Effect of cimetidine on biotransformation of enflurane in man

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This study was designed to test the hypothesis that administration of clinical doses of cimetidine could affect the metabolic degradation of enflurane to inorganic fluoride via inhibition of the mixed function oxidase enzyme (MFOE) system. In Part 1 of the study 38 female patients undergoing gynaecologic surgery received, double blind, either cimetidine, 300 mg PO the night prior to surgery and 300 mg IV 30 minutes prior to anaesthesia induction or a placebo. In Part 2, 24 patients received either cimetidine as in Part 1, but with continued administration for 24 hours into the postoperative period, or a placebo. Anaesthesia in all cases was with enflurane in oxygen, via a closed circuit.

In both Parts 1 and 2 of the study there were no statistically significant differences between the two groups in serum fluoride levels at baseline, four hours or 24 hours postoperatively, or in the total urinary fluoride excretion during the first or second postoperative days. The authors speculate that this is due either to separate interactions of cimetidine and enflurane with the MFOE system or to the relatively low rate of enflurane metabolism.

Key words

METABOLISM: mixed function oxidase enzyme; BIOTRANSFORMATION: enflurane; DRUG INTERACTIONS: cimetidine.

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Presented in part at the Annual Meeting of the American Society of Anesthesiologists, Atlanta, Georgia, 1983, and the Annual Meeting of the Canadian Anaesthetists' Society, Toronto, Ontario, 1985.

Since Crandall *et al.*[1] first drew attention to the effects of inorganic fluoride on renal function in 1966, anaesthetists have been concerned about the metabolism of all fluoride-containing anaesthetics. Methoxyflurane has been shown to undergo sufficient metabolic degradation via the hepatic mixed function oxidase enzyme (MFOE) system to routinely cause fluoride levels in the nephrotoxic range.[2,3] The anaesthetic enflurane is in widespread clinical use and has a relatively well-defined risk of renal toxicity. Fluoride concentrations after enflurane anaesthesia are usually well below the level of clinical nephrotoxicity,[4] although impairment of renal concentrating ability has been demonstrated in volunteers.[5] The histamine H_2 receptor blocker cimetidine is known to inhibit the metabolism of several drugs including diazepam, warfarin, theophylline and propranolol via inhibition of the MFOE system.[6] With fluoride production specifically in mind, and with concerns about the toxic effects of metabolized hydrocarbons in general, we investigated whether it might be possible to decrease fluoride production under enflurane anaesthesia by administering clinical doses of cimetidine during the perioperative period.

Methods

This study was approved by the Dartmouth-Hitchcock Medical Center Institutional Review Board. The study was divided into two parts. Part 1 was completed and analyzed prior to the initiation of Part 2. In both Parts 1 and 2, female patients aged 18–65 gave written informed consent to participate in the study. All patients were ASA physical status I or II and were scheduled to undergo gynaecological surgery for non-malignant disease. Patients were excluded from the study if they gave a preoperative history of liver or kidney disease or if they were taking medications known to interfere with the MFOE system.

In Part 1, 38 patients were prospectively random-

TABLE I Patient data (mean ± SD)

	N	*Weight (kg)*	*Enflurane (ml liquid)*	*Duration anaesthesia (minutes)*
Part 1				
Cimetidine	18	66.3 ± 10.0	20.9 ± 5.5	125 ± 37
Control	20	69.2 ± 11.8	20.2 ± 5.9	129 ± 44
Part 2				
Cimetidine	12	69.5 ± 10.6	18.6 ± 6.1	155 ± 32
Control	12	70.4 ± 18.4	17.7 ± 7.9	128 ± 67*

*$p < 0.05$.

ized to receive either cimetidine 300 mg PO the night prior to surgery and 300 mg intravenously 30 minutes prior to anaesthesia induction (cimetidine group) or a placebo PO the night prior to surgery and 2 ml normal saline intravenously 30 minutes prior to anaesthesia induction (control group). Preoperative medication was diazepam 0.2 $mg \cdot kg^{-1}$ PO in all patients. Anaesthesia was induced with 3–4 $mg \cdot kg^{-1}$ of thiopentone followed by 1–1.5 $mg \cdot kg^{-1}$ of succinylcholine to facilitate endotracheal intubation. Anaesthesia was then maintained with enflurane in oxygen via a closed circuit system with quantitative delivery of enflurane calculated on the basis of body weight to achieve and maintain an end tidal enflurane concentration of approximately 1.3 MAC.[7] Blood samples for fluoride determination were drawn prior to anaesthesia induction (baseline fluroride) and four (4-hr fluoride) and 24 (24-hour fluoride) hours after termination of anaesthesia. All serum samples were kept frozen in plastic containers until analysis. Urine was collected in two 24-hour aliquots beginning with anaesthetic induction and refrigerated at 4°C until analysis was performed.

