Effects of chronic oral cimetidine on apparent liver blood flow and hepatic microsomal enzyme activity in man

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SUMMARY Cimetidine 200 mg three times daily and 400 mg at night was given to 10 subjects for four weeks. Apparent liver blood flow was measured by indocyanine green clearance and microsomal enzyme activity by antipyrine clearance, before and after cimetidine. There was no reduction in indocyanine green clearance but antipyrine clearance, as expected, was significantly reduced by 15% at four weeks. Chronic cimetidine treatment does not reduce apparent liver blood flow and is therefore unlikely to be of use in the treatment of portal hypertension. The cimetidine associated hepatic enzyme inhibition appears to persist with prolonged treatment. Therefore patients on chronic cimetidine remain vulnerable to certain drug interactions.

Propranolol has been proposed as a treatment for portal hypertension as it lowers portal venous pressure¹ and prevents recurrent gastrointestinal bleeding in cirrhotics.² Though no toxic effects related to propranolol were observed in these cirrhotics,² cimetidine was suggested as an alternative to propranolol.³ Cimetidine associated changes in indocyanine green clearance and propranolol kinetics in normal subjects have been interpreted as showing a reduction in apparent liver blood flow.⁴ The usefulness of these findings in cirrhotics with portal hypertension, however, has been questioned.⁵ Another histamine H₂ receptor antagonist, ranitidine, has also been shown to reduce apparent liver blood flow in normals,⁶ though the technique criticised.⁷ In a recent study,⁸ cimetidine given intravenously to cirrhotics who had bled from oesophageal varices, failed to lower portal hypertension.

These studies with cimetidine and ranitidine have examined the effects on apparent liver blood flow and portal pressure after single doses, or short courses of these drugs. The findings of such acute studies may well be inapplicable to patients on chronic treatment with H₂ receptor antagonists. We therefore studied the effect of a four week course of cimetidine on apparent liver blood flow. In previous

studies a relationship between hepatic microsomal enzyme *induction* and apparent liver blood flow has been noted.^{9, 10} Consequently, we also examined the enzyme inhibiting effect of cimetidine to determine whether there was a relationship between enzyme inhibition and a change in apparent liver blood flow.

Methods

SUBJECTS

Six healthy men and four healthy women aged 20 to 45 years completed the study which was approved by the hospital ethical committee. All were non-smokers, drank only moderate amounts of alcohol and were not on any medication including the oral contraceptive pill. Plasma indocyanine green kinetics and antipyrine kinetics were determined in each subject before and after a four week course of cimetidine 200 mg three times per day and 400 mg at night.

After an overnight fast subjects rested supine for one hour. The experimental conditions were standardised as previously described.¹¹ Indocyanine green kinetics were then measured after a single intravenous bolus of 0.5 mg of dye per kilogram body weight. Venous blood samples were taken from the opposite arm at three minute intervals for 21 minutes. Before an indocyanine green injection was given, a venous blood sample was collected for measurement of blood haematocrit by automated methods on a Coulter Super-S counter. Indocyanine

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green plasma concentrations were measured by a spectrophotometric method.¹²

After the indocyanine green kinetics had been performed, antipyrine 1200 mg was administered as a freshly prepared solution and venous blood samples collected before and after three, six, nine, 12 and 24 hours after the dose. Plasma antipyrine was measured by a high performance liquid chromatographic method,¹³ modified by the use of 20% acetonitrile in 0.05 M phosphate buffer at pH 6.5 as mobile phase.

Plasma clearance, volume of distribution and plasma half life of indocyanine green were calculated from log concentration time curves as previously described.¹⁴ Whole blood clearance of indocyanine green was assumed to be equivalent to apparent liver blood flow and calculated as follows:

Apparent liver blood flow

$$= \frac{\text{Plasma clearance of ICG} \times 100}{[100 - \text{haematocrit} (\%)]}$$

Plasma antipyrine half life was calculated from least squares regression analysis of the log plasma concentration-time profile. Assuming complete absorption, negligible first pass metabolism and a one compartment model for antipyrine,¹⁵ the apparent volume of distribution of antipyrine was estimated as:

$$\text{Apparent volume of distribution} = \frac{\text{Dose}}{\text{Cpo}}$$

where Cpo is the back extrapolated plasma concentration at time zero. Plasma clearance of antipyrine was calculated as:

Plasma clearance

$$= \text{apparent volume of distribution} \times \frac{0.693}{T_{1/2}}$$

where $T_{1/2}$ is the half life of antipyrine and 0.693 a constant.

Statistical comparisons were made using Student's *t* test for paired data. Significance was assumed at $p < 0.05$.

Results

There were no adverse effects to cimetidine, antipyrine or indocyanine green in this study. Complete data were available from all subjects for indocyanine green kinetics, but from only eight subjects for antipyrine kinetics.

