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 proton kinetins 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 (<1%) 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 (1.83) is further evidence that the groups were not clinically comparable. Cisapride is known to be relatively inept in treating GORD. Many studies have confirmed that the “stepped approach” is appropriate in gastro-oesophageal reflux disease (GOR). In studies of the effects of treatments, non-randomised comparisons can result in incorrect conclusions. To avoid the limitations of this study, a prospective randomised trial with representative patients must be carried out to determine which treatment approach, “step up” or “step down”, is best for treating patients with GORD and dyspeptic symptoms in general.

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Cost effectiveness of treatment for gastro-oesophageal reflux

EDITOR,—Eggleston et al (Gut 1998;42:13–16) concluded from their observational study that the “step up” approach, starting with a proton kinetic or H₂ receptor antagonist, represents the most cost effective initial therapeutic strategy for the treatment of patients with a diagnosis of uncomplicated gastro-oesophageal reflux disease (GORD). In studies of the effects of treatments, non-randomised comparisons can be affected by confounding factors and in our opinion this has resulted in the wrong conclusions being drawn from this study. Therapeutic interventions are commonly prompted by an indication. Primary care physicians selectively treat patients exhibiting more severe GORD with omeprazole and less severe symptoms with cisapride or ranitidine. Thus, by the very rationality of the decision to intervene, treatment differs between patients with GORD with respect to the outcome criterion in efficacy assessment.

The authors minimised confounding by indication by excluding 511 of 790 patients with a diagnosis of dysphagia or complicated GORD or whose condition was sufficiently complex to require immediate specialist referral. Restricting subject selection indeed introduces a change in the magnitude of the conclusions drawn by the authors are incorrect conclusions. To avoid the limitations of this study, a prospective randomised trial with representative patients must be carried out to determine which treatment approach, “step up” or “step down”, is best for treating patients with GORD and dyspeptic symptoms in general.

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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). In 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 abstract10 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 for the purpose of the database and 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 unsuccessful resolution 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 miscategorisation. 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 257 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 reduced severity of the 'treatment' that would be the case with any other treatment.

The authors do not state whether the general practitioner (GP) consultations attributed to the different treatment groups were all specifically for GORD. No information was provided as to how the authors have separated out 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 number 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 over the long-term of observing any difference between treatment groups would be diminished, resulting in the finding 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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12 Eggleston A, Wiggnerch, Haycon A. Outcome research: a prospective comparison of prescription data (Mediphas® UK) on cisapride (CIS), ranitidine (RAN) and omeprazole (OM) [abstract]. Gut 1996;39(suppl 3):A106.
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 incorporated into the analysis as and when such evidence is generated. Information about cost is useful only when considered jointly with information about clinical outcomes and further research concerning the long term cost and outcome of treatment is currently in progress.

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 aim of good prescribing is to segment general patient populations 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 presentations of disease, as assessed by aminotransferase concentrations and more rapid cure. There is another potential clinical significance to the interpretation of their in vitro results and that is non-steroidal anti-inflammatory drugs (NSAIDs) may increase the risk of developing drug induced hepatotoxicity in this unpredictable, hypersensitivity type of liver injury. Guthmann and Rodriguez¹ showed that patients taking an NSAID plus one other drug known to cause sporadic liver injury were at almost twice the risk of being admitted to hospital with biochemical and clinical evidence of liver disease than those taking a potentially hepatotoxic drug alone (table 1).

In their discussion, when referring to the clinical significance of the presence of prostaglandin producing suppressor cells in patients with GORD, they state that, “patients in which this phenomenon was detected had a less severe disease, as assessed by aminotransferase concentrations and more rapid cure.” There is potential clinical significance to the interpretation of our in vitro results, namely that non-steroidal anti-inflammatory drugs (NSAIDs) may increase the risk of developing drug induced hepatotoxicity in this unpredictable, hypersensitivity type of liver injury. Guthmann and Rodriguez¹ showed that patients taking an NSAID plus one other drug known to cause sporadic liver injury were at almost twice the risk of being admitted to hospital with biochemical and clinical evidence of liver disease than those taking a potentially hepatotoxic drug alone (table 1).

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Liverpool L69 3GH, UK

Table 1 Risk of admission to hospital with drug induced liver injury in those taking NSAIDs plus one other drug known to cause sporadic liver injury

<table>
<thead>
<tr>
<th>NSAID</th>
<th>Hepatotoxin</th>
<th>Controls</th>
<th>Cases</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>−</td>
<td>−</td>
<td>294</td>
<td>7</td>
<td>Reference</td>
<td>0.6 to 7.0</td>
</tr>
<tr>
<td>+</td>
<td>−</td>
<td>99</td>
<td>5</td>
<td>2.1</td>
<td>2.5 to 19.4</td>
</tr>
<tr>
<td>−</td>
<td>+</td>
<td>67</td>
<td>11</td>
<td>6.9</td>
<td>4.2 to 32.0</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>40</td>
<td>11</td>
<td>11.6</td>
<td></td>
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CI, confidence interval.

Diagnostic value of T cell reactivity in drug induced hepatitis

Borror,—I read with interest Maria and Victorino’s work (Gut 1997;41:334–40) on the diagnostic value of specific T cell reactivity to drugs in 95 cases of drug induced liver injury. They are to be congratulated on assembling the largest group of patients with suspected drug induced hepatotoxicity and attempting to assess causality using their lymphocyte test.