Part 2 of the study was similar to Part 1 except that half the patients received cimetidine 300 mg PO the night prior to surgery, 300 mg IV 30 minutes prior to induction of anaesthesia and 300 mg IV every six hours thereafter for a total of five intravenous doses (cimetidine group); the remaining patients received a placebo as in Part 1 (control group). Medication administration during Parts 1 and 2 was double-blind. Serum fluoride levels[8] and total urinary fluoride excretion[9] were then measured (Orion fluoride electrode, Model 194-09, Orion Research Incorporated, Cambridge, Massachusetts). Group means were compared by one-way analysis of variance and statistical differences were considered significant when $p < 0.05$. Statistical significance was assessed by nonparametric analysis (Kruskal-Wallis).[10]

Results

In Part 1 of the study there were 18 patients in the cimetidine group and 20 patients in the control group. In Part 2 there were 12 patients in each group. In Part 1 there were no significant differences between the control and cimetidine groups in total enflurane dose, body weight, or duration of surgery. In Part 2 there was no significant difference in total enflurane dose or weight. The patients in the cimetidine group had a slightly longer duration of surgery (Table I).

The results of the serum and urine fluoride analysis for Part 1 are summarized in Table II. There is no statistically significant difference between the two groups in the levels of fluoride prior to anaesthesia, four hours after anaesthesia or twenty-four hours after anaesthesia. In addition, total fluoride excretion in the urine during the first

TABLE II Results – Part 1 (mean ± SD)
Serum fluoride levels ($\mu mol \cdot L^{-1}$)

Group	*Baseline*	*4-Hour*	*24-Hour*
Cimetidine	5.6 ± 0.9	16.2 ± 1.5	13.3 ± 1.4
Control	4.7 ± 0.9	17.9 ± 1.9	14.5 ± 2.1
Total urine fluoride (mg)			
	1st 24 hr	*2nd 24 hr*	*Total 48 hr*
Cimetidine	19.5 ± 2.4	19.7 ± 3.2	39.8 ± 5.1
Control	26.0 ± 4.3	24.6 ± 4.5	51.4 ± 8.7

TABLE III Results – Part 2 (mean ± SD)
Serum fluoride levels ($\mu mol \cdot L^{-1}$)

Group	*Baseline*	*4-Hour*	*24-Hour*
Cimetidine	2.3 ± 2.6	8.1 ± 4.3	5.8 ± 1.7
Control	2.6 ± 3.7	8.0 ± 2.3	7.3 ± 2.9
Total urine fluoride (mg)			
	1st 24 hr	*2nd 24 hr*	*Total 48 hr*
Cimetidine	21.7 ± 14.7	10.6 ± 4.9	28.1 ± 11.2
Control	16.1 ± 7.0	11.4 ± 11.2	29.6 ± 21.0

two postoperative days was not statistically different between the two groups.

In Part 2 of the study there were again no differences in serum fluoride levels between the two groups (Table III). During the first and second 24-hour periods there was no significant difference in urinary fluoride excretion between the two groups. There was also no significant difference in total 48-hour urinary fluoride excretion.

Discussion

Concerns regarding the organ toxicity of inhaled anaesthetic agents have been prevalent since chloroform came into widespread use over a century ago.[11] It is interesting to compare the attitudes towards chloroform with those regarding contemporary inhalational agents. Despite persistent evidence of toxicity and the dangers of chloroform administration, advocates continued to argue in its favour until relatively recently.[12] The current climate, perhaps enhanced by the publicity surrounding the issue of halothane hepatotoxicity, often seems to condemn all potent inhaled agents even in the face of records of safety undreamed of a few years ago. A more balanced approach to the issue of drug toxicity would be to identify the patient population at risk and then attempt to abolish or attenuate the risk of toxicity.

Previous workers have questioned whether prior or concomitant administration of non-anaesthetic drugs can alter the metabolic disposition of enflurane.[13] To date, this has involved exclusively the demonstration of increased metabolism, perhaps due to enzyme induction. This is of great clinical importance since substantial evidence suggests that it is the metabolites of inhalational agents, more than the unaltered agents, which contribute to organ toxicity.[14] To our knowledge, the present study represents the first clinical attempt to diminish the production of toxic metabolites of anaesthetic agents via the use of a known MFOE inhibitor.

