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Comparison of Halothane, Enflurane and Isoflurane Kidney Effects Through Alanine Aminopeptidase/Urine Creatinine Values

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SUMMARY

The kidney effects of halothane, enflurane and isoflurane were evaluated by using the ratio of urinary excretion of alanine aminopeptidase (AAP) to urine creatinine. Thirty patients in ASA class 1 or 2 were studied. None had renal disease nor received nephrotoxic drugs.

Groups 1, 2 and 3 received halothane, enflurane and isoflurane respectively. Creatinine and AAP activities in urine spot tests, serum creatinine and BUN levels were determined preoperatively and on the first and second postoperative days. Urine AAP activity and AAP/urine creatinine values increased significantly on the first and second postoperative days compared with the preoperative values in all groups ($P < 0.05$). The present study did not reveal any significant difference in the kidney effects of halothane, enflurane and isoflurane through AAP/creatinine in spot urine values.

Key Words: ANAESTHETICS, VOLATILE: halothane, enflurane, isoflurane; KIDNEY: tubular function, aminopeptidases

Inhalation anaesthetics containing fluoride may cause subclinical nephrotoxicity that cannot always be demonstrated through routine blood biochemistry such as blood urea nitrogen (BUN), serum creatinine levels, creatinine clearance, urine concentrating ability or through blood and urine levels of inorganic fluoride[1,2].

Alanine aminopeptidase is a brush border enzyme of the proximal renal tubule[3]. The increase in the ratio of urinary excretion of alanine aminopeptidase (AAP) to urine creatinine in spot urine has been reported to be a sensitive indicator for evaluation of drug-induced renal tubule cellular damage[4,5].

A prospective clinical study was therefore performed to evaluate the kidney effects of halothane, enflurane and isoflurane on renal tubules through AAP/urine creatinine values.

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METHOD

Following ethics committee approval and written informed patient consent we studied 30 patients in ASA class 1 or 2 scheduled for general, orthopaedic or gynaecological surgeries. None had renal disease or had received nephrotoxic drugs. Patients who required blood, plasma expander or dextrose solutions were excluded.

The patients were premedicated with pethidine hydrochloride 1 mg/kg IM and atropine sulfate 0.015 mg/kg IM, 45 minutes before operation. Normal saline (0.9%) 5 ml/kg/h was used intravenously for all patients throughout the procedures.

The patients were randomly classified into three groups. Induction of anaesthesia was performed with thiopentone sodium 4 to 5 mg/kg IV and vecuronium bromide 0.1 mg/kg IV and endotracheal intubation performed. Oxygen and nitrous oxide were used during maintenance of anaesthesia for all patients. Halothane (0.5-1.0%) was used in group 1, enflurane (0.5-1.5%) was used in group 2 and isoflurane (0.5-1.5%) was used in group 3.

Peroperative systolic and diastolic arterial pressure, heart rate and $EtCO_2$ were recorded. Patients who experienced hypotension (arterial pressure less than 80 mmHg) or bradycardia (heart rate less than 60 beats/min) attacks throughout the procedure were excluded from the study groups.

Creatinine level and AAP activity in spot urine and

BUN, serum creatinine levels were determined. Urine AAP/urine creatinine values were calculated.

Blood and urine samples were obtained preoperatively and on the first and second days postoperatively. All samples were obtained between 8.00 a.m. and 12.00 a.m. because of the diurnal variation of AAP[5]. Urine samples were stored at −20 °C and measurements were performed within 20 days. The activity of AAP was assayed spectrophotometrically by the method of Jung and Scholz[6]. The assay is based on the conversion of alanine-4-nitroanilide in the presence of AAP to alanine and 4-nitroaniline. Assay of urine creatinine, serum creatinine and BUN were all performed by using standard automated methods in the clinical laboratory with an ASTRA-8 autoanalyser (Beckman Instruments).

The data were analysed by Student's t test and ANOVA. The criterion of statistical significance was $P<0.05$ for all comparison.

RESULTS

The demographic data of the patient groups were similar (Table 1).

Serum creatinine levels significantly decreased in group 1 on the first and second postoperative days compared to the preoperative values ($P<0.05$). This decrease was only significant on the first postoperative days in group 2 and 3 ($P<0.05$). There were no significant differences among the three groups.

BUN levels significantly decreased in group 2 on the first postoperative day compared with the preoperative values ($P<0.05$). There were no significant differences among the three groups (Table 2).

Urinary AAP activity in spot urine increased significantly on the first and second postoperative days in all groups ($P<0.05$). There were no significant differences among the groups (Table 3).

AAP/creatinine values increased significantly on the first postoperative days and remained increased on the second postoperative days compared to the preoperative values in all of the groups ($P<0.05$). AAP/creatinine values did not reveal any differences among the groups (Figure 1).

TABLE 1

Demographic characteristics of the patients (SD)

	Group 1 (Halothane)	Group 2 (Enflurane)	Group 3 (Isoflurane)
Sex (F/M)	7/3	9/1	10/0
Age (years)	39.0 (5.89)	41.0 (3.31)	36.8 (2.76)
Duration of operations (min.)	148.5 (19.2)	124.0 (19.1)	142.3 (22.1)

TABLE 3

Urine AAP values (nmol/ml) (SD)

	Group 1 (Halothane)	Group 2 (Enflurane)	Group 3 (Isoflurane)
Preoperative	0.009 (0.005)	0.034 (0.012)	0.025 (0.019)
Postoperative 1 day	0.124 (0.011)*	0.134 (0.009)*	0.139 (0.008)*
Postoperative 2 day	0.139 (0.011)*	0.144 (0.014)*	0.123 (0.009)*

* $P<0.005$ refers to changes from preoperative values.

