Correspondence

Transdermal scopolamine and gastric acid secretion

SIR,—Richardson and Feldman¹ recently presented results in this journal where transdermal scopolamine (TDS) failed to inhibit gastric acid secretion in their patients with duodenal ulcer. They pointed out that their findings were at variance with two earlier reports according to which transdermally applied scopolamine reduced basal gastric acid secretion by 65%² and nocturnal acid secretion by 75%³ in duodenal ulcer patients. The negative results of Richardson are at variance also with additional findings obtained in patients and healthy volunteers. Thus, Konturek *et al* recently reported that TDS after a nine day treatment period reduced basal and sham feeding induced gastric acid secretion by 40% and 46% in 10 patients with chronic duodenal ulcer disease.⁴ Moreover, based on studies in 18 healthy volunteers basal acid secretion was inhibited by 61%, pentagastrin stimulated acid secretion was reduced by 67% (n=6), betazol stimulated acid secretion by 60% (n=7), peptone stimulated acid secretion by 24% (n=10)⁵, and bethanechol stimulated acid secretion by 76% (n=7).⁶ But, basal acid secretion was inhibited also in a long term double blind randomised, placebo controlled crossover study in four volunteers after one week by 72%, after two weeks by 76%, after three weeks by 62%, and after four weeks by 73%. Peptone stimulated acid secretion was reduced by 45% after the first week, by 40% after the second, and by 24% after the third week. After treatment for four weeks no change of peptone stimulated acid secretion was observed.⁷ Nocturnal acid secretion was suppressed by TDS in seven volunteers by 35%.⁸

Richardson and Feldman have no explanation for the disagreement of their data with the other reports. They assume scopolamine was absorbed through the skin and that the amount was insufficient to cause a significant reduction in gastric acid secretion. Even if the assumption of a delivery from the TDS of about 0.1 µg/kg/h scopolamine is correct, however, it has not been shown that the drug was available systematically in their patients. Ineffectivity could also be resulting from a low rate of bioavailability which may not permit the drug to reach a concentration in blood above threshold or minimal effective levels to block access of acetylcholine to its receptors. In several studies where TDS was effective,^{2-5,7} bioavailability of scopolamine has been validated by analysis of urinary concentrations. Pharmacological effects, such as changes of pupillary size, slight impairment of near vision or dry mouth, should be expected at least

in some of their patients. Richardson and Feldmann do not mention such effects. All other studies cited by us support the notion that the amount of drug delivered by a transdermal scopolamine system and absorbed through the skin is sufficient to markedly inhibit basal, stimulated and nocturnal gastric acid secretion both in healthy volunteers and patients with chronic duodenal ulcer disease. We, therefore, conclude that further studies on scopolamine for longterm inhibition of gastric acid secretion in the prophylaxis of peptic ulcer disease are warranted. This seems to be especially important in the light of more recent findings. In patients with duodenal ulcer, relapse rate one year after treatment with a synthetic prostaglandin were two-fold higher than with ranitidine.⁹ There are also indications that a H₂-blocker, such as ranitidine will lose its effectiveness in reducing gastric acid secretion with continued therapy.¹⁰

K H ANTONIN AND P R BIECK

*Human Pharmacology Institute,
Ciba-Geigy GmbH,
Ob dem Himmelreich 7,
D-7400 Tübingen, West Germany.*

References

- 1 Richardson CT, Feldman M. Effects of transdermal scopolamine, alone or in combination with cimetidine, on total 24 hour gastric acid secretion in patients with duodenal ulcer. *Gut* 1986; **27**: 1493–7.
- 2 Gleiter CH, Antonin KH, Brodrick T, *et al*. Transdermal scopolamine and basal acid secretion. *N Engl J Med* 1984; **311**: 1378.
- 3 Walt RP, Kalman CJ, Hunt RH, *et al*. Effect of transdermally administered hyoscine methobromide on nocturnal acid secretion in patients with duodenal ulcer. *Br Med J* 1982; **284**: 1736–8.
- 4 Konturek SJ, Kwiecien N, Obtulowicz W, *et al*. Effects of low-dose anticholinergic treatment with transdermal scopolamine (TS) on vagally and pentagastrin stimulated gastric acid secretion in duodenal ulcer (DU) patients. *Dig Dis Sci* suppl 10: 1986; **31**: 282S.
- 5 Scheurlen M, Antonin KH, Bieck PR. Effect of low-dose anticholinergic treatment with transdermal scopolamine (TRANSDERM™ V) on gastric acid secretion. *Scand J Gastroenterol* 1982; suppl 78: **17**: 112.
- 6 Gleiter CH, Antonin KH, Bieck P. Zur Wirkung von transdermal appliziertem Scopolamin auf die cholinerg stimulierte Magensäuresekretion. *Verh Dtsch Ges Inn Med* 1983; **89**: 604–7.
- 7 Gleiter CH, Antonin KH, Cremer G, *et al*. Four weeks of treatment with transdermally applied scopolamine (Scopoderm TTS®). Presented at the IUPHAR 9th Congress of Pharmacology, London, 1984; 259P.
- 8 Dammann HG, Wolf N, Walter TA, *et al*. Wirkung von TTS-Scopolamin auf die menschliche Säuresekretion. *Klin Wochenschr* suppl IV 1985; **63**: 60.
- 9 Lauritsen K, Havelund T, Laursen LS, *et al*. Enprostil and ranitidine in prevention of duodenal ulcer relapse:

one year double blind comparative trial. *Br Med J* 1987; **294**: 932-4.

