Cost effectiveness of treatment for gastro-oesophageal reflux disease in clinical practice

EDITOR,—I was interested to read the paper by Eggleston et al (Gut 1998;42:13–16) purporting to show that a “step up” approach using prokinetics and H₂ receptor antagonists in the management of gastro-oesophageal reflux disease (GORD) is more cost effective than omeprazole in a general practice setting. I do not think the conclusions drawn are supported by data presented.

The MediPlus database does not permit systematic evaluation of the severity of GORD symptoms and so there is no certainty that the three patient groups (who received omeprazole, ranitidine or cisapride) were comparable. Patients were excluded from the study if they had initially been referred to hospital (<15%) because they were regarded as suffering from “more complicated GORD”. No evidence is presented for this assertion. It is well recognised that there is no correlation between the severity of a patient’s symptoms and the extent of any oesophagitis.¹ The fact that patients on omeprazole received more prescriptions in the six month study period (2.96) than those on cisapride (1.85) is further evidence that the groups were not clinically comparable. Cisapride is known to be relatively ineffective in the treatment of GORD symptoms.

The paper makes no evaluation of clinical success, basing the evaluation entirely on cost with the implicit assumption of equivalence in clinical efficacy between omeprazole, ranitidine and cisapride, which many other controlled studies have shown not to be the case. The conclusions drawn by the authors are all flawed. The authors have provided no evidence that the “stepped approach” is appropriate in GORD. Many studies have confirmed that omeprazole is more cost effective.² The recent reduction in the price of omeprazole makes this cost advantage even greater.

The conclusion, “such chronic dependence on drug therapy appears to be a particular problem with...omeprazole and represents a further argument in favour of a step up approach aimed at initially targeting prescribing of this powerful drug on a highly selected patient group”, is not supported by the evidence from the study nor by references. Moreover, the keenness of patients to take omeprazole is a reflection of its effectiveness. Given the central role of gastric acid in GORD reducing oesophageal exposure to this corrosive agent is a rational approach to the management of this disease. Antacid/alginate combinations provide short lived symptomatic relief. The H₂ receptor antagonists and cisapride have some efficacy in treating GORD but there is now abundant evidence in the literature to show that proton pump inhibitors are the most effective agents in this disease.

Unlike the H₂ receptor antagonists, proton pump inhibition does not suffer from the drawback of tolerance, and omeprazole heals regardless of the grade of oesophagitis on endoscopy. Short term resolution with omeprazole is a better indicator of healing of any underlying oesophagitis than with H₂ receptor antagonists.

In conclusion, treatment with proton pump inhibitors provides cost effective management across the GORD spectrum, resolves patients symptoms, improves their quality of life and reduces the underlying pathology, preventing the development of complications such as stricture, and reducing hospital referrals.

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Cost effectiveness of treatment for gastro-oesophageal reflux disease

EDITOR,—A reading of the recent article by Eggleston et al (Gut 1998;42:13–16) left several unanswered questions and concerns. The first issue was the authors’ statement that clinical equivalence between cisapride, ranitidine, and omeprazole had been established for uncomplicated gastro-oesophageal reflux disease (GORD) by standard practice. To my knowledge, there are no published studies which have reported a similar finding of clinical equivalence of omeprazole to either cisapride or ranitidine. A quick review of the literature revealed 11 studies in which omeprazole was statistically significantly better than cisapride or ranitidine in GORD.1–11

