Gut, 1985, **26**, 217–220

Leading article

Upper gastrointestinal bleeding: the trials of trials

About 30 000 people are admitted to hospitals in the United Kingdom each year with upper gastrointestinal bleeding and about 3000 of these will die. Mortality rates have changed little in the last 40 years, although as the patients with bleeding are increasingly likely to be elderly there are some grounds for persuading ourselves that standards of treatment have gone up.

If we are to improve our treatment then we need to conduct clinical trials, to provide sound bases for judgment between the useful and the ineffective. In determining outcome the clinician can use relatively soft determinants, rebleeding rates or transfusion requirements, or operation rates; a determinant influenced by clinical judgement about need, or he can use the hard ultimate determinant of the death rate. In consecutive case series gastroenterologists generally measure outcome by giving simple overall percentage death rates, although in doing so they often ignore two basic facts; the age mix of their population and the contribution to death rates from serious associated disease such as advanced extragastrointestinal malignancy.

In conducting controlled trials in patients with bleeding it is commonplace for reliance to be placed upon transfusion or rebleeding rates, and also to rationalise results *post hoc* by ascribing deaths in one treatment group or another to the inevitable consequences of other serious diseases, to misallocation of initial treatment and so forth.

The contrast with practices in carrying out controlled trials in heart diseases is marked. There, clinicians have generally accepted that mortality rates have paramount importance and that overall intention-to-treat analyses should form the basis for conclusions. Why the difference? One obvious reason is that mortality rates from upper gastrointestinal bleeding are about half those from acute myocardial infarction and therefore trials must be much larger to achieve reliable conclusions. The uncertainties of trial data in patients with haematemesis and melaena can be illustrated by considering histamine H_2 antagonists. In only one of 12 such trials where the value of treatment has been compared with that of placebo, were there more than five deaths recorded in placebo treated patients (even then a number far too small to permit reliable comparisons with the treated groups.)[1–12]

Assessment is complicated by at least three other problems. Where sets of data do not show overall differences of substance there is an understandable but dangerous and misleading tendency to carry out subgroup analyses. Such analyses are prone to throw up chance variations which can then be accepted and rationalised by the unwary. Thus we learn in one paper that histamine H_2 antagonist treatment appeared useful in

duodenal but not gastric ulcer,[2] whilst in two others the opposite conclusion was reached.[1 12] On all occasions overall analyses having failed to show convincing differences. Sets of data which appear largely the same can also appear in different publications which makes the body of work which supports a particular conclusion seem much larger than it really is.[13–17] Finally, what seems to be the same trial may be reported at multiple stages during its conduct.[12 18 19] Again, chance variation must occur, and statistical tests of significance, where the implicit assumption made in designing the test was that a single analysis only would be done, seem to have been inappropriately applied.

If we really wish to obtain meaningful answers we must collect meaningful sets of data and analyse them properly. Sadly often we do not.

What progress has then been made in devising drug treatments for acute upper gastrointestinal bleeding associated with peptic ulceration? Given the low overall mortality rates it seems almost inevitable that the data obtained in a single study, however large, must fail to convince on its own. Drugs which have been considered apart from the histamine H_2 antagonists include antifibrinolytics and somatostatin.

Although the histamine H_2 antagonist data sets have been generally too small to allow confident conclusions, there are accepted mathematical techniques which allow these to be combined while making due allowance by weighting for the contributions by size of individual series. When this is done it appears that a trend favouring treatment may be discernible whether measured in terms of rebleeding, operation or death rates. Such an impression needs confirming by a large (and inevitably) multicentre trial. (Collins and Langman unpublished data).

Tranexamic acid has been used in at least four studies;[9 20–22] in all of these trends in favour of the treated groups have been detected, but in only one was mortality significantly lowered, and this despite there being no apparent change in rebleeding or operation rates.[9] The body of data is, however, at least as good as that to support the use of histamine H_2 antagonists.

In the current issue of *Gut* we find data suggesting that somatostatin might be added to the list of effective agents. Two previous trials have been reported and one is in press.[24] The first[23] included three groups of 20 patients with haemorrhage associated with anti-inflammatory drug use randomised to receive somatostatin, ranitidine or placebo. Results differed dramatically, 12 placebo treated and 10 ranitidine treated but only one somatostatin treated patient required operation. Furthermore, haemorrhage ceased within 12 hours in all the remaining somatostatin recipients, but did not ease for at least 40 hours in any of the ranitidine or placebo recipients. The second[13] included 10 pairs of patients allocated to test and control groups with clinical benefit being greater in seven of the 10 pairs in the somatostatin treated patients, while in the remaining three pairs no difference was discernible. In the current study 95 patients were treated with somatostatin or placebo, and less operations were needed in the treated than in the controls (5/46 and 14/49 respectively). Five patients died, four somatostatin treated and one placebo treated, but the authors suggest that three of these deaths were unrelated to bleeding.

The treatment appears safe but is expensive and must be given by continuous infusion since drug half-life and its related effect are extremely

short. Readers must make their own judgement as to whether the body of data is such as to convince them that the treatment is useful and should be generally applied.

The tribulations of assessment are further emphasised by findings in the trial in press where 630 patients were randomly allocated treatment with a 72 hour somatostatin or placebo infusion. Rebleeding was less common in somatostatin than in placebo recipients (22% compared with 28%: not significant) but operation rates were virtually identical and the death rate was slightly higher in the treated than in the controls (9·8% and 7·9% respectively).[4]

M J S LANGMAN

Department of Therapeutics,
University Hospital,
Nottingham

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