In their discussion, when referring to the clinical significance of the presence of prostaglandin producing suppressor cells in patients with GORD, they state that, “patients in which this phenomenon was detected had a less severe disease, as assessed by aminotransferase concentrations and more rapid cure.” There is another potential clinical significance to the interpretation of their in vitro results and that is non-steroidal anti-inflammatory drugs (NSAIDs) may increase the risk of developing drug induced hepatotoxicity in this unpredictable, hypersensitivity type of liver injury. Guthmann and Rodriguez¹ showed that patients taking an NSAID plus one other drug known to cause sporadic liver injury were at almost twice the risk of being admitted to hospital with biochemical and clinical evidence of liver disease than those taking a potentially hepatotoxic drug alone (table 1).

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Reply

EDITOR,—We showed that the in vitro phenomenon of putative prostaglandin producing suppressor cells demonstrated in patients with drug induced hepatitis was significantly associated with a less severe form of disease and a more rapid cure. It is possible to speculate that this in vitro phenomenon could also occur in vivo and play a part in the down regulation of the immune response triggered by the drug or its metabolites. We think that Dr Bartle’s point suggesting that there is another potential clinical significance to the interpretation of our in vitro results, namely that non-steroidal anti-inflammatory drugs (NSAIDs) may increase the risk of developing drug induced hepatotoxicity, is a very interesting possibility. Our own epidemiological data are consistent with the results of the epidemiological study presented by him, showing that patients taking NSAIDs have an increased risk of developing liver injury induced by other drugs. In fact, we compared the frequency of NSAID consumption in our population with drug induced liver injury with two different adult populations integrated into prospective studies, one consisting of patients admitted to our internal medicine unit in the University Hospital and the other consisting of patients followed in the primary care setting (table 1). Patients with drug induced hepatitis took significantly more NSAIDs than the control populations (χ² test, p=0.0001).

We are grateful to know in Maria and Victorino’s group of patients how many were taking an NSAID in addition to the suspected hepatotoxin and whether this was higher than in their control groups or a standard adult population.

Given the large number of patients that consume NSAIDs, even a small increase in the risk of potentiating hypersensitivity reactions to other drugs, including organs other than the liver, could represent a major health issue.

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

<table>
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<tr>
<td>Number of cases</td>
<td>136</td>
<td>277</td>
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<tr>
<td>Mean age</td>
<td>46.7</td>
<td>63.9</td>
</tr>
<tr>
<td>Number taking NSAIDs</td>
<td>43</td>
<td>406</td>
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<tr>
<td>Percentage</td>
<td>32</td>
<td>14</td>
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</table>

* Took NSAID in the 15 days prior to admission.

¹ Guthmann SP, Rodriguez LAG. The increased risk of hospitalisations for acute liver injury in a population with exposure to multiple drugs. Epidemiology 1993;4:496–501.

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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 and background, the term excellent would surely be adequate to describe the three different papers contained 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 even case reports. Sometimes, 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, mentioned as an ethical reference by the authors on the same page. As recently pointed by Angell, 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 to 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 so far and, therefore, the length and composition of ideal eradication therapy has to be determined in large multicentre trials.

Inclusion of post-treatment controls. If we compare treat- ment with an effectiveness of over 80% and perform a six week UBT (assuming a sensitivity and specificity of 90% for the technique, the predictive value of a positive result will rise to almost 100%. Therefore, a second test will only add cost to the study, and will lead to the exclusion of a valuable percentage of patients with false negative results in the second test.

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 duodenal ulcer are assumed to have a 90% prevalence of H pylori infection. Data have been calculated with the accuracy 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 is assumed to be 80%. Data have been calculated for sensitivity and specificity of 90% for the UBT.

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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 a gluten sensitive enteropathy. They found that 29 patients with DH were significantly less likely to be smokers than matched and unmatched 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 patient charts with biopsy confirmed DH status in these patients. A review of over 200 of our existing database to evaluate smoking habits of patients with DH, we did a preliminary review of these patients eight (8.9%) were smokers, whereas 17.1% of the Utah population aged 20 years or older are smokers, whereas 17.1% of the Utah population aged 20 years or older are smokers, whereas 17.1% of the Utah population aged 20 years or older are smokers.

One study (Smith JB, Fenske NA. Cutaneous manifestations of 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 unmatched controls.

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 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 findings.

References

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 tragic 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 alcoho lic 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 reduce 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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Sir Francis Avery Jones BSG Research Award 1999

Applications are invited by the Education Committee of the British Society of Gastroenterology who will recommend to Council the recipient of the 1999 Award. Applications (TWENTY COPIES) should include:

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A bibliography of relevant personal publications
An outline of the proposed content of the lecture, including title
A written statement confirming that all or a substantial part of the work has been personally conducted in the UK or Eire.

Entrants must be 40 years or less on 31 December 1998 but need not be a member of the BSG. The recipient will be required to deliver a 40 minute lecture at the Annual Meeting of the Society in March 1999. Applications (TWENTY COPIES) should be made to the Honorary Secretary, BSG, 3 St Andrews Place, London NW1 4LB, by 1 December 1998.
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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