Correspondence

Cimetidine versus ranitidine in short term healing of duodenal ulcers

SIR,—Quatrini *et al* (*Gut* 1984; **25:** 1113–7) refer to the now familiar difficulty of statistically proving differences, other than large ones, in comparative trials of ulcer healing drugs. In the 12 published studies which compared cimetidine and ranitidine in short term healing of duodenal ulcers (full references available upon request) the differences between the healing rates on the two drugs reached statistical significance only once.[1] In our own study,[2] we observed a higher rate of healing in the ranitidine group compared with the cimetidine group, although this difference also did not reach statistical significance (Fisher's exact test; $p=0{\cdot}12$). Because of the small number of patients in the study, it was possible that we were constructing a type 2 or β error – that is, falsely accepting the null hypothesis. We therefore attempted to compare healing rates with cimetidine and ranitidine in all published trials in duodenal ulceration.

Of the 12 studies published, 10 reported higher healing rates in the ranitidine group. This is analogous to tossing a coin 12 times and getting 10 heads (or 10 tails); the probability of this happening, tested with the binomial distribution, is less than 0.05. We further analysed data only from those studies which were blinded, four week trials of cimetidine 1 g per day (as 200 mg tds, 400 mg nocte) *versus* ranitidine 300 mg per day (as 150 mg bd). Eight studies (1333 patients) fulfilled these criteria, and as far as we could ascertain from available data, they were comparable in design, mean age of patients, sex ratios, and percentages of smokers. This total number of patients approaches that calculated by Peterson and Elashoff[3] to be needed to confidently show a 10% difference between two treatments when the less effective therapy is successful in 70% of patients. Of 657 patients receiving cimetidine, 450 were healed endoscopically at four weeks (68%) compared with 500 of 676 taking ranitidine (74%). Using χ^2 testing with Yate's correction, the difference in healing rate in favour of ranitidine is statistically significant ($\chi^2=4{\cdot}61$, $p<0{\cdot}05$).

With the reservation that any studies which favoured cimetidine over ranitidine might perhaps have been done, but not published, it seems likely that ranitidine is marginally more effective than cimetidine in short term healing of duodenal ulcers.

D BRIAN JONES AND NEVILLE D YEOMANS

Department of Medicine, McMaster University, Hamilton, Ontario, Canada,
and
Department of Medicine, University of Melbourne, Melbourne, Victoria, Australia.

References

1 Zeiton P, d'Azenar P. International multicentre clinical trial of ranitidine in duodenal ulcer: comparison with cimetidine. In: Misiewicz JJ, Wormsley KG, eds. *The clinical use of ranitidine*, Oxford: Medicine Publishing Foundation, 1982: 141–5.
2 Jones DB, Hanson RG, Mihaly GW, *et al*. Double-blind controlled trial of ranitidine versus cimetidine in the treatment of duodenal ulceration. *Aust NZ J Med* 1982; **12:** 547–9.
3 Peterson WL, Elashoff J. Placebo in clinical trials of duodenal ulcer: the end of an era? *Gastroenterology* 1980; **79:** 585–7.

Reply

SIR,—Jones and Yeomans pooled together the results of eight blind studies on four week treatments of 1333 duodenal ulcer patients, and found that ranitidine (150 mg bid) presents a 6% advantage on ulcer healing over cimetidine (200 mg tid, 400 mg nocte), which is statistically significant. With some reservations, these results and the method by which they were obtained are very probably valid. It should be pointed out, however, that with very large samples small differences can reach the level of statistical significance but the strength of association between the variables may still be quite weak.[1] Indeed the contingency coefficient C, calculated from Jones and Yeomans' figures, is only 0·06. This is connected with an important question which should be asked: is the difference found clinically important?

Before starting our study we were aware that the cimetidine and ranitidine healing rate probably did not differ greatly in short term treatments. What we did not know was if ranitidine would show a large advantage over cimetidine when the latter had failed to heal the ulcer previously. This possibility had been suggested by open studies and it would have been of practical as well as theoretical interest because it would have implied a possible, albeit improbable, difference in the mechanism of action of the two drugs.

Our study certainly does not exclude a difference between the two treatments in healing 'cimetidine-resistant' ulcers; it simply suggests that if a difference exists it is not a large one. Furthermore, it confirms that a most important variable in the healing of these ulcers is the duration of treatment.[2] To show a small difference is significant, a very large series is necessary; however, apart from the impossi-

bility of recruiting so many patients the demonstration of such a small difference does not seem to us really important from the theoretical or clinical point of view.