The results of indocyanine green kinetics are summarised in Table 1. There was no change in the half life of indocyanine green after cimetidine. The

Table 1 Indocyanine green (ICG) kinetics before and after cimetidine 1 g per day for four weeks, in 10 subjects (mean $\pm$ SD)

	Before cimetidine	After cimetidine	<i>p</i> value*
ICG half life (min)	3.70 $\pm$ 0.71	3.74 $\pm$ 0.78	NS
ICG volume of distribution (litres)	33.36 $\pm$ 10.27	39.67 $\pm$ 16.21	NS
ICG clearance (ml/min)	621.8 $\pm$ 121.7	727.1 $\pm$ 206.3	NS
Apparent liver blood flow (ml/min)	1081.1 $\pm$ 188.7	1283.0 $\pm$ 374.1	NS

* Student's *t* test for paired data.

NS = not significant.

mean volume of distribution of indocyanine green, clearance of indocyanine green and apparent liver blood flow increased by 19, 17, and 19% respectively after cimetidine, but these changes were not significant.

Antipyrine kinetics are summarised in Table 2. There was a 15% reduction in antipyrine clearance and 18% increase in antipyrine half life after cimetidine. These changes were significant. Apparent volume of distribution of antipyrine was not altered by cimetidine.

There were no correlations between changes in indocyanine green kinetics and changes in antipyrine kinetics in individual subjects.

Discussion

The absence of a significant change in indocyanine green clearance in this study clearly shows that the reductions in apparent liver blood flow previously observed⁴ after single doses or short courses of cimetidine are not maintained during a full four week course of treatment. The reduction in antipyrine clearance, however, shows that the enzyme inhibiting effect of cimetidine may continue throughout treatment.

Table 2 Antipyrine kinetics before and after cimetidine 1 g per day for four weeks, in eight subjects (mean $\pm$ SD)

	Before cimetidine	After cimetidine	<i>p</i> value*
Antipyrine half life (h)	12.2 $\pm$ 2.0	14.3 $\pm$ 3.4	<0.05
Antipyrine volume of distribution (litres)	38.1 $\pm$ 5.6	36.0 $\pm$ 7.5	NS
Antipyrine clearance (ml/min)	36.5 $\pm$ 3.7	30.9 $\pm$ 7.1	<0.05

* Student's *t* test for paired data.

NS = not significant.

In the context of regional blood flow, this finding is not altogether surprising. The cimetidine-associated decrease in effective renal plasma flow observed after one and seven days of treatment had returned to basal values after three weeks of cimetidine treatment.¹⁶ Another study examined the effects of cimetidine on cerebral blood flow after a single intravenous dose, and found no reduction in young or elderly subjects.¹⁷ Bolus injections of cimetidine 400 mg were noted to produce only transient (10 minute) decreases in systemic and pulmonary arterial pressure, but no changes in cardiac output.¹⁸ Chronic oral cimetidine 400 mg four times daily, however, produced no demonstrable cardiovascular changes.¹⁹

In the present study we did not examine the effects of a single dose or a short course of cimetidine on apparent liver blood flow. Therefore we are unable to state whether there was any reduction in apparent liver blood flow in our subjects. It is possible that there may have been some reduction in apparent liver blood flow at the start of treatment which had disappeared after four weeks of treatment. Another possible but unlikely explanation for our findings is a cimetidine-associated change in the intrinsic hepatic extraction ratio of indocyanine green such that it offset the change in hepatic blood flow and resulted in an unchanged value for indocyanine green clearance.

Acute intraportal administration of histamine receptor antagonists in normals and in patients with portal hypertension secondary to hepatosplenic schistosomiasis, suggests a role for H₁ rather than H₂ receptor antagonists in the pathogenesis of portal hypertension.²⁰ In animals, administration of histamine into the hepatic artery leads to vasodilatation, while intraportal administration leads to a rise in portal vascular resistance.²¹⁻²³ These responses to histamine are blocked by H₁ receptor antagonists but not by H₂ receptor antagonists.²³ On the basis of our findings, and the failure of intravenous cimetidine to lower portal pressure in patients with cirrhosis and portal hypertension,⁸ we cannot support the suggested use of cimetidine as a treatment for portal hypertension.³ In man it is unlikely that other H₂ receptor antagonists such as ranitidine, or currently available H₁ receptor antagonists will be found useful in the treatment of portal hypertension.

In contrast with the possible transient effect of cimetidine on liver blood flow, the effect on microsomal enzyme activity appears to persist. We have previously noted a similar reduction in antipyrine clearance after a three day course of cimetidine 400 mg four times per day.²⁴ This reduction in hepatic microsomal enzyme activity is

probably the basis for a large number of interactions between cimetidine and other drugs,²⁵ the notable pharmacokinetic ones being with anticoagulants,²⁶ anticonvulsants,^{27 28} and adrenoceptor antagonists.^{4 29 30} The present study shows that compensatory mechanisms, if any, do not reduce this enzyme inhibiting effect during four weeks of chronic therapy with cimetidine. Consequently patients on chronic cimetidine treatment remain vulnerable to such drug interactions.

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