- 10 Prichard PJ, Jones DB, Yeomans ND, *et al.* The effectiveness of ranitidine in reducing gastric acid-secretion decreases with continued therapy. *Br J Clin Pharmacol* 1986; **22**: 663-8.

Reply

SIR,—We appreciate the comments of Dr Antonin and Professor Bieck. As pointed out in the introduction to our manuscript, we agree that our observations differ from those of other investigators. Our experiments were, however, carried out under randomised, double blinded controlled conditions, not always the case in other studies.¹ We evaluated for the first time the effect of TDS on total 24 hour acid secretion and measured acid secretion under basal conditions, in response to food, between meals and during the night. We evaluated the effect of TDS on gastric acid secretion when the drug was used alone and when it was used in combination with cimetidine. We could not show an effect of the medication on acid secretion in either case.

While we did not measure urine levels of scopolamine, as suggested, we assume that the drug used by our patients was similar to that used in other studies as it was sent to us as coded medication directly from the manufacturer, Ciba-Geigy Corp, Summit, NJ, USA. It is possible that the bioavailability of TDS varies from batch to batch and that we received a preparation with relatively low bioavailability.

CHARLES T RICHARDSON AND MARK FELDMAN
Dallas Veterans Administration
Medical Center,
4500 S, Lancaster Road,
Dallas, Texas, 75216
USA.

Reference

- 1 Walt RP, Kalman CJ, Hunt RH, Misiewicz JJ. Effect of transdermally administered hyoscine methobromide on nocturnal acid secretion in patients with duodenal ulcer. *Br Med J* 1982; **284**: 1736-8.

Vagal control of gastric alkaline secretion

SIR,—The paper of Professor Konturek and co-workers on the vagal control of gastric alkaline secretion (*Gut* 1987; **28**: 739-44) was very informative. Most of the findings are well in agreement with those of Feldman *et al*¹ and Forsell *et al*.² A comparison between the non-selective anti-muscarinic atropine and the M1-selective anti-muscarinic pirenzepine with respect to gastric alkaline secretion has, however, not been reported before.

Unfortunately, this comparison has not been carried out in an appropriate way, and the results do therefore not support the authors' conclusions, that M2-receptors rather than M1-receptors are involved in the regulation of gastric alkaline secretion. It is well known that the dose/effect relation between atropine and pirenzepine is 1:5 to 1:10 in weight units concerning the inhibition of exocrine glands using parenteral application.³

It would have been logical, therefore, to compare considerably higher doses of pirenzepine than the maximum 20 µg/kg chosen for atropine. It should be remembered that 10 mg is the smallest dose of pirenzepine available for parenteral application in clinical use, and that the highest dose given in the study of Konturek and coworkers to a volunteer of 70 kg body weight was 1.4 mg.

In conclusion, I feel that the question of whether gastric alkaline secretion is an M1- or M2-receptor dependent process is not yet clarified.

REINHOLD W STOCKBRÜGGER

Marbachtalklinik,
D-8730 Bad Kissingen,
West Germany

References

- 1 Feldman M. Gastric H⁺ and HCO₃⁻ secretion in response to sham feeding in humans. *Am J Physiol* 1985; **248**: G188-91.
- 2 Forsell H, Stenquist B, Olbe L. Vagal stimulation of human gastric bicarbonate secretion. *Gastroenterology* 1985; **89**: 581-6.
- 3 Jaup BH. Studies on the mode of action of pirenzepine in man with special reference to its anticholinergic muscarinic properties. *Scand J Gastroenterol* 1981; **16**: suppl 68: 1-26.

Reply

SIR,—We greatly appreciate Dr Stockbrügger's comments concerning our recent paper.¹ He raised an interesting theoretical point that our suggestion concerning the involvement of M2 rather than M1 subtypes of muscarinic receptors in the stimulation of gastric alkaline secretion may not be properly documented, because doses of pirenzepine used were too low.

The existence of at least two types of muscarinic receptors (M1 and M2) is based entirely on the comparison of the pharmacological effects of classical antimuscarinic drugs such as atropine, which is believed to be a non selective antagonist and to block M1 and M2 receptors. It is also based on actions of newer agents such as pirenzepine,² or telenzepine,³ which are considered to be more selective by blocking M1 receptors. Hirschowitz and