REVIEW

PEPTIC ULCER DISEASE AN OVERVIEW OF MANAGEMENT

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The 20th century has witnessed a remarkable rise and fall in the incidence of peptic ulceration. Despite a great deal of improvement in our understanding of the pathophysiology of ulcer disease, we have no convincing explanation for these changes.

The disease has become markedly less common in most Western societies in the last decade, at the same time it is showing a marked increase in the so called developing communities, where it remains a major cause of symptoms which impair the quality of life, cause a substantial drain on the resources and significant cause of both elective and emergency admissions to hospitals.

EPIDEMIOLOGY

It is not understood why approximately 10% of the population suffer from ulceration in the course of their life, nor which events initiate the ulcer[1]. Significant advances have recently been made in the diagnosis, and medical and surgical treatment of the peptic ulcer. Endoscopy has opened the way to accurate diagnosis and it offers an exciting prospect for better assessment and detection of bleeding points, which together with the ability to biopsy the lesion means a greater diagnostic accuracy. Identifying the proper candidate for each treatment modality has become a challenging task, which has indicated an achievement in our struggle to conquer this disease. Safer, more effective and better utilised drugs have been introduced and with it we have seen the emergence of advanced improved surgical therapy.

The prevalence of peptic ulcer disease (PUD) not only varies historically but there also seem to be considerable geographical variations, although there are few reliable data from most countries. The difference may suggest the importance of socio-economic factors in the pathogenesis of PUD which is, for example, more common in the South of India than the North. In Europe, PUD presents a bigger problem in the U.K. than in France or Scandinavia, for instance the annual incidence varies from 132/100,000 in Denmark to 270/100,000 in Scotland in a comparable period of time[2].

AETIOLOGY

PUD is thought to be due to an imbalance between defensive and agressive factors. Defence factors include mucus secretion, bicarbonate and possibly endogenous prostaglandins. Aggressive factors include acid and pepsin. Important factors in the pathogenesis of gastric ulcers are reflux of bile and pancreatic enzymes into the stomach,

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and stasis of gastric contents. Recently however, endogenous prostaglandins as well as prostaglandins in pharmacological doses have been shown to increase mucus and bicarbonate secretions in animals and this may explain why aspirin and non-steroidal inflammatory agents which decrease prostaglandin secretion may predispose to mucosal injury[3].

PUD often occurs in families; Doll and Kellock have convincingly proven that brothers, sisters and fathers of ulcer patients develop the disease significantly more often than matched controls[4]. The analysis of accumulated data has given rise to the impression that a genetic component is certainly involved with PUD, but that the pathogenesis as a whole has to be seen as a multifactorial process. Recent studies have corroborated the hypothesis that genetic influences are involved[5].

It has been proven that subjects with the blood type O have a greater chance of developing PUD, and that people that do not secrete ABH blood group substances to body fluids are also faced with a 50% higher risk. Another approach to the problem has been opened by a newly developed radioimmunoassay method; serum group I pepsinogens are elevated in 2/3 of PUD patients. This special biochemical attribute is probably inherited in an autosomally dominant way[6].

The obvious factor to examine in seeking an environmental cause of ulcer is diet. Knowledge in this regard is fragmentary, basically because it has proved impossible to conduct reliable retrospective case control studies in examining dietary habits. In India and Africa it has been suggested that diets containing a high fibrous residue may be protective but if this is so it is unclear whether such properties are related to the physical characteristics of the diet or to other unknown features[7].

A bacterium, Campylobacter pyloridis has been shown to be associated with PUD. The bacterium is usually present in the gastric antrum and is not found in patients without gastritis or peptic ulceration.

PUD proved to be a more common disease in individuals who had been habitual consumers of coffee and cola-type soft drinks, whilst milk seemed to be protective and no association was noted with tea or alcohol intake[8].

DIAGNOSIS

The diagnosis of PUD is made either by barium meal or endoscopy, and if we are to argue that there is a heirarchy of investigations which may be used, in the rank order: endoscopy, double contrast radiology and single contrast radiology. Each is liable to its own limitations and errors but in the absence of certain diagnostic touchstones for proper comparison, endoscopy still appears to have the edge. This is because of the extension of diagnostic information afforded by direct biopsy[9].

In a small prospective study from Holland the authors concluded that single contrast barium radiology retained a place in the initial investigation of patients with dyspepsia. On balance however, the evidence does suggest that double contrast techniques are more accurate, utilising no more time or resources and should be the radiological method of choice[10].