In a review of the reference abstract1 in which the case for clinical equivalence is postulated, the conclusion of equivalence was highly dependent upon the authors’ definition of treatment failure. I take exception to the authors’ definition that use of medication for longer than three months was a failure to achieve adequate symptom control. This does not have the ability to distinguish between continuing a medication in order to maintain successfully achieved symptom resolution and continued use of medication due to uncontrolled persistence of symptoms. Initiation of maintenance therapy after successful symptom resolution would not require any change in dosage in the case of omeprazole as 20 mg once daily is the recommended dose for long-term maintenance. Defining success as any use of medication for less than three months that did not involve a change in drug also opens up the possibility of misclassification. Those patients who stop using a drug as a result of treatment failure and who do not return for further care would not only be misclassified in this retrospective analysis as a success but could erroneously contribute to a lower economic burden in the therapy group. Using these methods, the authors state that case records for a total of 257 patients were evaluated. However, there is a discrepancy between the abstract and the manuscript on the number of eligible patients. The abstract talks about 279 patients and the manuscript refers to 257 patients. Additionally, why do the authors, with a database like MediPlus™ UK, which has more than one million patients, end up with a sample size of only 257 patients?

In the Discussion, the authors state that if more severely affected patients were selectively treated with omeprazole, one would expect to see increased non-drug resource use in this group. Since this did not occur, the authors consider this as supportive evidence that they had effectively controlled for this selection bias. An alternative explanation for the finding is patients taking omeprazole were more severely ill due to physician selection bias but omeprazole has superior clinical efficacy in GORD compared with ranitidine and cisapride thus the omeprazole patients resource utilisation level is a reflection of a severity level that would be the case with any other treatment.

The authors do not state whether the general practitioner (GP) consultations attributed to the drug treatment groups were all specifically for GORD. No information was provided as to how the authors have separated our GORD related GP consultations from visits for other illnesses. Such a process should be accomplished by a reviewer blinded to treatment allocation, if undertaken. The absence of information leads to a conclusion that the amount of GP consultations in table 1 represents visits for all health reasons. As treatment would have had a positive effect on reducing GORD related visits one would expect to see increased non-drug resource use in this group. Since this did not occur, the finding in the result displayed in table 1.

The authors have based their analysis on an assumption of clinical equivalence which, in this case, is beyond the power of retrospective analysis to prove. Even if the three medications were clinically equivalent, there are a number of other unanswered questions from the manuscript that make it difficult for an unqualified acceptance of the authors’ conclusions.

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Reply

EDITOR,—We welcome the quantity and quality of debate generated by our paper and in this response. The paper has fulfilled its principal objective. Many of the issues raised in the resulting correspondence, however, relate to methodological limitations of database analyses that were well rehearsed in the original paper and therefore will not be addressed in detail. For example, we recognise the potential difficulties arising from the randomised nature of the study but feel that restriction is essential in enabling the analysis to reflect reality more accurately. The paper also explicitly acknowledges the potential for selection bias in the choice of drugs and specifically examines its potential implications for the interpretation of the results obtained.

The patient cohorts seemed to be closely similar in both demographic characteristics and gastrointestinal and non-gastrointestinal medical history. In addition, a selection bias would be expected to lead to a greater intensity of health care resource consumption in patients receiving omeprazole. This did not occur and therefore no evidence is available to support the charge of selection bias.

The limitations of the study are difficult if not impossible to overcome with currently available data and should not distract us from the main focus of the study, which was to undertake an initial comparison of the therapeutic strategies available to clinicians in the treatment of mild to moderate GORD. The data contained in the paper is merely used to illustrate the general principles of decision making in this therapeutic area, as in any other, requires an informed and sensitive balance of the costs and benefits arising from each strategy.

The clinical outcomes underlying the cost analysis have been reported in a separate publication and provide the necessary clinical springboard for our analysis. The analysis simply indicates that for this particular group of patients (first episodes of uncomplicated GORD) the hypothesis of short term outcome equivalence in practice was not disproved by the clinical database analysis. Evaluating long term comparative outcome in practice would require a modelling approach that evaluated in detail quality of life and clinical outcomes together with the long term pattern of resource use for patients following different therapeutic strategies. An extensive and growing literature exists to inform such a model and research in this area is currently under development.

