

Renal Function in Fischer 344 Rats with Chronic Renal Impairment after Administration of Enflurane and Gentamicin

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To assess the potential for producing nephrotoxicity in rats with abnormal renal function, the renal effects of enflurane or halothane anesthesia, 1 MAC for two hours, were examined in six groups of six Fischer 344 rats each with surgically induced chronic renal impairment. As an additional predisposing factor, gentamicin, 5 mg/kg/day, was administered for one week before and for one week after anesthesia to three of the groups, one anesthetized with enflurane, one anesthetized with halothane, and one unanesthetized. No significant change in renal function could be attributed to either anesthetic agent. Serum inorganic fluoride levels four hours and 24 hours after enflurane anesthesia were similar in the gentamicin-treated and the non-gentamicin-treated groups. Clinically small but statistically significant increases in serum creatinine concentration and urinary flow occurred in all three gentamicin-treated groups during the period of treatment. Anesthesia with either enflurane or halothane in rats with chronic renal impairment treated with gentamicin did not result in additional renal damage. (Key words: Anesthetics, volatile: enflurane; halothane. Antibiotics: gentamicin. Ions: fluoride. Kidney: failure; toxicity. Toxicity: renal.)

IN 1973, Mazze and Cousins¹ described a patient with methoxyflurane-induced F^- nephropathy in whom renal impairment was markedly aggravated by the postoperative administration of gentamicin. They subsequently demonstrated in Fischer 344 rats, an animal model for anesthetic and aminoglycoside antibiotic nephrotoxicity, that there was toxic interaction between methoxyflurane and gentamicin.² Enflurane is also metabolized to F^- but to a lesser extent than is methoxyflurane. Its administration does not result in clinically significant renal dysfunction in surgical patients and volunteers without renal disease,^{3,4} nor has toxic interaction between gentamicin and enflurane been reported. However, there have been three reports of patients with abnormal

renal function whose conditions worsened following enflurane anesthesia.⁵⁻⁷ This study was carried out to determine whether enflurane anesthesia would aggravate surgically induced chronic renal impairment in Fischer 344 rats concurrently treated with gentamicin.

Methods

Sixty 11-month-old, male, Fischer 344 rats[¶] were bedded on ground corn cob,** four to a cage, and quarantined for a week prior to experimentation. Room temperature was maintained at $21 \pm 1^\circ C$ and artificial light was provided from 6 A.M. to 7 P.M. each day. Rat chow^{††} containing 21 mg/kg of F^- and tap water containing 1 ppm of F^- ($52.6 \mu M$) were allowed *ad libitum* throughout the experiment, which lasted 154 days. Figure 1 depicts the experimental schedule. On day zero, rats were placed in metabolic cages. To measure renal function, three 24-hour urine samples were collected, one the day before, one the day of, and one the day after a 2-ml sample of tail blood was obtained. Serum and urinary samples were analyzed for sodium, potassium, F^- , urea nitrogen and creatinine concentrations and osmolality. Hematocrit was measured on all blood samples using a micromethod; body weight was determined two to three times weekly. Sodium and potassium concentrations were determined with an Instrumentation Laboratories #143 Flame Photometer and F^- concentration was measured with an Orion Ion Specific F^- electrode and #801 Ionalyzer.⁸ Urea nitrogen and creatinine samples were analyzed with a Technicon AutoAnalyzer II and osmolality was measured with an Advanced Cryomatic Osmometer, Model 3CII. Twenty-four-hour sodium, potassium, F^- , urea nitrogen, creatinine and osmolal excretions were determined. Urea nitrogen and creatinine clearances were calculated and expressed in ml/min/100 g body weight.