Since peak serum fluoride levels are thought to correlate best with the occurrence of nephrotoxicity,[3] we chose to examine the level of fluoride four hours after termination of anaesthesia because of previous work that demonstrated peak levels to occur at that time.[15] We found considerable variation in fluoride levels between individuals – a response which has been previously documented. There were no significant differences in serum fluoride levels between the groups at any time. This was true despite our attempt to control as many variables during enflurane exposure as possible. For example, we studied only female patients (more constant ratio of body fat and water content to total body weight), and enflurane was delivered quantitatively via a closed circuit technique which, in comparison to inspired MAC-hours, eliminates the impact of factors such as alveolar ventilation, circuit design, and fresh gas flow rate as considerations in anesthetic uptake.

Total enflurane metabolism as estimated from quantitative urinary fluoride excretion also varied considerably between individuals. Alterations in fluoride clearance can be influenced by such factors as urinary pH[16] and extracellular fluid volume.[17] Although not specifically addressed in our study, these effects should have been balanced between the two groups on the basis of randomization. Therefore, since individual variation in enflurane excretion persisted, even after controlling for such factors as delivered dose, body fat content, and drugs known to induce the hepatic MFOE system, this variability seems likely to be a result of individual variation in hepatic metabolism.

The absence of an effect of cimetidine pretreatment (Part 1) on total 48-hour urinary fluoride excretion is not surprising given the long duration of enflurane metabolism. This is presumably due to protracted release of enflurane from depot storage in body fat and the comparatively short half-life of cimetidine. Our original thesis was that inhibition of the MFOE system by cimetidine would decrease fluoride production under enflurane anaesthesia. We were unable to demonstrate such an effect even with continued administration of cimetidine for 24 hours into the postoperative period (Part 2). Com-

parison of the total first 24-hour excretion of fluoride/ml enflurane delivered yielded no significant difference between groups (1.13 mg fluoride/ml enflurane-cimetidine group; 1.02 mg fluoride/ml enflurane-control group; $p = 0.7$).

The dosage of cimetidine used in this study was similar to that which has been shown to impede hepatic metabolism of other drugs. Since we could demonstrate no change in enflurane metabolism, we speculate that cimetidine and enflurane have separate interactions with the MFOE system. An alternative explanation might be due to the relatively low rate of enflurane metabolism. Since a relatively small percentage of a delivered dose of enflurane is metabolized, it might be difficult to detect an effect from a competitive inhibitor such as cimetidine.

In summary, standard doses of cimetidine pretreatment as commonly utilized for antacid prophylaxis in anaesthesia had no significant effect on enflurane metabolism as reflected in peak serum fluoride levels or total urinary fluoride excretion during the first 48 postoperative hours. Continued administration of cimetidine for 24 hours into the postoperative period also did not alter the metabolic degradation of enflurane to inorganic fluoride nor did it affect fluoride blood levels.

Acknowledgements

The assistance of Laurie Hildebrande for the laboratory analysis, and Kristin Lanphear and Donna Dempsey for help in preparing the manuscript is gratefully acknowledged.

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Résumé

Cette étude a été conçue afin de vérifier que l'hypothèse de l'administration de cimetidine à des doses cliniques peut affecter la dégradation métabolique de l'enflurane en fluorure inorganique par inhibition de la "mixed function oxidase enzyme system (MFOE)." Dans la première partie de l'étude 38 patients devant subir une chirugie gynécologique ont reçu à double insu soit de la cimétidine 300 mg PO la veille de la chirurgie et 300 mg IV 30 minutes avant l'induction de l'anesthésie, ou du placebo. Dans la deuxième partie, 24 patients ont reçu soit de la cimetidine comme pour la première partie avec l'administration continue pour 24 heures dans la période post-opératoire, ou du placebo. Pour tous les cas l'anesthésie était accomplie avec de l'enflurane dans l'oxygène dans un circuit fermé.

Aucune différence statistiquement significative n'était observée entre les deux groupes dans les deux parties 1 et 2 quant au taux de fluore sérique lors du contrôle, quatre heures et 24 heures post-opératoires ou dans le fluore total urinaire excrété le premier et le deuxième jour post-opératoire. Les auters supposent que ceci peut être dû soit aux interactions séparées de la cimetidine et de l'enflurane sur le système MFOE ou au taux de métabolisme relativement bas de l'enflurane.