Deaths from peptic ulceration

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Abstract

Deaths due to peptic ulceration can be prevented only by curing the ulcer and preventing the ulcer diathesis permanently by either medical or surgical means. Recurrence of ulcers after drug treatment is a major problem, so continuous treatment is often necessary, but there is no evidence that this decreases mortality. Surgery is the only means of permanently removing the ulcer diathesis in most patients, and subsequent mortality is low. A reasonable balance has to be achieved between the two kinds of treatment to prevent most deaths from peptic ulcer.

Introduction

We should not be complacent about peptic ulceration, which accounted for 4259 deaths in England and Wales in 1983.¹ Eleven thousand people die each year of carcinoma of the stomach and a similar number of carcinoma of the breast, while 5000 die of cancer of the pancreas. Thus peptic ulcer remains in the league table of major killers but with one fundamental difference from these other disorders in that some deaths from peptic ulcer are potentially preventable, whereas malignant neoplasms of the bronchus and upper gastrointestinal tract carry little hope of long term or improved survival in the foreseeable future.

Preventing deaths

How can we prevent deaths from peptic ulceration? Ninety five per cent of such deaths occur in patients over the age of 55,¹ the mean age at death for men being 69 and for women 74.² Duodenal ulcers, once established, run a lifelong course of exacerbations and remissions with spontaneous healing in all but a small proportion of patients.³ Both men and women over the age of 50 with duodenal ulcers run a 25% risk of major haemorrhage during the next decade of their life.⁴ Of those who bleed, two thirds will rebleed. The corresponding figures during the same decade of life for perforation are 9% and 7% for men and women, respectively. The mortality from bleeding (10%) is the same today as it has been throughout this century.^{5,6} and perforation also carries at least this mortality.^{7,8} These complications account for the deaths associated with peptic ulceration.

The only way in which we can prevent these deaths is by curing the ulcer and preventing the ulcer diathesis permanently. This could be achieved by either medical or surgical means. About 75% of ulcers heal with a one month course of H₂ receptor blocking agents, and a two month course will heal 90%.⁹ The healing rate at four to six weeks in patients treated with placebo is 43%.¹⁰⁻¹⁴ Most of these patients will develop recurrent ulceration within six months to a year after stopping treatment¹⁵⁻¹⁷; indeed, immediately treatment is stopped secretion of acid returns to pretreatment levels as the vagus nerve, parietal cell mass, and G cell mass remain intact. Current antiulcer drugs can partially interrupt the clinical course of ulcer disease, but only as long as they are given in adequate dosage. Prolonging treatment for up to two years does not confer any subsequent long term benefit.¹¹ We do not know how efficient these drugs are over a period of 10 years, but continuous treatment, or at least continuous maintenance treatment, without respite would seem to be essential to prevent recurrence. After the second or third course of cimetidine subsequent courses seem to be less effective at controlling symptoms, though non-compliance is almost certainly a factor in this.¹⁸

A recent study of maintenance treatment taken at night found that at one year the rate of relapse was between 23% and 37% with H₂ receptor antagonists.¹⁹ It has been estimated, using a mathematical model, that the rate of recurrence is 2.5% a month during maintenance treatment and 8.5% a month after treatment is stopped.^{18,20} With these rates of recurrence most patients would still be at risk even if maintenance treatment was continued as the diathesis persists for most of adult life in many patients and fatal complications occur late in life. Furthermore, follow up in existing studies is at best confined to one or two years, as these drugs have been available for only eight years. Changes in the aggression of the diathesis with age and failure to comply with treatment over many years would probably put additional patients at risk of recurrence and its complications. Omeprazole, which blocks adenosine triphosphatase in the parietal cells, healed 41 of 43 ulcers after four weeks' treatment, but within six months one third of the patients had had a proved recurrence with a median time to relapse of 10 weeks.²¹ What, too, of the long term consequence of complete achlorhydria? Although the prevalence of peptic ulceration is declining, the mortality remains constant, and the decline in prevalence preceded the introduction of the H₂ receptor antagonists. There is no evidence that the overall mortality from peptic ulceration has been influenced by these drugs.

