CIMETIDINE PRETREATMENT AND HALOTHANE HEPATOTOXICITY

Sir,—The recent article by Dr Ray and co-workers [1] discussed a complex problem, but did not mention a possibility which needs to be considered. The study involved premedicating patients with large doses of cimetidine, with the assumption that this drug would inhibit the biotransformation of halothane which was given later for anaesthesia. The finding that plasma concentration of glutathione S-transferase (GST) increased in these cimetidine-pretreated patients following halothane and also in patients not "metabolically inhibited" led the authors to conclude that metabolism of the anaesthetic is not connected to the mild hepatic damage perceived as increases in plasma GST. Some investigators had theorized that the increase in GST in a population of patients receiving halothane was a result of the quantitatively small reductive pathway of biotransformation. The authors' conclusion that metabolism may play no role in the increase in GST concentration may well be the case, but there has been an oversight I wish to bring to their attention.

Animal studies indicate that the two pathways of halothane biotransformation may display different levels of inhibition. Fiserova-Bergerova [2] demonstrated in rats that isoflurane inhibited the oxidative biotransformation of halothane to a far greater extent than the more rugged reductive biotransformation pathway. In fact, reductive biotransformation was enhanced under the circumstances of her experiments. If this were the case with cimetidine in the study from Edinburgh, then the reductive biotransformation of halothane may have continued, with subclinical damage as indicated by the increased concentrations of GST.

Studies of this nature should examine plasma concentrations of metabolites. Without this observation, it cannot be assumed that biotransformation is inhibited.

B. R. BROWN, JR
Tucson

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Sir,—Thank you for the opportunity to reply to Dr Brown's letter. Dr Brown suggests that the increased GST concentration noted after halothane anaesthesia may result from the formation of reductive metabolites of halothane. Consequently, although cimetidine may inhibit halothane metabolism by an oxidative pathway, it may not prevent, or may even augment, the formation of non-oxidized metabolites. We cannot deny that this may be possible; however, evidence suggests that cimetidine inhibits both pathways.

Plummer and colleagues [1] investigated the influence of cimetidine on halothane metabolism in rats. Using measurements of exhaled metabolites 2-chloro-1,1,1-trifluoroethane and 2-chloro-1,1-difluoroethylene, and of urinary fluoride excretion, they found that reductive metabolism was inhibited by cimetidine. Wood and co-workers [2] demonstrated inhibition of oxidative metabolism by cimetidine. However, using urinary fluoride excretion as the only indicator of reductive metabolism, they were unable to demonstrate inhibition, but acknowledged the limitations of this method alone.

In man, the pattern of enflurane metabolism suggests that such metabolism is unlikely to be the cause of the similar changes in plasma GST that occur after anaesthesia with both enflurane and halothane [3]. Enflurane is metabolized only by an oxidative pathway; cimetidine does not influence its metabolism [4, 5]. Oxidative enflurane metabolites, therefore, must generate the same picture of damage as the reductive metabolites of halothane that Dr Brown proposes. This is not consistent with the common metabolic basis for liver dysfunction caused by the two agents, proposed by Christ and colleagues [6].

Although there is animal evidence to suggest that cimetidine inhibits both oxidative and reductive metabolism of halothane, we agree that measurement of plasma concentrations of metabolites would be the only certain means of determining that halothane metabolism had been inhibited.

D. C. RAY
A. F. HOWIE
G. J. BECKETT
G. B. DRUMMOND
Edinburgh

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PCA or PAA?

Sir,—We wish to draw readers' attention to a comment in the recent symposium issue of the journal on postoperative pain control. In the editorial, Dr Armitage suggested that patient-controlled analgesia (PCA) be administered in conjunction with a continuous "background" infusion [1]. Our reading of the original article [2] found the rationale of this approach, but not the advocacy. We believe that there is now much evidence that the hybrid technique of patient-augmented analgesia (PAA) is no more effective than PCA alone.