Renal insufficiency was produced surgically by the method of Kaufman *et al.*⁹ Rats were operated upon on two occasions, employing pentobarbital anesthesia, 6 mg/kg, ip. At the first procedure, day 21, the upper and lower poles of the left kidney were excised. Seven

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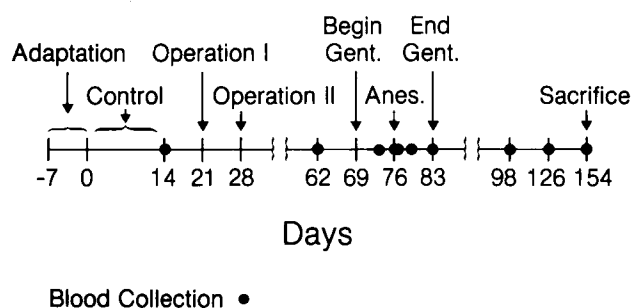


FIG. 1. Experimental schedules for all groups. Abbreviations: Anes. = day of anesthesia; Gent. = gentamicin, 2.5 mg/kg, twice daily.

days later, a right nephrectomy was performed. Four weeks later, renal function of the 39 surviving rats was again determined. On the basis of these studies, three rats were discarded from the experimental group: two had severe renal failure and were unlikely to survive the experiment; the third had only minimal renal impairment. The remaining 36 rats were randomly allocated into the six groups of six animals each (table 1). On day 69 of the experiment a 15-day course of gentamicin, 2.5 mg/kg, ip *b.i.d.*, was commenced in rats of Groups 2, 4 and 6. In a pilot study, it had been established that this dose resulted in blood levels in the clinical therapeutic range (5–10 $\mu\text{g/ml}$).¹⁰ Control animals received equivalent volumes of physiologic saline solution by ip injection. On day 8 of gentamicin treatment, rats of Groups 1 and 2 were placed in a plexiglass chamber and were exposed to compressed air, 4–6 l/min, for two hours. Rats of Groups 3 and 4 were placed in a similar chamber and received 1 per cent halothane in compressed air. Rats of Groups 5 and 6 were placed in a third chamber and exposed to 2 per cent enflurane in compressed air for two hours. Inspired anesthetic concentrations were monitored with an Hewlett-Packard model 5830A gas chromatograph and inspired oxygen concentration with an Instrumentation Laboratories #401 oxygen analyzer. Rectal temperatures of representative rats were monitored with a multichannel Yellow Springs Tele-Thermometer; body temperature was maintained in the normothermic range with the

aid of a heated water mattress placed under the chamber floor. After recovering from anesthesia, rats were returned to their metabolic cages.

Daily 24-hour urine samples were collected for two weeks beginning with the first day of gentamicin treatment. Blood samples were collected 5, 9, 11, and 15 days after the start of gentamicin treatment (days 73, 77, 79, and 83) for assessment of renal function. An additional 0.5-ml sample was obtained from every animal four hours after anesthesia (day 76) for measurement of F^- ; peak F^- levels after enflurane anesthesia usually occur at this time in rats.¹¹ Serum gentamicin levels were determined one hour after injection on days 73, 79, and 83 and one hour before injection on day 72, using a radioimmunoassay method.^{‡‡}

After gentamicin treatment was completed, rats were housed in communal cages, four animals to a cage. They were returned to metabolic cages for six-day periods beginning two weeks, six weeks, and ten weeks later, to assess any late changes in renal function. On day 154, rats were killed by decapitation and a blood sample was obtained from each for biochemical studies.

Group means \pm SE for each variable were determined and differences among groups established by analysis of variance and Newman-Keuls *post-hoc* test. Intragroup differences were determined by *t* tests for paired data. $P < 0.05$ was considered significant.