What is the cost of long term maintenance treatment? Maintenance treatment with cimetidine (400 mg daily) would cost £1000 a decade and with ranitidine (150 mg daily) £1800.²² We do not know for how long such treatment would be required, but, given that stopping treatment almost inevitably leads to a recurrence of ulcer, many patients would require the drug for three, four, or even more decades. Over such a long period, with rates of recurrence of 2.5% a month being reported,^{18,20} almost all ulcers would recur, at least temporarily, within a period of four years, thus placing a question mark over the efficacy of long term maintenance treatment. Ideally we should strive for a complete cure of the ulcer diathesis, for even if the ulcer is present for only some of the time this renders the patients at risk of potentially fatal complications with increasing age. Therefore we must express more concern towards rates of relapse than towards the rate of spontaneous or drug induced healing, which is almost inevitably intermittent. To alter the long term course of duodenal ulcer disease in any appreciable way requires permanent or persistent reduction in secretion of acid to a level not yet accurately defined.³ While it is true to say "no acid, no ulcer," "no vagus, no ulcer" may be equally true in the absence of the rare Zollinger-Ellison syndrome.

The case for surgery

Surgery offers the only means of permanently removing the ulcer diathesis in most patients, and after highly selective vagotomy 99% of the time will be free of recurrence.²⁰ But what is the risk? Elective surgery for peptic ulcer has become much safer. By 1950 the mortality for gastroenterostomy in 10 274 patients was 3.8% and for gastrectomy in 3710 patients with duodenal ulcer the mortality was 2.8%.²² Truncal vagotomy and antrectomy had a mortality of 1.6% and a rate of recurrence of ulcer of 0.6% in 3584 patients studied between 1946 and 1977,²³ and before 1970 the mortality for truncal vagotomy and drainage was 0.8% in 6490 cases.²⁴

Surgery that preserves the pylorus is safer than its predecessors as well as having a lower morbidity. Johnston reported a mortality of 0.3% after highly selective vagotomy in 5539 cases.²⁵ Half of the deaths were due to abdominal complications, in particular ischaemic necrosis of the lesser curvature, and half were due to non-specific complications of surgery—namely, myocardial infarction (four), pulmonary embolism (three), and pneumonia (two). Rates of recurrence of ulceration of less than 5% at five years have been reported and should be achieved with good operative technique.²⁶⁻²⁸ A modification of highly selective vagotomy, anterior lesser curve seromyotomy with posterior truncal vagotomy, has recently been shown to have a mortality of one (0.16%) in 605 cases and a similarly low morbidity,²⁹ the one death being due to a myocardial infarction that was possibly unrelated to the surgery. There were no cases of ischaemic necrosis of the lesser curvature, dumping did not occur, and diarrhoea was present in only three cases (0.5%). The rate of recurrence of ulcer in Great Britain is currently 2%, though these operations were performed over the past five years, chiefly the past two years. The average duration of stay in hospital was six days, which cost the health service roughly £500 on each occasion. Thus elective surgery for peptic ulcer can be very safe, with a mortality of 0.2% or less, whereas the complications of peptic ulcer (bleeding and perforation) and surgery for them have a

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mortality some 50 times as great. Ninety five per cent of deaths from complications of ulcer occur in patients over the age of 55. Those occurring after elective surgery, however, would generally be in younger people and thus "front load" the mortality equation and increase the loss in life years.

Gear compared highly selective vagotomy with long term maintenance treatment with cimetidine over one to four years in 44 patients.³⁰ The rate of recurrence was 10% after highly selective vagotomy and 54% in the group given cimetidine. Andersen and his colleagues compared highly selective vagotomy performed for recurrence of ulcer after an eight week course of cimetidine with repeated eight week courses of the drug on relapse.^{31 32} After three years the rate of cumulative operations was 74% in the "full dose, stop" group and 60% in the group given repeated cimetidine. When nocturnal maintenance treatment was used after healing and was continued the proportion coming to surgery for recurrence in the three years was still 30%.

According to the Registrar General's figures, about 24 000 new cases of peptic ulcer occur each year, though this is undoubtedly an underestimate. Assuming that the ulcer diathesis of these patients remains with them between the ages of 50 and 60, bleeding would be expected in 6000 of these patients and perforation in 2400 during that decade.^{2 4} There would thus be 600 deaths after haemorrhage and 240 deaths after perforation. Of those who bleed, 4000 would be expected to rebleed, accounting for a further 400 deaths. Reperforation after simple oversewing of the ulcer would occur in 240 patients accounting for a further 24 deaths. The process could be continued, but taken thus far 1264 deaths would have occurred from peptic ulcer. Looked at in this way the figures account for only 29% of all deaths from ulcer, but, as I stated, the Registrar General's figures are a gross underestimate.

