agents. We are pleased to be able to give preliminary results of the effect of edrophonium administered during coronary angiography. The results of this study will be published, indicating that edrophonium was not associated with spasm or other abnormality of the coronary arteries. Therefore we stand by our suggestion that edrophonium is a safer provocative agent than ergometrine, which is itself used to provoke coronary artery spasm.

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Reference


Cimetidine on apparent liver blood flow

SIR.—We were interested to read the paper by Daneshmend et al in the February issue of Gut (Gut 1984; 25: 125–8) on the lack of effect of cimetidine on apparent liver blood flow. The work contains two fundamental assumptions whose validity may be questioned and that may influence the interpretation of the authors’ findings. In addition, there are some minor errors and omissions.

Firstly, the authors calculate indocyanine green clearance by fitting a single compartment model to the plasma disappearance of the dye. Although this is frequently done, a two compartment model is more appropriate for describing the disposition of indocyanine green and sizeable errors occur in calculating clearance if the less complex model is adopted. Secondly, the authors equate clearance of indocyanine green with apparent liver blood flow, a simplification which always underestimates real liver blood flow as the hepatic extraction of indocyanine green is less than unity. This might be acceptable in paired studies if hepatic extraction remained constant but we for instance have observed that in normal subjects cimetidine impairs hepatocellular uptake of indocyanine green by mean 13-5%, and similar results have been reported in patients with liver disease. Moreover, hepatic extraction of the dye is itself altered by changes in blood flow. The changes in indocyanine green clearance reported by Daneshmend and colleagues therefore may not directly reflect changes in real liver blood flow because hepatic extraction was not measured.

The authors do not state the time of the second indocyanine green injection in relation to the last dose of cimetidine. If this interval were longer than a few hours, plasma concentrations of cimetidine would be low and a transient effect on liver blood flow might be missed. Antipyrine clearance, however, would still be affected as enzyme inhibition is unlikely to reverse so rapidly.

A less serious error occurs in Table 1. The initial volume of distribution of indocyanine green is usually little more than the plasma volume, but the mean value given is 33-36 litres, which is probably a typographical mistake. Finally, we are surprised that the 19% average increase in indocyanine green clearance did not reach statistical significance. Presumably the large inter-individual variation and the small number of subjects introduced a type II error.

There is unfortunately a conflicting literature on the possible effects of cimetidine on liver blood flow and this conflict has yet to be resolved.

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References


Reply

SIR.—We thank you for giving us the opportunity to comment on the letter from Drs Graingger, Marigold, and Thompson.
Some of the criticisms we cannot accept and we do not wish to change the interpretation of our data. The plasma concentration decay in the subjects studied fitted a one compartment model perfectly adequately and in our experience a biphasic decay is seen only rarely in the absence of hepatic dysfunction. There can be no error of interpretation resulting from this mode of calculation. Dr Grainger and colleagues are correct in their criticisms of the use of indocyanine green clearance itself as an index of hepatic blood flow and this is acknowledged in our text. Recently it has been shown that not only cimetidine but also ranitidine may reduce the extraction ratio of indocyanine green in cirrhotic patients. We know of no similar evidence in animals or subjects with normal hepatic function, but if the H₂ blockers do indeed reduce the extraction ratio of the dye then much of the previous work purporting to show that they reduce liver blood flow is invalidated.

It is true that changes in liver blood flow have been shown to have a small effect on the extraction ratios of some highly cleared drugs but the relevance of this fact to the interpretation of our data escapes us. There are no grounds for presuming that a type II error has been made in the analysis of our data. In the first place the direction of the small and statistically insignificant change in mean indocyanine green clearance was opposite to the a priori expectation. Secondly, despite the variability in indocyanine green clearance studying 10 subjects should produce a sufficiently powerful experiment to detect clinically important changes.

We would agree that the literature is becoming confused on the issue of H₂ blockers and changes in liver blood flow and would reiterate our belief that this aspect of their pharmacology has in the past been overemphasised.

We thank Dr Grainger and colleagues for pointing out the typographical error. The volumes of distribution of indocyanine green as printed would be in decilitres.

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Reference