Molina reported that vagally stimulated acid secretion in gastric fistula dogs was equally sensitive to inhibition by atropine or pirenzepine, the difference in ED50 being within one order of magnitude. They postulated therefore, that vagal stimulation of gastric acid secretion involves a muscarinic pathway with high affinity for pirenzepine or M1 receptors. In contrast, Soll found that the potency of pirenzepine in inhibiting acid production in the isolated parietal cells was about 100 times less than that of atropine and postulated that muscarinic receptors of these cells are mainly of M2 type. This difference between atropine and pirenzepine in vivo and in vitro studies has been explained by the additional action of pirenzepine on M1 receptors on the postganglionic cholinergic neurons of the stomach.

In our study on gastric alkaline secretion the potency ratio between atropine and pirenzepine was at least 5:1, because the dose of atropine as low as 5 μg/kg caused significant suppression of gastric alkaline secretion, while pirenzepine even at a dose of 20 μg/kg was without any influence on basal or vagally stimulated alkaline secretion. This suggests the involvement of M2 rather than M1 receptors, but I agree that using higher doses of pirenzepine could provide stronger support for our conclusion. In our recent studies on gastric fistula dogs, pirenzepine and telenzepine in a dose as large as 80 μg/kg were without any influence on gastric alkaline secretion, but atropine suppressed this secretion at a dose of 5 μg/kg. Moreover, Safsten and Flemstrom recently reported that in rats pirenzepine may stimulate duodenal alkaline secretion possibly by acting through the M1 receptors in the brain. We did not observe such a stimulatory effect on gastric alkaline secretion in man or dogs, probably because the drug does not penetrate the blood brain barrier in these species.

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References


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Cimetidine and ranitidine on basal and ACTH-stimulated steroidogenesis

Sir,—Recently you published an article on the above by Kenyon et al (Gut 1986; 27: 1143–6). Using isolated bovine adenocortical cell suspensions, the authors evaluated the effect of a wide range of doses of cimetidine and ranitidine (10–1000 mcg/ml) on basal and ACTH-stimulated synthesis of cortisol, corticosterone, and deoxycorticosterone, in vitro. Under these conditions, the authors reported that cimetidine and ranitidine inhibited ACTH-stimulated corticosterone and cortisol synthesis. Cimetidine also decreased basal cortisol synthesis and increased ACTH-stimulated deoxycorticosterone synthesis. From their data, the authors postulated: (1) that cimetidine and ranitidine were capable of inhibiting cortisol and corticosterone synthesis in man in vivo; (2) that the inhibitory concentrations of drug observed in their study might be achieved in man after bolus intravenous dosing or by selective adrenal accumulation of drug; and (3) that cimetidine exerted its effect on steroid synthesis through cytochrome P-450 dependent enzyme inhibition. The article deserves comment if only to clarify certain points and correct several inaccuracies.

It is not true1–4 that ranitidine ‘does not interfere with the metabolism of other drugs.’ Whether this effect of ranitidine on drug metabolism is related to its inhibition of cortisol and cortisone synthesis, as shown by Kenyon et al., is conjectural. The authors assumed that reversible binding by ranitidine to cytochrome P-450 does not occur. It has been shown, however, that ranitidine is capable of binding to cytochrome P-450, but has a 10-fold lower binding affinity than cimetidine.5–8 In this case, the inhibition of cortisol and cortisone synthesis probably does not involve inhibition of cytochrome P-450-mediated hydroxylation.

The effects observed by Kenyon et al occurred with drug concentrations that were, as they indicated, far in excess of those achieved in normal clinical use. An intravenous bolus dose of cimetidine (300 mg) has
been shown to produce serum concentrations of 3·50 to 7·43 µg/ml at approximately 15 minutes after injection, declining steadily thereafter. These levels are far below the inhibitory concentrations (100-1000 µg/ml) used in this study.

