medical City in Baghdad, Iraq. These patients were smokers and social drinkers (consuming no more than 14 units per week – a unit equals half a pint of beer, a glass of wine, or a standard measure of spirits) who did not indulge heavily or have any previous history of alcoholism, who drank coffee every day and who initially presented with a

history strongly suggesting peptic ulceration. None had been previously treated for ulceration, however, all patients had a family history of peptic ulcer disease. The cases studied had no history of abdominal surgery; reflux oesophagitis; significant gastrointestinal disorders; recent ingestion of steroids, aspirin, or other nonsteroidal anti-inflammatory drugs; significant cardiorespiratory, renal or hepatic disorders. Prior approval of the Ethical Committee on Human Experimentation at the Hospital was obtained and every patient gave written informed consent. They were then endoscoped under sedation. Eight patients (Table I) had solitary duodenal ulcers larger than 0.5 cm in diameter (but not giant ulcers, i.e. less than 2.5 cm in diameter) situated at the anterior wall of the first part of duodenum. The remaining patients had solitary pre-pyloric gastric ulcers adjacent to the lesser curvature of about 1 cm in diameter. Histological examination, which was repeated every time endoscopy was carried out, showed no evidence of malignancy. Immediately after the diagnosis was made, all patients were urged to quit smoking and drinking alcohol and to reduce their coffee intake. Between the diagnosis and healing of ulceration, none of the patients were given any anticholinergics, potassium tablets, steroids, phenothiazines, antibiotics or nonsteroidal anti-inflammatory drugs.

Table I
Demographic features

Patient	Age (years)	Sex	Duration of ulcer symptoms before treatment (months)
1	22	M	3
2	24	F	4
3	36	M	2
4	29	M	2
5	28	F	4
6	32	M	2
7	23	M	3
8	21	M	4
9	43	F	3
10	48	F	2
11	51	M	2
12	53	M	1

All the patients were smokers and social drinkers

The patients were treated on an out-patient basis. Initially all were given cimetidine tablets (SK and F, Hertfordshire, U.K.), 400 mg twice daily, and advised to chew Maalox antacid tablets (Rorer, Eastbourne, U.K.) (27 mmol acid neutralizing capacity) for pain relief to a maximum of 12 tablets daily. No special dietary regimen was advised. Patients were supplied with special charts to monitor their compliance. The returned medication was inspected and counted prior to each endoscopic examination.

To detect any drug-induced adverse effects, a thorough physical examination coupled with standard haematology and serum biochemistry measurements and urine examination were performed before commencing treatment with radical scavengers and repeated when the ulceration healed.

Results

Three patients with duodenal ulceration (24 year old woman and the 23 and 36 year old men) and two patients with gastric ulceration (48 year old woman and 51 year old man) stopped smoking after they were told of their diagnosis. All the patients stated that they had completely abstained from drinking alcohol and significantly reduced their coffee intake immediately after their peptic ulceration had been detected. In all cases symptomatic relief was rapidly achieved and the use of antacids never extended beyond the first two weeks after commencing treatment with cimetidine. Endoscopy was repeated after six weeks of treatment and none of the ulcers were found to have healed or to have clearly reduced in size, therefore, cimetidine was increased to 800 mg twice daily. When the endoscopic examination was repeated six weeks later, all ulcers were observed to have remained unchanged. At this stage, the ulceration was labelled refractory and 120 mg tripotassium dicitratobismuthate tablets (De-Noltab, Brocades Ltd., Surrey, U.K.) were added to the therapeutic regimen in a dose of 1 tablet four times daily. Endoscopy four weeks later showed no change and therefore the bismuth tablets were replaced by allopurinol (Burroughs Wellcome Co., Research Triangle Park, N.C., U.S.A.), 50 mg orally four times daily, in the 24 year old woman and in the 22, 29 and 36 year old men with duodenal ulceration and in the 43 year old woman and 51 year old man with gastric ulceration and by dimethyl sulphoxide – pharmaceutical grade, B.P. (DMSO) (Sigma, St. Louis, Mo., U.S.A.), 500 mg orally four times daily, in the remaining patients (four cases of duodenal ulceration and two cases of gastric ulceration). When endoscopy was repeated four weeks after treatment with free radical scavengers, all the ulcers were noted to have completely healed (an intact gastric or duodenal mucosa without any breaches).