What if these 24 000 patients had all presented with symptoms of peptic ulcer before their complications? If they were submitted to elective surgery before the age of 50 (either highly selective vagotomy or anterior lesser curve seromyotomy with posterior truncal vagotomy with an operative mortality of 0.2%) 48 deaths would occur postoperatively. If the prevalence of recurrent ulcer was as high as 10% after surgery to preserve the pylorus and these recurrences were treated by elective truncal vagotomy and antrectomy, with a mortality of 1%, there would be a further 24 deaths and a further 14 ulcers. Thus 72 deaths would occur if all 24 000 patients underwent elective surgery, compared with 1264 if they did not; moreover most of the surgical group would have their ulcers permanently cured. Thus it would seem, using these approximations based on the figures available, that 94% of patients who die from ulcers might be saved by elective surgery before the development of complications of peptic ulceration.

Achieving a balance

The accuracy of these figures will clearly be questioned, for it is impossible to know the exact prevalence of the disorder. Additionally, some patients will develop bleeding or perforation before their ulcer has become manifest clinically. These patients would be expected to have a higher mortality after operation, but if they are treated before the age of 50 this mortality is low. The ulcer diathesis tends, however, to stay with people, and the older they become the more likely they are to suffer a fatal complication. A reasonable balance has to be achieved, as there would be no justification for operating on all chronic peptic ulcers on diagnosis. In my own practice the last 100 patients who underwent elective surgery for ulcer had had a mean duration of symptoms before operation of 10 years, but most were under the age of 50. Perhaps elective surgery should be recommended for those whose ulcer returns after two separate two month courses of an H₂ receptor antagonist; those who have repeatedly relapsed at an early date after stopping treatment;

and those whose symptoms become resistant to H₂ receptor antagonists. The fact remains that surgery offers the only hope of permanently curing the ulcer diathesis and thus preventing deaths from ulcers. Such a policy has the potential to prevent most deaths from peptic ulcer.