There is no evidence to suggest that cimetidine accumulates in the adrenals after intravenous injection. The report of De Natale et al.10 referred to a study by Cross,18 who evaluated the longterm retention of metiamide and cimetidine in animals using whole body autoradiography; Cross did not report cimetidine accumulation or retention in the adrenals. Finally, in numerous publications,19-32 cimetidine and ranitidine have been reported to have no significant effect on the diurnal rhythm of plasma cortisol, maximum cortisol response to insulin, or other cortisol stimulatory factors; and the interaction of the H2 receptor antagonists with liver enzyme systems has not been associated with disturbed synthetic processes in the adrenals in vivo.

In conclusion, the extrapolation of these interesting in vitro studies with bovine adrenal cells to the clinical situation appears to be unwarranted at present.

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References


Reply

sir,—In their comments on our original paper, Karlstadt et al claim that ranitidine may have qualitatively similar effects to cimetidine on drug metabolism and also that cimetidine can have no clinically significant effect on adrenocortical function. In support of their claims they selectively cite a large number of abstracts, letters and papers only a few of which are relevant to either issue.

In respect of the first point, we referred to the work of Henry et al to support our statement that ranitidine does not interfere with hepatic metabolism of other drugs. Karlstadt et al have considered extrahepatic metabolism also and include six papers in their list of 14 in which ranitidine’s effects on the metabolism of other drugs has been ascribed to interference either with intestinal absorption or with the cholinergic system. Two of the letters cited do describe single case reports of possible interference with theophylline metabolism. Breen et al, however, in a formal study found that cimetidine, but not ranitidine, interfered with the clearance of theophylline and antipyrine. Similarly, the concern expressed by Liiopoulou et al in a letter about adverse effects of ranitidine on quinidine metabolism in one of their patients has yet to be formally confirmed. The plasma clearance of nifedipine was not significantly affected by ranitidine. The effects of ranitidine on warfarin clearance described by Desmond et al have not been observed by others. It is interesting that ranitidine has been shown to interfere with the clearance of one β-blocker, metoprolol, but not with that of propranolol or atenolol (see also review 15). In in vitro studies, hepatic microsomal cytochrome P-450 has been shown to bind ranitidine with an affinity which is 10 fold less than that of cimetidine. This weak affinity was noted in the introduction to our paper and may account for the in vitro effects of ranitidine on fentanyl metabolism. Clinical differences of ranitidine and cimetidine on drug metabolism are a result of not only their relative cytochrome binding affinities but also because the normal daily ranitidine dose is one-fifth that of cimetidine.

The second point that Karlstadt et al take exception to is our suggestion that under certain circumstances cortisol secretion may be impaired in vivo by cimetidine. We were careful to point out that with normal oral treatment, plasma concentrations of cimetidine and ranitidine are 100-fold and 4000-fold less than corresponding IC₅₀ values for the in vitro inhibition of cortisol synthesis. Even if cortisol biosynthesis were to be affected in vivo, it is likely that plasma concentrations would be unchanged as pituitary ACTH would compensate appropriately. In vivo inhibition might be apparent under conditions of stress— for example, haemorrhage, or after maximal doses of ACTH. In some of the papers cited by Karlstadt et al to support their argument, cortisol data are not presented. In others only the effects of the less potent adrenocortical inhibitor, ranitidine, are considered. In another, the effects of cimetidine on parenterally administered cortisol rather than cortisol production are considered. The works of May et al and Coiro et al provide indirect evidence that ACTH-mediated cortisol release is unimpaired. We are grateful to Karlstadt et al for bringing to our attention the work of Valk et al which reported a 45% reduction in urinary free cortisol excretion after six weeks of cimetidine treatment. This may, however, not be the most serious adverse consequence of cimetidine treatment. Adrenal steroids play a vital role in physiological response to haemorrhagic shock. It is therefore crucial to establish that the cortisol response to gastric bleeding is not impaired by high intravenous bolus dose of cimetidine. It is this situation, which is not uncommon, which needs to be investigated more thoroughly.

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Additional references

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