The basis for a clinician’s choice between cisapride, ranitidine and omeprazole in a study, as in all others, unknown given the complex array of factors determining such a choice. It is specifically because of such complex influences, which are not captured in randomised clinical trials, that analyses of prescribing in practice are so important, given that they implicitly incorporate the myriad of factors that influence real life prescribing behaviour. It is important, however, to recognise that evidence generated from clinical trials and observational studies of this nature should be perceived as being mutually supportive in generating evidence to guide clinical decision making. Obviously the same data cannot give rise to conflicting interpretations and we are not, necessarily, providing the only possible interpretation of the information generated.

The Nijmegen group question the “inappropriate” use of the term “cost effectiveness analysis” which is often used to refer to all forms of economic evaluation. The term, however, more properly refers to a particular type of evaluation in which costs are defined and measured in natural units and
costs are measured in monetary terms. Our analysis is structured in a manner that facilitates a direct comparison of the costs per patient relieved of symptoms. Such a structure enables outcome variations to be directly related to cost, and further research concerning the long-term cost and outcome of treatment is clearly of great importance.

The Nijmegen group’s reference to “effect modification” and its potential effect of diluting variations between the therapeutic options is irrelevant in the context of our paper. The case for good prescribing is to some extent general population patients to ensure that the therapeutic requirements of individual patients are optimally met by the prescriber. Obviously, in their day to day workload primary care physicians also frequently encounter patients with recurrent GORD as well as with H₂ refractory and complicated GORD. Cost effectiveness calculations on “undefined GORD” would inevitably favour omeprazole given that it causes the greatest suppression of acid secretion in patients with severe disease. We make no claims concerning the applicability of the analysis to undefined GORD but simply assert that the extent of acid suppression generated by omeprazole may not be necessary for first episodes of uncomplicated GORD. If this is the case, then hard pressed clinicians will be able to conserve their scarce health care resources for investment elsewhere.

Dr Crawley questions the numerical basis for the analysis. Our sample was generated as a random selection from the entire eligible MediPlus database for 1995 using the software random number based sample selection function. The sample chosen was selected on the basis of manageability given that an individual review of each patient record was required. The reduction from 279 to 257 patients was simply to increase the level of patient homogeneity as outlined in the original paper. Both Crawley and Bate also refer to a large body of evidence supporting the clinical and economic superiority of omeprazole. Unfortunately, for our purposes the vast majority of such evidence is irrelevant given that it does not specifically analyse prescribing in practice for new patients referred at the primary care level with mild to moderate GORD. Dr Crawley’s belief in the superiority of omeprazole due to the lack of need for dose titration is puzzling. The British National Formulary’s recommendation for GORD is for 20 mg daily for four weeks, followed by 40 mg for four to eight weeks as required, reduced to 10 mg for long term management, increased to 20 mg if symptoms recur. Dr Crawley’s further belief that patients may respond to treatment failure by simply doing nothing also is difficult to substantiate. It is reasonable to assume that individual patients exhibit a personal threshold of tolerance to the symptoms of GORD above which they seek professional advice. Such a threshold will vary significantly between patients but is likely to be fairly stable within the same patient. In such circumstances it is difficult to see why a patient would not seek further professional advice in cases where the initial prescription did not reduce symptomatology below their personal threshold.

Table 1 Consumption of NSAIDs by patients with drug induced hepatic injury and two control populations

<table>
<thead>
<tr>
<th>Patients with drug induced hepatitis</th>
<th>Patients admitted to hospital</th>
<th>Population of a health centre</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases</td>
<td>136</td>
<td>1723</td>
</tr>
<tr>
<td>Mean age</td>
<td>46.7</td>
<td>44.6</td>
</tr>
<tr>
<td>Number taking NSAIDs</td>
<td>43</td>
<td>206</td>
</tr>
<tr>
<td>Percentage</td>
<td>32</td>
<td>14</td>
</tr>
</tbody>
</table>

* Took NSAID in the 15 days prior to admission.
has to be viewed with caution. In fact, it has been shown that prostaglandin E₂ has a protective effect in cases of hepatitis induced by hepatotoxic agents and cytotoxic viruses, both in animal models and in humans,

suggesting that a non-immunological mechanism may also be involved in this association.