Upper gastrointestinal endoscopy allows better assessment of ulceration and detection of bleeding points which may be missed in up to 25% of cases on radiological examination. In addition it allows the biopsy of lesions for histological assessment, giving greater diagnostic accuracy, which may reach 90 - 95%. It is particularly essential to biopsy the gastric ulcer, multiple biopsies from the base and edge should be obtained to ensure that a carcinoma is not missed. In addition the process of healing in gastric ulcers is best followed by endoscopy as further biopsies can be taken if healing does not occur, barium studies should also demonstrate the healing of the ulcer. It is easier to follow the healing of duodenal ulcers with endoscopy, as barium studies of the duodenum may remain abnormal even after the ulcer has healed[3]. Gastric acid secretion tests (either basal or in response to histamine, pentagastrin or insulin) are not necessary for the assessment of an uncomplicated duodenal ulcer.

MEDICAL MANAGEMENT

Antacids

The aim of the treatment is to produce symptomatic relief, enhance ulcer healing and prevent relapse. In treating ulcers, the physician faces the dilemma of choosing among many available drugs with equal efficacy, including low dose simple antacids[11]. The principle behind the use of this group of agents is, of course, quite old, and baking soda (sodium bicarbonate) has been a time honoured remedy for ulcer. Significant developments have occured recently, the first of which is the large scale use of liquid aluminium and magnesium hydroxide, which are efficiently utilised, have a prolonged action when given postprandially, and rarely cause complications. Secondly, randomised controlled trials have demonstrated the efficacy of these compounds when they are given as an an intensive regimen (30 ml 1 and 3 hours after each meal and at bedtime)[12].

Calcium antacids may cause rebound hyperacidity, and because of sodium load, sodium bicarbonate should be avoided especially in patients with renal and cardiac insufficiency. The milk-alkali syndrome of high serum calcium leading to renal failure which was associated with the use of sodium bicarbonate and milk diets, is now seldom seen.

Anticholinergics

Among the old group of drugs, anticholinergics remain controversial. Recent study suggests that they have a significant acid-inhibitory action, even in relatively small doses unlikely to be associated with troublesome side effects. Pirenzepine and trimipramine related to the imipramine group of anti-depressants have shown statistical superiority over placebo. Developed in the early 1970's, they have shown ulcer healing properties with negligible toxic adverse effects in human studies, however, like other anticholinergics they should be avoided in patients with acute glaucoma or prostatism.

H2 receptor antagonists

The last decade has seen the development of new drugs for duodenal ulceration and reassessment of the therapeutic value of old ones. The benefit-risk ratio for drugs is becoming better known. The introduction of cimetidine (Tagmet) in the seventies revolutionised the treatment of PUD, since that time ranitidine (Zantac) has been introduced. They both heal 80-90% of ulcers in six weeks. The usual dose of cimetidine is 400 mg twice daily, or 800 mg at night which is more effective. The desirability of a single bedtime dosage is partly due to the convenience and expected improvement in patient compliance, and also to the appropriateness of dosing in relation to the night-time acid secretion which has been shown to be the major pathological factor in ulcer disease[13].

Side effects of cimetidine are seldom a problem. It inhibits the liver enzyme cytochrome P450 and so potentiates the effects of drugs such as warfarin, propranolol or theophylline by increasing their plasma half-lives. A mild anti-androgenic effect may occur causing gynaecomastia or galactorrhoea. Ranitidine on the other hand is remarkably free of side effects, it has only been on the market for four years and its safety, particularly for long term use, needs assessment[14].

On the basis of data from several controlled trials, it can be predicted that therapy with H2 receptor antagonists should heal 80-90% of PUD within 6 weeks as compared with 30-40% in placebo treated patients. It is important to recognise that we are referring to an acceleration of healing, for the natural history of most duodenal ulcers will lead them to resolve spontaneously over a period of weeks or months, even if only to recur again in the future. The clinician and even more so the patient, should care not only about the healing of the crater but also about symptoms, which often abate before the endoscopist determines that the ulcer has healed completely. Many patients can be rendered asymptomatic a few days after beginning an effective medical treatment more rapidly than can placebo treated patients.

Concern has been expressed about the possible carcinogenic effect of long-term inhibition of gastric acid secretion with H2 receptor antagonists. Elevation of gastric luminal pH would favour bacterial overgrowth with consequent conversion of nitrates to nitrites and

hence production of carcinogenic nitrosamines. At this time there is no firm evidence to implicate either cimetidine or ranitidine as human carcinogens and there is no contra indication to their use on those grounds. Experience of both drugs in long-term usage is limited, and they should be prescribed with care and circumspection. Either should heal approximately 80-95% of ulcers after four and eight weeks respectively. With maintenance treatment, the relapse rate for patients with PUD is reduced from 8.5% to 2.5%. Recent trials have suggested that ranitidine treated patients relapse less frequently than cimetidine treated patients. Ranitidine possibly causes a more prolonged decrease in gastric acidity[1].