M QUATRINI, G BASILISCO AND P A BIANCHI
Cattedra di Patologia Medica III
Instituto di Clinica Medica I
University of Milan, Italy

References

1 Linton M, Gallo PS Jr. *The practical statistician.* Monterey, California: Brooks Cole Publishing Company, 1975: 330–3.
2 Bardhan KD. Non-responders to cimetidine treatment, part 2. In: Baron JH, ed. *Cimetidine in the 80s.* Edinburgh: Churchill Livingstone, 1981: 42–57.

Appropriate statistical test in comparative ulcer healing studies

SIR,—The recent paper by Lam *et al*[1] draws attention to the possible value of tripotassium dicitrato bismuthate (TDB) in the treatment of cimetidine-resistant duodenal ulcers and, in the process, highlights an important aspect of the burgeoning problem of medical statistics. In the study 25 patients whose ulcers had not healed after four weeks of treatment with cimetidine (1 g/day) were randomised to a further four weeks of treatment with either TDB (four tablets/day) or cimetidine (1·6 g/day). Ulcer healing occurred in 10 of 12 patients receiving TDB and five of 13 patients receiving cimetidine. These results are tabulated below, with expected frequencies in brackets:

	Healed	*Unhealed*
TDB	10 (7·2)	2 (4·8)
Cimetidine	5 (7·8)	8 (5·2)

The χ^2-test with Yates' correction for continuity[2] was allegedly used to assess the difference in healing between the two groups, and this was claimed to be significant at the 2% level. Scrutiny of the data, however, suggests that this significance was achieved using the χ^2-test ($\chi^2 = 5{\cdot}24$, $p<0{\cdot}02$ as in the text) and not the χ^2-test with Yates' correction ($\chi^2 = 3{\cdot}53$, $p>0{\cdot}05$). Fisher's test of exact probability for the data gives a p value of 0·0286 (one tail). As there is, *a priori*, no reason to suspect that TDB is necessarily better than cimetidine the two-tailed value of 0·057 applies, which is again not significant at conventional levels.

In view of these findings, and because 2×2 tables are so commonly used in gastroenterology to analyse the results of comparative ulcer healing studies, review of the criteria for choosing when to use the χ^2-test, Yates' correction, and Fisher's exact test seemed warranted. There was no consensus as to what constitutes the smallest expected frequency or number of observations which will provide reliable results using the χ^2-test.[3] On the use of Yates' correction or Fisher's test for 2×2 tables the most frequently quoted authority is the time-honoured Cochran, who stated:[4] 'Use Fisher's exact test (i) if the total N of the table is <20, (ii) if 20>N<40 and the smallest expectation is less than 5. If N>40 use χ^2 corrected for continuity if the smallest expectation is less than 500'. Now that tables of significance levels for Fisher's test have been published for N up to 60[5], however, it has been considered preferable to use these for all sample sizes up to 60 irrespective of the values of the individual cells, and to use Yates' correction for all other 2×2 tables with expected frequencies of 5 or more in each cell.[6 7] There would appear to be no place for an unmodified χ^2 test in analysis of 2×2 tables in comparative clinical trials as carried out at present.

It seems, therefore, that however one interprets the above criteria Lam *et al*[1] have used inappropriate methods to analyse their data. This in no way detracts from the interest of their paper, however, or the conclusion drawn from the later cross over part of the study which achieved significance at the 2% level with both Fisher's test and the χ^2-test with Yates' correction.

E BOYD AND I N MARKS
Gastrointestinal Clinic,
Department of Medicine,
University of Cape Town,
Cape Town, South Africa

References

1 Lam SK, Lee NM, Koo J, Hui WM, Fok FH, Ng M. Randomised crossover trial of tripotassium dicitrato bismuthate versus high dose cimetidine for duodenal ulcers resistant to standard dose cimetidine. *Gut* 1984; **25:** 703–6.
2 Snedecor GW, Cochrane WG. *Statistical methods,* Ames, Iowa: Iowa State University Press, 1967.
3 Roscoe JT, Byars JA. An investigation of the restraints with respect to sample size commonly imposed on the use of the Chi-square statistic. *J Am Statist Ass* 1971; **66:** 755–9.
4 Cochran WG. The χ^2-test of goodness of fit *Ann Math Statist* 1952; **23:** 315–45.
5 Documenta Geigy. *Scientific Tables,* 7th ed. Macclesfield: Geigy Pharmaceuticals, 1970.
6 Langley R. *Practical statistics.* New York: Drake Publishers Inc, 1971.
7 Armitage P. *Statistical methods in medical research.* Oxford: Blackwell Scientific Publications, Oxford, 1971.