Liver function after sevoflurane or isoflurane anaesthesia in neurosurgical patients

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Purpose: Although both sevoflurane and isoflurane are thought to be less hepatotoxic than halothane or enflurane, recent case reports have described liver injury after sevoflurane or isoflurane anaesthesia. There are no studies comparing liver function after sevoflurane or isoflurane anaesthesia. The purpose of this study was to compare serum liver enzyme concentrations in patients receiving either sevoflurane or isoflurane anaesthesia prospectively.

Methods: Ninety patients scheduled for elective neurosurgery were studied. Serum concentrations of aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (TBil), alkaline phosphatase (ALP), γ -glutamyl transpeptidase (GTP), and lactate dehydrogenase (LDH) were measured before and, 1, 2, 3, 7, and 14 days after either sevoflurane (45 patients) or isoflurane (45 patients) anaesthesia.

Results: AST, ALT and GTP increased peaking seven days after anaesthesia, especially in the isoflurane group. The numbers of patients with abnormal values in AST and ALT were not different in the isoflurane from that in the sevoflurane group. The increase in TBil peaked one day after anaesthesia in both groups.

Conclusion: Even in a small number of patients, isoflurane induced an elevation of serum levels of liver enzymes more frequently than did sevoflurane three to 14 days after anaesthesia.

Objectif : Quoique le sévoflurane et l'isoflurane soient censés être moins hépatotoxiques que l'halothane ou l'enflurane, on a rapporté de récents cas de lésion hépatique à la suite d'anesthésie avec le sévoflurane ou l'isoflurane. Aucune étude comparative de la fonction hépatique n'a été faite après une anesthésie avec le sévoflurane ou l'isoflurane. L'objectif de la présente étude était de comparer de façon prospective les concentrations sériques d'enzymes hépatiques chez les patients qui ont reçu une anesthésie avec le sévoflurane ou l'isoflurane.

Méthode : Quatre-vingt-dix patients devant subir une neurochirurgie élective ont participé à l'étude. Les concentrations sériques d'aspartate-aminotransférase (AST), d'alanine-aminotransférase (ALT), de bilirubine totale (BT), de phosphatase alcaline (PAL), de γ -glutamyl transpeptidase (GTP) et de lactate-déshydrogénase (LDH) ont été mesurées avant l'anesthésie, puis 1, 2, 3, 7 et 14 jours après l'anesthésie avec le sévoflurane (45 patients) ou avec l'isoflurane (45 patients).

Résultats : L'AST, l'ALT et la GTP ont augmenté, surtout dans le groupe de l'isoflurane, avec une concentration maximale sept jours après l'anesthésie. Le nombre de patients présentant des valeurs anormales d'AST et d'ALT n'était pas différent selon les groupes d'isoflurane ou de sévoflurane. L'augmentation de BT était à son maximum un jour après l'anesthésie dans les deux groupes.

Conclusion : Même dans un petit groupe de patients, l'isoflurane provoque une élévation des niveaux sériques d'enzymes hépatiques selon une plus grande fréquence que ne le fait le sévoflurane de 3 à 14 jours après l'anesthésie.

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SINCE starting to use sevoflurane and isoflurane, we have questioned their effects on liver function because abnormal serum concentrations of liver enzymes seemed to be increased compared with those observed after enflurane anaesthesia. Some studies have compared liver function after sevoflurane or isoflurane anaesthesia and after halothane or enflurane anaesthesia.^{1,2} Although both sevoflurane and isoflurane are less hepatotoxic than halothane and enflurane,^{1,2} recently, some cases of liver dysfunction have been reported after sevoflurane anaesthesia.^{3,4} Fulminant liver failure⁵ and necrosis⁶ were also reported after isoflurane anaesthesia. However, no abnormalities were seen when liver function after sevoflurane or isoflurane anaesthesia were compared. The purpose of this study was to compare serum liver enzyme concentrations after sevoflurane and isoflurane anaesthesia prospectively.