Gastric ulcerations heal more slowly than duodenal ulcers, therefore, most patients should be treated for eight weeks before endoscopic review to check ulcer healing. In this situation it is better to spread out the doses of the H2 receptor antagonist; i.e. cimetidine 200 mg t.d.s. after meals with 400 mg at bedtime, or ranitidine 150 mg b.d.

PROTECTIVE ULCER COATING AGENTS

Bismuth

Recently protective ulcer coating agents have been introduced and tri-potassium di-citrato bismuthate (TDB) is one agent which seems to function by forming a protective barrier over the ulcer surface. It is of equal efficacy in healing and preventing recurrence of both gastric and duodenal ulcers but some bismuth is absorbed and excreted by the kidneys, hence the drug should be avoided in patients with renal insufficiency, and it is probably unsuitable for long-term maintenance therapy. The drug is usually well tolerated, though it may discolour the teeth and darken the stool, hence it should not be used for long-term treatment[15].

Sucralfate

Sucralfate (antepsin) 1 gm q.i.d. before meals, also speeds healing by an unknown mechanism. It is an aluminium salt of sucrose sulphate, it binds to the ulcer base and prevents acid pepsin bile salts from reaching the ulcer. Complications, except for constipation, are infrequent. Comparison of sucralfate with cimetidine in PUD have yielded very similar results with either drug, after four and eight weeks of treatment[16].

MUCOSAL STRENGTHENING AGENTS

Carbenoxolone (biogastrone, duogastrone) has proved efficacy in the treatment of gastric and duodenal ulcers, possibly by an effect on mucus production. It is now much less frequently used because of salt and water retention and hypokalaemia, hence it is unsuitable for patients with cardiac or renal insufficiency.

NEW DRUGS

New drugs have been developed which cause profound inhibition of gastric acid secretion, and an associated rise of plasma gastrin concentration. Potentially the most exciting new drug is omeprazole which acts by blocking the H+—K adenosine triphosphatase in the parietal cell, which is believed to be the gastric acid "pump". Single doses of 60-80 mg completely eradicate pentagastrin and meal stimulated acid secretion for two to four days in humans, but it has not had extensive clinical trials, and its toxicity is unknown[17]. Omeprazole has proven beneficial for most patients with Zollinger-Ellison syndrome, who are refractory to H2 antagonists[18]. Prostaglandin analogues appear to have a cytoprotective action, independent of its ability to inhibit gastric secretion. New histamine H2 receptor antagonists (famotidine, nizatidine etinidine and tiotidine) tend to be more potent than cimetidine or ranitidine.

RELAPSING AND RECURRENT ULCERS

Peptic ulcer is a relapsing disease with an annual symptomatic relapse rate of 14%. Patients with three to four relapses per year should have a course of treatment for each episode. Patients with few and only short symptom-free periods should be considered for long-term maintenance therapy. The maintenance dose of cimetidine is 400-800 mg at night and ranitidine 150-300 mg at night. After six to twelve months, withdrawal may be attempted. Continued long-term treatment is advisable for patients with severe cardio-

'respiratory disease and others in whom surgery should be avoided.

Nevertheless, all ulcers are not equally responsive to medical treatment, some patients improve very rapidly whereas, as indicated earlier, others fail to show healing even after eight weeks of intensive therapy. Of this 15-20% of patients, most will eventually respond if the treatment is prolonged. In some patients a change of treatment may be beneficial, such as switching to tri-potassium di-citrato bismuthate. Overall results of the trials showed that TDB healed 85% of H2 blocker resistant duodenal ulcers. Other possible treatments include combinations of sulcralfate with an H2 blocker and pirenzepine with an H2 blocker.

FAILURE TO HEAL

An undetermined number of patients appear to be truly refractory to medical therapy, and more studies need to be carried out to determine why they are so refractory and how their resistance to treatment may be overcome. Further investigation with endoscopy must be carried out to confirm the presence of active ulceration. If an ulcer is identified biopsies should be taken to rule out duodenal lymphoma, tuberculosis, tumour eroding through from the pancreas, or the rare occurrence of Crohn's disease. Finally the patients fasting plasma gastrin concentration should be measured, and acid output studies must be performed to exclude Zollinger-Ellison syndrome.

SURGERY

Surgical management should be reserved for those PUD patients who have a continuing haemorrhage, perforation or pyloric stenoses. Other indications are frequent and symptomatic relapse of ulceration uncontrolled by medication, and repeated relapse after treatment is stopped or whilst on maintenance therapy. The indications for surgery on gastric ulceration are the same, furthermore, if gastric carcinoma cannot be excluded, operation is advisable.

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