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Guidance for trials in Helicobacter pylori infection

Editor,—Your prestigious journal has recently published a supplement on guidelines for clinical trials in Helicobacter pylori infection (Gut 1997;41(suppl 2):S1–23). We welcome these guidelines, and as it would be expected from the authors’ experience, would be valuable to decide the three different criteria published in the supplement. There are, however, at least two key points that merit discussion before these guidelines are generally applied by the scientific community.

Firstly, a methodological point. Double blind, randomised, controlled, well planned and developed trials do provide very sound and solid scientific evidence for evaluating efficacy. However, other types of trials, even uncontrolled, can give very valuable data on effectiveness, and cannot be discarded as long as methods and analysis are correct. In fact, some of the most cited articles are uncontrolled but very elegant studies and some are only pilot reports. Sometime other methodological rules are avoided but good science is produced.

Secondly, an ethical point. In the guideline the following sentence is included, “In phase III studies, aiming at regulatory approval of a new drug regimen, one of the reference groups should be given a treatment known to result in no eradication of H pylori...” This assertion is clearly in conflict with the Declaration of Helsinki states, “In any medical study, every patient—including those of a control group, if any—should be assured of the best proven diagnostic and therapeutic method”. If prospective study subjects have peptic ulcer disease, current recommendations are mandatory: H pylori should be eradicated. In fact, the same group of authors have very recently stated in Gut that, “...H pylori eradication is strongly recommended in all infected patients with a diagnosis of duodenal or gastric ulcer disease, past or present...”, a sentence based on “unequivocal supporting evidence”. I think that patients should come first and methodology second, and strongly suggest that this sentence should be removed from the guidelines, or at least limited to pathologies with “equivocal” evidence such as functional dyspepsia.

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Clinical trials in Helicobacter pylori infection

EDITOR,—We read with great interest the excellent guidelines for clinical trials in Helicobacter pylori infection published last September (Gut 1997;41(suppl 2):S1–23). The recommendations almost without exception, are extremely useful. We feel, however, that one or two points might be expanded, or deserve extra comment.

As the working party states, most of the studies published on eradication therapy are non-comparative or are not large enough to reach a definite conclusion. This is because the sample size required to rule out a 10% difference between treatment groups for a two-branch comparative study is nearly 600 patients. To our knowledge no studies of this size have been published to date and, therefore, the length and composition of ideal eradication therapy has to be determined in large multicentre trials.

To our knowledge no studies of this size have been published to date and, therefore, the length and composition of ideal eradication therapy has to be determined in large multicentre trials.

Figure 1 Predictive value of a positive serological test for H pylori in patients with duodenal ulcer. Positive predictive value = 72/(72+2) × 100 = 97.2%. Patients with a positive serological test are assumed to have a 90% prevalence of H pylori infection. Data have been calculated in their own study and specificity of 80% for the serological test.

Figure 2 Value of a negative UBT to evaluate cure of H pylori infection after treatment. Negative predictive value = 72/(72+2) × 100 = 97.2%. The eradication rate assumed to be 80%. Data have been calculated for sensitivity and specificity of 90% for the UBT.

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5. 1987;1063–9.
Dermatitis herpetiformis and cigarette smoking

EDITOR—Some time ago a study by Snook and colleagues (Gut 1996;39:60–2) found cigarette smoking to be less prevalent among those with coeliac disease. This prompted Lear and colleagues (Gut 1997;40:289) to evaluate smoking status in patients with dermatitis herpetiformis (DH), an autoimmune blistering skin disease that also presents with dermatitis herpetiformis (DH), an autoimmune blistering skin disease that also presents with a gluten sensitive enteropathy. They found that 29 patients with DH were significantly less likely to be smokers than matched and unsmoked controls.

