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.

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REFERENCES

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-difluoroethane, 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.

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REFERENCES

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-suggested analgesia (PAA) is no more effective than PCA alone.
In a study of two PCA devices, a similar number of demands were made by patients using the device that also administered an infusion as those using pure PCA [3]. Second, in a prospective study comparing PCA and PAA [4] there was no difference between the techniques with respect to either pain relief or demand rate, although there was a higher incidence of major adverse effects with PAA. PCA has been compared with PAA using two infusion rates for the background infusion [5]. Again, the infusion did not either improve pain control or reduce demand rate.

From these studies we conclude that, when morphine is used for PCA, a concurrent infusion adds to the total dose of drug without a commensurate improvement in analgesia. The case for automatically prescribing a background infusion, however attractive on theoretical grounds, is not made.

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REFERENCES

Sir,—The article by Mitchell and Smith stops short of unequivocal advocacy of patient-controlled analgesia in conjunction with a continuous "background" infusion, but the authors refer to work from their department which "suggests that the 'low dose infusion + bolus' technique with morphine yields marginally better results than bolus alone." This finding is at variance with the work quoted by Owen and Mather, and they may well disagree with it, but I do not think I seriously misrepresented what Mitchell and Smith actually wrote.

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PROPHYLACTIC EPHEDRINE INFUSION IN OBSTETRIC ANAESTHESIA

Sir,—We read with interest the correspondence on the case report of Drs Stone, Thorburn and Lamb [1]. In their reply [2] the authors say that "the value of the use of prophylactic ephedrine is not clear". The case in question is that of a patient who was given a spinal block after failure of an extradural and, when the block ascended too high, finally received a general anaesthetic and IPPV. The value of prophylactic ephedrine in the management of hypotension associated with high sympathetic block is perfectly clear, particularly in obstetric anaesthesia [3]. The administration of a fluid load takes time and, in a patient who already has received a preload, the most rapid and effective treatment is to infuse ephedrine in a clear solution containing ephedrine 30 mg in 500 ml.

In our unit, after a crystalloid preload of 1 litre, this is started from the moment the spinal anaesthetic has been injected, and the rate of infusion is adjusted according to arterial pressure. If the infusion is "piggy-backed" into the i.v. line via a 21-gauge needle, and run initially at the fastest rate, this usually produces the correct rate of infusion.

As the use of prophylactic ephedrine is indicated in obstetrics, perhaps its use should be extended also to other situations during spinal anaesthesia in which a large fluid preload may cause problems. We hope that this clarifies the role of ephedrine, and that the simple technique described may help others who wish to use spinal anaesthesia in obstetrics but are concerned about hypotension.

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REFERENCES

Sir,—Thank you for the opportunity to reply to Drs Frazer and Edwards, who question our statement that, in relation to obstetric anaesthesia, the value of prophylactic ephedrine is not clear.

We would not deny that, in certain clinical situations, ephedrine has been shown to reduce the incidence of hypotension. However, hypotension continues to be reported as a problem associated with the use of extradural anaesthesia for Caesarean section [1]. We would also argue that the value of a prophylactic measure lies both in the absence of unwanted effects and in the reliability of the measures taken. Rolbin and colleagues [2] have demonstrated that unacceptable hypertension may result from the use of prophylactic ephedrine and the reliability is uncertain. Therefore we cannot agree with Drs Frazer and Edwards that the value of prophylactic ephedrine in the management is perfectly clear.

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