DISCUSSION

AAP is not normally filtered into the glomeruli, because of its large molecular size ($M_r=240.000$). Urinary excretion of AAP rises in proximal tubular stress or injury states, such as toxic and ischaemic acute tubular necrosis, urorenal neoplasms, acute transplant rejection, severe jaundice, acute glomerulonephritis and acute pyelonephritis. An increase in urinary AAP without clinical evidence of renal insufficiency in patients with normal renal function could be observed. The indicator of renal tubular function such as creatinine and BUN may be unable to detect subclinical renal damage. Although elevated urinary AAP is a nonspecific finding, it is a highly sensitive indicator for evaluation of drug nephrotoxicity[3,7].

Inhalational anaesthetics containing inorganic fluoride such as halothane, enflurane and isoflurane are used in current practice worldwide. Inorganic

TABLE 2

Serum BUN and creatinine values (mg/dl) (SD)

	Group 1 (Halothane)		Group 2 (Enflurane)		Group 3 (Isoflurane)	
	BUN	Creatinine	BUN	Creatinine	BUN	Creatinine
Preoperative	13.8 (1.1)	0.9 (0.1)	13.5 (2.8)	0.8 (0.1)	9.4 (1.1)	0.8 (0.1)
Postoperative 1 day	9.3 (1.1)	0.8 (0.1)	8.7 (1.1)*	0.6 (0.0)*	8.1 (0.8)	0.7 (0.0)*
Postoperative 2 day	11.0 (0.5)	0.7 (0.1)*	8.0 (0.7)	0.67 (0.00)	9.2 (1.3)	0.8 (0.1)

* $P<0.005$ refers to changes from preoperative valaues.

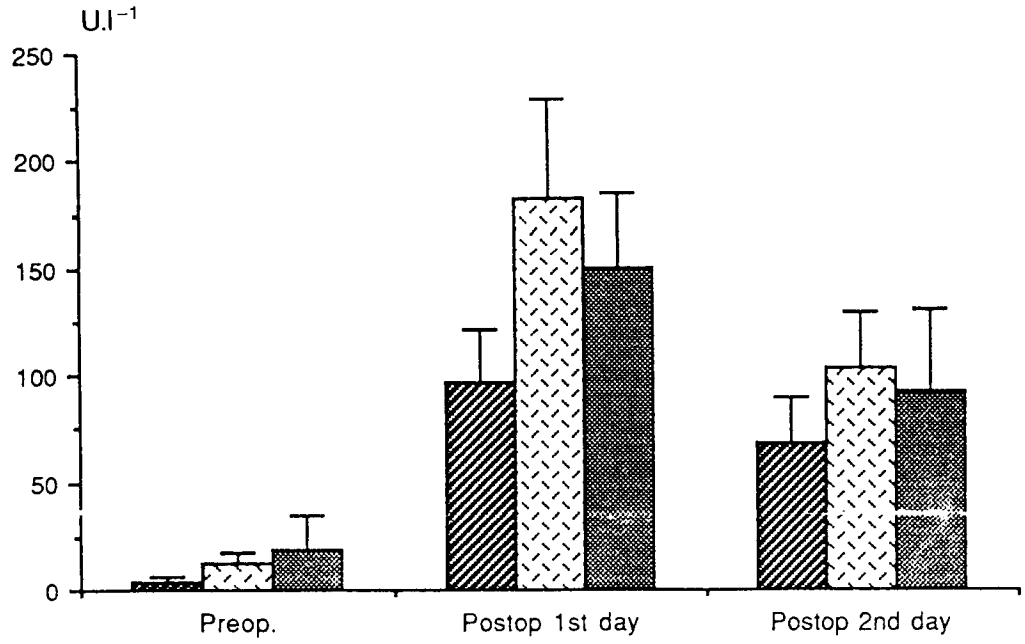

FIGURE 1: Urine AAP/creatinine ratios (U.l^{-1}) (SEM).

fluoride may damage the renal tubule and this effect is characterized by vasopressin-resistant polyuria[2,7]. Previous studies comparing the nephrotoxicities of inorganic fluoride-containing anaesthetics revealed halothane to have less kidney effect and enflurane more potential nephrotoxicity[2,7,8]. However the three diferent agents have not previously been compared through AAP/creatinine in spot urine values.

In our study, the postoperative decreases in some groups of BUN and serum creatinine values may result from reduced protein intake, increased intravenous fluid administration and increased diuresis or a low sensitivity of this test for detecting nephrotoxicity.

Our patients did not have tubular stress or injury states like renal operation or nephrotoxic drugs such as aminoglycosides and cephalosporins. Motuz et al[7] found no increase in urinary AAP in a control group who underwent anaesthesia with nitrous oxide/opioid, but they found increases following enflurane. This appears to be the only evidence implicating the volatile anaesthetics as the causative agents. We believe that this uniform difference in AAP/creatinine values should result from the sensitivity of this test for nephrotoxicity.

Although all of the three inorganic fluoride-containing inhalational anaesthetics showed kidney effects through elevated AAP/urine creatinine values following anaesthesia, the present study did not reveal any statistically significant differences between halothane, enflurane and isoflurane effects.

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