As we also have a large population of patients with DH, we did a preliminary review of our existing database to evaluate smoking status in these patients. A review of over 200 patients charted at the first biopsy confirmed DH (granular IgA in papillary dermis) revealed smoking information on 105 patients. Fifteen of these patients were less than 20 years of age at disease onset and thus were eliminated from the study, leaving 90 evaluable patients. Of these patients eight (8.9%) were smokers, whereas 17.1% of the Utah population aged 20 years or older are smokers, thus confirming the findings of Lear et al that patients with DH are less likely to be smokers than those in the general population.

The reasons for this finding are not fully clear. It is well known that cigarette smoking adversely affects the skin, although a few conditions have been reported where smoking may have a beneficial effect. Likewise, when it comes to the gastrointestinal tract, smoking may have adverse effects in the case of Crohn’s disease, yet beneficial effects in ulcerative colitis.

How do we explain this apparent beneficial effect of smoking when it comes to DH? It is likely that the immunosuppressive effects of smoking play a role in this autoimmune disease, yet there are other autoimmune skin diseases, such as psoriasis, which are made worse and not better by smoking. One study found decreased serum IgA in smokers which may also play a role. Finally, the well-known vasoconstrictive effects of nicotine could play a role at least in the cutaneous manifestations of DH.

As we found our DH patients more likely to be non-smokers, does this mean that if they take up the habit their DH will go away or even improve? We don’t know, but it seems unlikely. We also doubt our institutional review board would ever approve a study to find out. This study was a preliminary review and does not prove that being a non-smoker is a risk factor for DH. It may be only one variable of the equation, and other likely much more important confounding factors such as genetics and other environmental factors play a greater role. Further more complete studies are needed to confirm our finding.

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Tomorrow’s challenge in liver transplantation: diminishing the imbalance between donor organ availability and need

EDITOR—It was with great interest that we read Periera and William’s article (Gut 1998;42:883–5) reviewing the problem of the great imbalance between the limited number of donor livers versus the increasing need for transplantation in the UK and possible remedies to this tragiic situation: strategies to increase the number of actual donations from the annual pool of potential donors. This great imbalance between allograft supply and demand is a challenging problem which confronts transplant centres everywhere. Furthermore, as medical science advances and clinical epidemiological analysis of post-transplant outcomes become clearer, we find that diseases that were previously either absolutely or relatively contraindicated for transplantation, such as chronic hepatitis B, with acute alcoholic cirrhosis, are now conditions potentially treatable by transplantation, further widening the differential between those in need of a transplant and number of available organs.

Clearly, Periera and Williams point out, there is a need to increase the numerator side of the organ supply: demand ratio and use every available organ. It must be emphasised, however, that the need to reduce the denominator side of this ratio—that is, reduce the need for transplantation, is equally as great. Currently, alcoholic cirrhosis and chronic hepatitis C (HCV) infection are the two most common indications for transplantation for liver disease in British Columbia, comprising 15 and 22% of all transplants as of 1997. These proportions are comparable to other centres across Canada and the United States. When one also considers that many of those infected with HCV acquired the infection from intravenous drug misuse and that alcohol consumption is reported to be an exacerbating factor in the progression of HCV towards cirrhosis, it is clear that primary prevention of behaviourally acquired liver disease could substantially decrease the donor supply: demand imbalance. The benefits of effective public health measures to reduce alcohol dependence, intravenous drug misuse, as well as immunisation of those at risk of hepatitis B, may not help those currently in need of a transplant but would be expected, over the next few decades, to impact favourably on pre-transplant waiting lists. The solution to today’s donor shortage lies not only with those actively involved in transplantation or organ procurement but, ultimately, with all who are involved in health care.

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NOTE

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Cost effectiveness of treatment for gastro-oesophageal reflux disease in clinical practice

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Gut 1998 43: 728-732
doi: 10.1136/gut.43.5.728

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