Subjects and methods

After institutional approval and informed consent, 90 patients (aged 45 to 70 yr), scheduled for neurosurgery (tumour resections), were divided into two groups (sevoflurane group and isoflurane group) of 45 patients each. Anaesthesia was induced with 0.1

mg·kg⁻¹ midazolam and 3 mg·kg⁻¹ thiopentone and was maintained with sevoflurane or isoflurane and nitrous oxide 67% in oxygen to maintain systolic blood pressure within 80% to 100% of baseline values. Intentional hypotension and blood transfusion were not used. Osmotic diuretics, anti-epileptic drugs and antibiotics were administered with the same protocol in all patients.

Serum concentrations of aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (TBil), alkaline phosphatase (ALP), γ -glutamyl transpeptidase (GTP), and lactate dehydrogenase (LDH) were measured one to three days before, 1, 2, 3, 7, and 14 days after surgery with commonly used methods at the central laboratory of our hospital.

All data are expressed as mean $\pm$ standard deviation (SD). Differences in AST, ALT, TBil, ALP, GTP, and LDH concentrations were analyzed using two way repeated measures analysis of variance (ANOVA) followed by unpaired *t* test for inter group differences and paired *t* test for time course differences. The differences in the number of patients with abnormal liver function between the groups were evaluated by chi-square test. A *P* value < 0.05 was considered statistically significant.

TABLE Serum levels of liver enzymes

Enzyme	Group	Days after surgery					
		Pre	1	2	3	7	14
AST 9-37* (IU·L ⁻¹)	Sev	20 $\pm$ 8	22 $\pm$ 8	20 $\pm$ 9	21 $\pm$ 7	23 $\pm$ 13	19 $\pm$ 12
	Iso	19 $\pm$ 5	23 $\pm$ 7	19 $\pm$ 6	27 $\pm$ 11*†	32 $\pm$ 13*†	22 $\pm$ 10
ALT 5-37 (IU·L ⁻¹)	Sev	20 $\pm$ 7	20 $\pm$ 11	22 $\pm$ 17	25 $\pm$ 12	30 $\pm$ 22	26 $\pm$ 18
	Iso	22 $\pm$ 7	19 $\pm$ 6	18 $\pm$ 7	32 $\pm$ 20*	49 $\pm$ 34*†	34 $\pm$ 21
Tbil 3-10 (mg·L ⁻¹)	Sev	5 $\pm$ 3	10 $\pm$ 4*	8 $\pm$ 5	6 $\pm$ 5	4 $\pm$ 3	4 $\pm$ 2
	Iso	6 $\pm$ 2	9 $\pm$ 5*	7 $\pm$ 4	6 $\pm$ 4	4 $\pm$ 2	4 $\pm$ 2
ALP 37-147 (IU·L ⁻¹)	Sev	97 $\pm$ 20	89 $\pm$ 30	87 $\pm$ 28	89 $\pm$ 27	97 $\pm$ 29	100 $\pm$ 31
	Iso	92 $\pm$ 19	88 $\pm$ 20	84 $\pm$ 25	91 $\pm$ 20	98 $\pm$ 32	101 $\pm$ 32
GTP 5-53 (IU·L ⁻¹)	Sev	24 $\pm$ 11	20 $\pm$ 14	23 $\pm$ 21	36 $\pm$ 24*	48 $\pm$ 32*	35 $\pm$ 27
	Iso	25 $\pm$ 14	32 $\pm$ 28	40 $\pm$ 37	85 $\pm$ 51*†	91 $\pm$ 75*†	65 $\pm$ 42*†
LDH 212-378 (IU·L ⁻¹)	Sev	321 $\pm$ 59	345 $\pm$ 64	324 $\pm$ 55	332 $\pm$ 66	334 $\pm$ 56	323 $\pm$ 62
	Iso	314 $\pm$ 43	319 $\pm$ 67	310 $\pm$ 41	330 $\pm$ 50	324 $\pm$ 43	317 $\pm$ 58

mean $\pm$ SD, *: *P* < 0.05 vs the control value (pre), †: *P* < 0.05 vs sevoflurane group, a): normal range, Pre: before anaesthesia, Sev: sevoflurane group, Iso: isoflurane group, AST: aspartate aminotransferase, ALT: alanine aminotransferase, TBil: total bilirubin, ALP: alkaline phosphatase, GTP: γ -glutamyltranspeptidase, LDH: lactate dehydrogenase