All the patients were observed to have adhered accurately to their therapeutic regimens. Allopurinol and DMSO were well tolerated and produced no significant drug related side effects or any obvious treatment incurred changes in the haematology or biochemistry values.

Discussion

Duodenal ulceration is caused by an imbalance between the erosive action of acid and pepsin on the one hand and the strength of duodenal mucosa resistance on the other. The weight of experimental and clinical evidence does not support the notion that acid is the primary and all important aetiological factor in the mechanism of this ulceration and proposes within this context a leading role for the integrity of the duodenal mucosa. Detrimental forces may impair the resistance of this mucosa leading to ulceration and thereafter to persistence of ulceration⁵⁻⁸.

Oxygen-derived free radicals may be generated during the development of duodenal ulceration from more than one source. Diffusion of acid into the duodenal mucosa changes its pH value which can then convert the enzyme xanthine dehydrogenase into the superoxide radical generating agent xanthine oxidase, an action that may also be achieved by the acid-induced irritation of the deeper layers of the duodenal mucosa. On the other hand, such an irritation triggers inflammatory cell infiltration and these cells can then generate free radicals by their oxidative bursts^{10,11}. In addition, oxyradicals may be produced by the microscopical injury resulting from acid diffusion into the duodenal mucosa^{10,11}. Recent experiments in the rat suggest that ischaemia of the duodenal mucosa is crucial for the development of acute ulceration of this mucosa^{12,13}. Any degree of tissue hypoxia or frank

ischaemia will initiate the production of oxygen-derived free radicals^{10,11}. Consequently, the duodenal mucosa may be exposed to a large enough dose of oxyradicals capable of injuring it independently or by rendering it susceptible to damage by acid.

Chronic gastric ulceration may occur in the hypersecretor patient where oxyradicals can be produced as outlined above, or develop with normal levels of acid secretion. In the latter circumstance, the aetiology is believed to be persistence of an ischaemic injury of the gastric mucosa⁴, which in turn converts xanthine dehydrogenase into the superoxide radical producing enzyme xanthine oxidase.

On the basis of these observations, it has been proposed that oxygen-derived free radicals are directly implicated in the mechanism of gastric and duodenal ulceration⁴⁻⁷. These radicals are detrimental to the integrity of the gastroduodenal mucosa in that they reduce its resistance to forces tending to breach it, maintain its injury, and impair its healing. It follows that scavenging free radicals stimulates the healing of gastric and duodenal ulceration and protects against their recurrence⁴⁻⁷.

Peptic ulceration failing to heal after three months of active treatment is described as being refractory⁸. In a study on refractory versus non-refractory duodenal ulcers, Bardhan⁹ found that the refractory state may develop any time during the course of ulcer disease but once developed, was usually permanent, and that the refractory ulcer patient tended to be younger, but with a longer ulcer history, to have bled more frequently in the past, to have a family history of ulcer disease, to have a larger ulcer and to have moderate or severe duodenitis. The present investigation studied patients with refractory peptic ulceration of the stomach and duodenum who remained unhealed after three months of active treatment with cimetidine. These patients were recruited because they were smokers and social drinkers, habits which may confer an adverse influence on the healing of peptic ulceration thereby enabling a more accurate assessment of whether oxyradical scavengers actually stimulate the healing of ulceration. Within this context, it is perhaps an advantage that some of the patients studied quit smoking immediately after the diagnosis of peptic ulceration had been made, thus allowing the healing potential of radical scavengers to be studied in the absence of smoking which is known to generate free radicals. This study employed two different scavengers. DMSO is a scavenger of hydroxyl radicals. Allopurinol is also a potent scavenger of these radicals¹⁴ besides inhibiting the enzyme xanthine oxidase, which is responsible for the formation of superoxide radicals³. Obviously results incurred by two agents are more convincing than those exhibited by just one drug. Moreover, similar results obtained by the use of two different medicines which only share one specific mechanism of action supports a role for this mechanism in the results, i.e. free radical scavenging in the healing of refractory ulcers. It follows that oxygen-derived free radicals exhibit a deleterious effect on the integrity of the gastroduodenal mucosa and impair the healing of peptic ulceration.