References

- Office of Population Censuses and Surveys. *Deaths in England and Wales 1979*. London: HMSO, 1984.
- Bonnevie O. Survival in peptic ulcer. *Gastroenterology* 1978;75:1055-60.
- Hirschowitz BI. Natural history of duodenal ulcer. *Gastroenterology* 1983;85:967-9.
- Pulvertaft CN. Comments on the incidence and natural history of gastric and duodenal ulcer. *Postgrad Med J* 1968;44:507-12.
- Dronfield MW, Atkinson M, Langman MJS. Effects of different operation policies on mortality from bleeding peptic ulcer. *Lancet* 1979;ii:1126-8.
- Hunt PS, Hansky J, Korman MG. Mortality in patients with haematemesis and melaena: a prospective study. *Br Med J* 1979;ii:1238-40.
- Watkins RM, Dennison AR, Collin J. What has happened to perforated peptic ulcer? *Br J Surg* 1984;71:774-6.
- Barker DJP, Power C, Lambert PM, Smith CL. Perforated duodenal ulcer in England and Wales: time trends and regional and urban differences. *Health Trends* 1981;13:13-5.
- Wormsley KG. Duodenal ulcers which do not heal. *Br Med J* 1984;289:1095.
- Semb LS, Berstad A, Myren J, *et al*. A double blind multicentre comparative study of cimetidine and placebo in short term treatment of active duodenal ulceration. In: Burland WL, Simkins MA, eds. *Cimetidine*. Amsterdam: Excerpta Medica, 1977:248-53.
- Bardhan KD, Saul DM, Balmforth GV, *et al*. The effect of cimetidine on duodenal ulceration. In: Burland WL, Simkins MA, eds. *Cimetidine*. Amsterdam: Excerpta Medica, 1977:260-71.
- Northfield TC, Blackwood WS. Controlled clinical trial of cimetidine for duodenal ulcer. In: Burland WL, Simkins MA, eds. *Cimetidine*. Amsterdam: Excerpta Medica, 1977:272-3.
- Albano O, Barbara L, Migoli M, *et al*. Short term cimetidine treatment in duodenal ulcer. Results from a controlled multicentre trial. In: Lucelli PE, ed. *Cimetidine*. Milan: Smith, Kline and French, 1978:149-56.
- Binder HJ, Cocco A, Crossley RJ, *et al*. Cimetidine in the treatment of duodenal ulcer: a multicentre double blind study. *Gastroenterology* 1978;74:380-8.
- Hansky J, Korman MG, Schmidt GT, Stern AJ, Shaw RG. Relapse rates of duodenal ulcer after healing with cimetidine or Mylanta. *Gastroenterology* 1980;78:1179.
- Martin DF, Hollanders D, Ravenscroft MM, Tweedle DEF, Miller JP. Differences in relapse rates of duodenal ulcer after healing with cimetidine or tripotassium dicitrato bismuthate. *Lancet* 1981;ii:7-10.
- Ippoliti A, Elashoff J, Valenzuela J, Cano R, Samhoff M, Koretz R. Recurrent ulcer after successful treatment with cimetidine or antacid. *Gastroenterology* 1983;85:875-80.
- Pounder RE. Model of medical treatment for duodenal ulcer. *Lancet* 1981;ii:29-30.
- Gough KR, Korman MG, Bardhan KD, *et al*. Ranitidine and cimetidine in prevention of duodenal ulcer relapse. *Lancet* 1984;ii:659-62.
- Sonnenberg A. Comparison of different strategies for treatment of duodenal ulcer. *Br Med J* 1985;290:1185-7.
- Cooperative study. Omeprazole in duodenal ulceration: acid inhibition, symptom relief, endoscopic healing, and recurrence. *Br Med J* 1984;289:525-8.
- British Medical Association and The Pharmaceutical Press. *British National Formulary*. No 9. London: British Medical Association and The Pharmaceutical Press, 1985:51-2.
- Sawyers JL, Herrington JL. Vagotomy and antrectomy. In: Nyhus LM, Wastell C, eds. *Surgery of the stomach and duodenum*. 3rd ed. Boston: Little, Brown and Co 1977: 343-65.
- Cox AG, Spencer J, Tinker J. Clinical results reviewed. In: Williams JA, Cox AG, eds. *After vagotomy*. Guildford: Butterworths, 1969:119-30.
- Johnston D. Operative mortality and post operative morbidity of highly selective vagotomy. *Br Med J* 1975;iv:545-7.
- Stoddard CJ, Vassilakis JS, Duthie HL. Highly selective vagotomy or truncal vagotomy and pyloroplasty for chronic duodenal ulcer: a randomised prospective clinical study. *Br J Surg* 1978;65:793-7.
- Goligher JC, Hill GL, Kenny TE, *et al*. Proximal gastric vagotomy without drainage for duodenal ulcer: results after 5-8 years. *Br J Surg* 1978;65:145-51.
- Dorricott NJ, McNeish AR, Williams JA, *et al*. Prospective randomised multicentre trial of proximal gastric vagotomy or truncal vagotomy and antrectomy for chronic duodenal ulcer. *Br J Surg* 1978;65:152-4.
- Taylor TV, Gunn AA, MacLeod DAD, *et al*. Mortality and morbidity after anterior lesser curve seromyotomy with posterior truncal vagotomy for duodenal ulcer. *Br J Surg* (in press).
- Gear MWL. Proximal gastric vagotomy versus long term maintenance treatment with cimetidine for duodenal ulcer. A prospective randomised controlled trial. *Br Med J* 1983;286:98-9.
- Andersen D, Amstrup E, Sorensen FH, Jensen KB. Surgery or cimetidine? I. Comparison of two plans of treatment: operation or repeated cimetidine. *World J Surg* 1983;7:372-7.
- Andersen D, Amstrup E, Sorensen FH, Jensen KB. Surgery or cimetidine? II. Comparison of two plans of treatment: operation or cimetidine as a low maintenance dose. *World J Surg* 1983;7:378-84.

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The effectiveness of tamoxifen in suppressing metastases from carcinoma of the breast suggests that it is logical to treat patients who have had local lumpectomy or more radical breast surgery with tamoxifen as a routine. Is this a reasonable approach to treatment?

This so called adjuvant treatment of breast carcinoma with endocrine therapy is already now under way, and several trials are in progress, most of which are based on tamoxifen. A large multicentre randomised trial in the United Kingdom is showing a considerable survival advantage for patients treated with tamoxifen compared with no treatment controls. Interestingly, this advantage for survival is seen in both premenopausal and postmenopausal patients, and currently it would appear that it is effective whether the

primary tumour has shown oestrogen receptor positivity or no receptors present. The great advantage of tamoxifen over chemotherapy is its lack of side effects and toxicity, and this would appear to be a promising form of adjuvant therapy. Nevertheless, I think caution is required, as the final results in breast cancer cannot be determined until many years have elapsed. For a critical review of controversies in the medical management of breast cancer, I would recommend Smith's article in the *Postgraduate Medical Journal*.¹ A further useful reference appeared in the *Lancet*.²—J MALPAS, professor of medical oncology, London.

- Smith IE. Controversies in the management of breast cancer. *Postgrad Med J* 1985;61:117-22.
- Nolvadex Adjustment Trial Organisation. Analysis at six years. *Lancet* 1985;ii:836-8.