FIGURE The number of patients who had abnormally high serum levels of liver enzymes and bilirubin

AST: aspartate aminotransferase, ALT: alanine aminotransferase, TBil: total bilirubin, ALP: alkaline phosphatase, GTP: γ -glutamyl transpeptidase, LDH: lactate dehydrogenase, Sevo: sevoflurane group, Iso: isoflurane group. The number of patients with abnormal value in AST, ALT and GTP were more in isoflurane group than in sevoflurane group, but not statistically significant.

Results

Demographic data of patients (age, sex, body weight, duration of anaesthesia) were not different between the two groups. The AST, ALT and GTP concentrations increased, peaking seven days after surgery, especially in the isoflurane group (Table). The number of patients with abnormal AST and ALT values were not different

in the isoflurane and sevoflurane groups (Figure). The increase of TBil peaked one day after surgery in both groups. There were no changes in ALP and LDH with time, although some patients had abnormally high LDH levels before surgery related to their brain tumour. No patients showed hepatitis or liver failure after surgery.

Discussion

In this study, serum concentrations of AST, ALT and GTP were higher after isoflurane than sevoflurane anaesthesia. Even though these changes did not result in liver failure, it is likely that the enzymes originated from damaged liver cells.

The factors which can induce liver damage after inhalation anaesthesia are 1) increased intracellular calcium concentration ($[Ca^{++}]_i$),⁷ 2) metabolites of anaesthetics,⁸ 3) decreased hepatic blood flow during anaesthesia, and 4) other drugs administered perioperatively.

Halothane and enflurane release more calcium from liver cells than does isoflurane. This may damage liver cells.⁷ No reports are available regarding the effect of sevoflurane on $[Ca^{++}]_i$. Thus, further studies are required to compare the effect on $[Ca^{++}]_i$ of sevoflurane and isoflurane.

Trifluoroacetyl acid (TFA) is the common metabolite of halothane and isoflurane.⁹ Covalent binding to subcellular proteins by the TFA chloride intermediate, generated by oxidative biotransformation by the cytochrome P-450 in the liver, is implicated as a mechanism of centrilobular necrosis of the liver.⁸ In contrast, sevoflurane appears to undergo limited biotransformation and has little or no systemic toxicity in human volunteers.¹⁰ We did not measure TFA concentration, however, TFA seems to be one of the factors which induce more liver cell damage in isoflurane anaesthesia.

Halothane, which induces liver damage more frequently than do isoflurane and sevoflurane, has been reported to decrease liver blood flow more than isoflurane.¹¹ In dogs, 1.5 MAC sevoflurane reduced portal blood flow more than isoflurane.¹² However, sevoflurane increased hepatic arterial blood flow.¹³ Thus, total (portal plus hepatic arterial) blood flow is similar during sevoflurane and isoflurane anaesthesia.¹⁴

Other drugs [e.g. midazolam, thiopentone, mannitol, GlyceolTM (osmotic diuretic, Chugai, Osaka, Japan), phenytoin, cefazolin] had some effects on liver function and liver blood flow. However, all patients in this study received the same drugs according to the protocol. Therefore, differences in liver enzyme concentrations between the two groups were not attributed to these drugs.

With the small number of patients in this study, we cannot conclude that isoflurane is worse than sevoflurane in terms of post operative liver function. However, we should note that liver cell damage appeared to be greater after isoflurane than after sevoflurane anaesthesia.

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