Correspondence

Infusion of methyl tertiary butyl ether in bile ducts of rabbits

SIR,—I was interested to read the paper from Professor Tritapepe's group (*Gut* 1989; **30:** 206–12). I feel it is important to emphasise that this work has little or no bearing on previously published human *in vivo* studies on the use of methyl tertiary butyl ether (MTBE) to treat choledocholithiasis.

The toxicity of MTBE in the extrahepatic biliary tree is directly related to the time corrected net volume exposure of the bile ducts to the chemical plus the extent of dispersal from the extrahepatic biliary tree which is itself influenced by the previously mentioned factor among others. Tritapepe's study reports continuous infusion of MTBE for 48 hours without an infusion/aspiration cycle, a technique which must maximise toxicity. My human choledocholithiasis MTBE treatment protocol results in bile duct clearance after intermittent, installation/aspiration sessions totalling eight hours (correctly expressed as 4 ml MTBE per 30 min × 4 per session × 4 sessions).[1] Continuous nasobiliary catheter drainage between treatment sessions also helps to control toxicity and minimises rises in the transaminases.

I have now treated choledocholithiasis in 23 elderly patients using MTBE delivered intermittently *via* a nasobiliary catheter, and 17 patients have achieved complete clearance of their bile duct stones. Post-treatment endoscopic retrograde cholangiography has uniformly shown a reduction in the size of the bile duct and subsequent biliary imaging in six patients (>six months after MTBE treatment) has failed to reveal any evidence of bile duct dilatation.

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Reference

1 Murray WR, LaFerla G, Fullarton GM. Choledocholithiasis – *in vivo* stone dissolution using methyl tertiary butyl ether (MTBE). *Gut* 1988; **29:** 143–5.

Reply

SIR,—We certainly agree with Dr Murray that it is unfair to extrapolate our animal data to humans treated with topical MTBE infusion. We wish to elucidate however, that rabbits received a daily MTBE dose of 1 ml/kg bw which was infused into the common bile duct (CBD) at a 1 ml/h rate. As the body weight was 3 kg, each rabbit was given a three hour continuous MTBE infusion per day. Therefore, Dr Murray's statement that animals were given 48 h MTBE infusion is incorrect. Referring to CBD dilatation in our two patients, we cannot exclude a fortuitous coincidence. As reported in the article,[1] one case increased CBD volume (+19·6%) *v* pre-treatment whereas the second one exhibited a reduction (−27·7%) which was minor compared with the three patients treated by saline flushing (mean decrease −88·5%). In view of this experience, we have replaced MTBE by a MTBE/ monooctanoin mixture (1:2; v:v). Preliminary findings suggest that this mixture is effective and well tolerated.[2]

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References

1 Tritapepe R, Pozzi C, Caspani P, Di Padova C. Unexpected dilatation of the common bile duct after methyl tertiary butyl ether (MTBE) in rabbits. Possible implications to findings in man. *Gut* 1989; **30:** 206–12.
2 Tritapepe R, Pozzi C, Caspani P, Di Padova C. Successful treatment of retained common bile duct (CBD) stones by a combination of methyl tert-butyl ether (MTBE) and monooctanoin(Mo). [Abstract]. *Hepatology* 1988, **8:** 1368.

Maalox versus cimetidine

SIR,—I have read with interest the paper presented by Dr Bardhan and his colleagues (*Gut* 1988; **29:** 1748) in which it is concluded 'Maalox TC three tablets bd are as effective as cimetidine 400 mg at bedtime in reducing DU relapse and both are superior to placebo'.

The authors base their view on measurements in evaluable cohorts of respectively 43/62 placebo recipients, 42/65 Maalox HS, 43/60 Maalox bd and 48/64 cimetidine takers. As in all clinical trials we need to be sure that the evaluable cohort fairly measures outcome. The authors are aware of this problem and so in their Tables (Table 4) postulate conclusions as if for instance all excluded patients remained ulcer free, and alternatively if all had relapsed.

They do not consider treatment withdrawals as failures, yet no treatment can be considered successful if patients cannot take it. There were 26 such withdrawals (see Table 5). Their inclusion as treatment failures gives rather a different slant to the prime analysis (see Table over page).

		Placebo	Maalox HS	Maalox bd	Cimetidine
I	Originally included	62	65	60	64
II	Authors' evaluable cohort	43	42	43	48
III	Total relapses recorded	24	16	9	11
IV	∴% relapses $\left(\frac{III \times 100}{II}\right)$	55·8	38·1	20·9	22·9
V	Withdrawals – side effects	3	7	12	4
VI	∴ Total evaluable cohort (II+V)	46	49	55	52
VII	Total treatment failures (III+V)	27	23	21	15
VIII	∴% failures $\left[\frac{VII \times 100}{VI}\right]$	58·7	46·9	38·2	28·8

Plainly, the percentage failure rate is not the same for Maalox bd and cimetidine, though the difference may be statistically insignificant because the study lacks sufficient power.

What the physician wants to know are the chances of successful completion of treatment and I would suggest my analysis more fairly reflects this need. In this context Table 2 of the paper may be unfortunately phrased. The withdrawals because of inability to tolerate treatment presumably are included mainly in the subgroup 'no second endoscopy'. If these were indeed mainly people who stopped treatment because of adverse effects then the Table is misleading.

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Reply

SIR,—We appreciate the very fair comments made by Professor Langman and would agree with him but, with respect, only if we were claiming that Maalox is a complete substitute for cimetidine in duodenal ulcer maintenance therapy – that is, equal in efficacy, freedom from side effects, convenience and costs.

Two considerations should be remembered when assessing our results. First, does antacid maintenance treatment reduce the chance of ulcer recurrence? Second, if it does, is such treatment a practical form of management? The two are of course related but it makes it easier to consider them seperately. On the first count, we feel the answer is 'yes'; but it is on the second count that the shortcomings of antacid treatment may show up.

Our work was essentially experimental to test the hypothesis that maintenance antacid therapy was capable of reducing duodenal ulcer relapse rate. This is why in the analysis apparently more weight was put on efficacy. Thus, anybody who violated the protocol in any way was excluded from efficacy analysis; they were later reintroduced using various hypothetical outcomes to see to what extent they influenced the results. Patients who were withdrawn for side effects but were otherwise evaluable were indeed included in efficacy analysis up to the point of withdrawal; if they were withdrawn without a further endoscopy, then they could not be evaluable when judged by ulcer relapse rates. If our results are judged solely by Professor Langman's recalculation (line 8 of his Table), then certainly Maalox does not appear to be so effective. But to restrict analysis in this manner would result in missing the central finding, namely, that antacid maintenance therapy does indeed reduce relapse rates (line 4 of Professor Langman's Table) which, after all, was the central point of the study. (In fact, three of the patients who withdrew from the Maalox BD group because of side effects were evaluable for efficacy, so the recalculations are 18 in line 7 and 32.7% in line 8).

We were of course aware from the outset that even if effective and free from side effects, chewing three tablets of Maalox twice daily was not as convenient as taking one cimetidine tablet at bedtime. But we felt, nonetheless, that treatment would perhaps be tolerated by the majority and therefore in this group we could reasonably test our hypothesis. In our view, given the data we reported, the prescribing physician can decide which treatment to use in a particular patient on the basis of their expectation that treatment will be well tolerated, also taking the cost of treatment into consideration.

We accept Professor Langman's criticism but given the clarifications above, feel our principal conclusion stands, namely, that in this experimental study, Maalox three tablets twice daily is indeed as effective as cimetidine 400 mg nightly in reducing duodenal ulcer relapse rates.

K D BARDHAN