Although bismuth chelate is a cytoprotective agent which promotes the healing of refractory ulceration⁸, its addition to the cimetidine regimen for one month did not influence healing. Conversely, supplementing cimetidine with radical scavengers resulted in complete healing of both the refractory gastric and duodenal ulceration within four weeks. It might be argued that DMSO and allopurinol produced their actions by other than scavenging radicals.

Since DMSO inhibits the oxidative function of inflammatory cells¹⁵, and such cells infiltrate the neighbourhood of peptic ulceration producing oxidative bursts that yield oxyradicals, the possibility exists that the actions of DMSO against oxyradicals were achieved via inhibition of inflammatory cell functions in addition to scavenging the hydroxyl radicals.

In a series of unpublished observations, it was noted that neither allopurinol nor DMSO exhibit any antibiotic effects against *Helicobacter pylori*, the pathogen implicated in the mechanism of peptic ulceration. The results of the present study cannot, therefore, be interpreted in terms of influences against *H. pylori*. The possibility exists, however, that the role of this pathogen in peptic ulceration is mediated by oxygen-derived free radicals because it causes inflammatory cell infiltration into the gastroduodenal mucosa and these cells generate oxyradicals.

Neither of the radical scavengers employed in this study incurred additional inconveniences or any significant side effects, thus demonstrating their suitability for treating peptic ulceration. A major advantage, however, may be achieved if the number of daily doses could be reduced without compromising efficacy. It must be stressed that although DMSO can be smelt in the breath, this was never a major source of inconvenience to any of the patients.

The results presented suggest that oxygen-derived free radicals are directly involved in the mechanism of refractory peptic ulceration and impair its healing. Scavenging these radicals stimulates the healing of ulceration thereby incurring a significant advantage in the management of a very troublesome condition.

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References

1. Butterfield JD, McGraw CP. Free radical pathology. *Stroke* 1978;9 : 443-445.
2. Del Maestro RF, Thaw HH, Bjork J, Planker M, Arfors KE. Free radicals as mediators of tissue injury. *Acta Physiol Scand* 1980; Suppl. 492 : 43-57.
3. Itoh M, Guth PH. Role of oxygen-derived free radicals in hemorrhagic shock-induced gastric lesions in the rat. *Gastroenterology* 1985;88 : 1162-1167.
4. Salim AS. Role of oxygen-derived free radicals in the mechanism of chronic gastric ulceration in the rat. Implications for cytoprotection. *Digestion* 1989;43 : 113-119.
5. Salim AS. Role of oxygen-derived free radicals in mechanism of acute and chronic duodenal ulceration in the rat. *Dig Dis Sci* 1990;35 : 73-79.
6. Salim AS. 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.
7. Salim AS. Oxygen-derived free radicals and the prevention of duodenal ulcer relapse : a new approach. *Am J Med Sci* 1990;300 : 1-6.
8. Piper DW. The refractory ulcer. *World J Surg* 1987; 11 : 268-273.
9. Bardhan KD. Refractory duodenal ulcer. *Gut* 1984;25 : 711-714.
10. Halliwell B. Tell me about free radicals doctor : a review. *J Roy Soc Med* 1989;82 : 747-752.
11. Sinclair AJ, Barnett AH, Lunec J. Free radicals and antioxidant systems in health and disease. *Br J Hosp Med* 1990;43 : 334-344.
12. Salim AS. Stress, the adrenergic hypothalamovagal pathway, and the aetiology of chronic duodenal ulceration. *J Psychosom Res* 1987;31 : 231-237.
13. Salim AS. Acute gastric mucosal injuries - origin of the stress-induced injury? A review. *Scot Med J* 1990; 35 : 3-8.
14. Moorhouse PC, Grootveld M, Halliwell B, Quinlan JG, Gutteridge JMC. Allopurinol and oxypurinol are hydroxyl radical scavengers. *FEBS Lett* 1987;213 : 23-28.
15. Beilke MA, Collins-Lech C, Solnle PG. Effects of dimethyl sulfoxide on the oxidative function of human neutrophils. *J Lab Clin Med* 1987;110 : 91-96.