Results

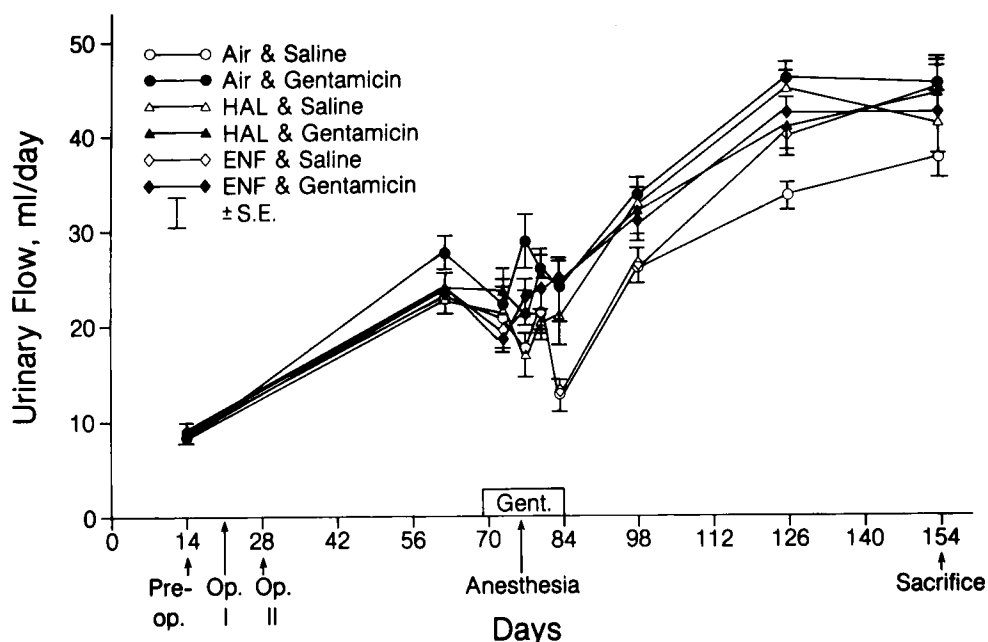
After operation, urinary flow increased by approximately twofold and osmolality decreased a reciprocal amount in every group (fig. 2, table 2); serum urea nitrogen increased by 85 per cent, serum creatinine increased by 65 per cent, and creatinine clearance decreased by 20 per cent (fig. 3, table 2). Hematocrit was slightly reduced, body weight remained stable, and urinary sodium and potassium concentrations decreased (data not shown). These changes are consistent with moderate impairment of renal function. Renal function was relatively stable throughout the period in which gentamicin and anesthetic treatments were administered, but had deteriorated perceptibly by day 126. Two rats treated with gentamicin and halothane (Group 4) died from renal failure, one each on days 152 and 153, prompting sacrifice of the remaining 34 animals on day 154. At that time it was found that several animals from every group, including those that were not anesthetized, had marked elevations of blood urea nitrogen

TABLE 1. Treatment Plan

	Gentamicin	Enflurane	Halothane
Group 1	No	No	No
Group 2	Yes	No	No
Group 3	No	No	Yes
Group 4	Yes	No	Yes
Group 5	No	Yes	No
Group 6	Yes	Yes	No

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FIG. 2. Urinary flow during the experiment. Urinary flows in all groups more than doubled after operation. Gentamicin treatment (closed symbols) resulted in statistically significantly greater urinary flow than did saline treatment (open symbols) after the ninth day of administration, but the difference was not sustained when gentamicin was discontinued.



and serum creatinine and were in terminal renal failure.

No significant change in renal function could be attributed to treatment with either enflurane or halothane. Exposure to enflurane resulted in an elevation of serum F^- four hours after anesthesia (fig. 4), and an increase in urinary F^- excretion (fig. 5). No significant difference in mean serum F^- concentrations could be demonstrated between the saline-enflurane-treated group ($25.4 \pm 2.8 \mu M$) and the gentamicin-enflurane-treated group ($21.7 \pm 2.1 \mu M$); by 24 hours serum F^- had almost returned to pre-anesthetic values. Urinary F^- excretion in the two groups were similar.

Blood gentamicin levels were in the therapeutic range (table 3). Antibiotic treatment resulted in clinically trivial but statistically significant changes in renal function in all three antibiotic-treated groups. These first became evident nine days after gentamicin treatment was initiated and persisted until the end of the antibiotic treatment period. Urinary flow (fig. 2) was maintained at a higher volume and serum creatinine (fig. 6) was elevated when compared with the non-gentamicin-treated groups. There was no renal toxic interaction between gentamicin treatment and either of the anesthetic treatments.

Discussion

The results of the present study indicate that either enflurane or halothane administered to Fischer 344 rats with moderate renal impairment is well tolerated and does not lead to further deterioration of renal

function. The results agree with those of an earlier investigation by Sievenpiper *et al.*,¹² who administered enflurane initially for two hours, and then three weeks later for six hours, to Fischer 344 rats that were sham-operated, had unilateral nephrectomy, or had the same mass of renal tissue removed as in this study. In both studies the specific toxic effects of the F^- load resulting from enflurane biotransformation and the nonspecific stress of anesthesia were well tolerated. In the present study, the administration of gentamicin caused additional minor deterioration of some measures of renal function. This was not unexpected, because in a previous study with Fischer 344 rats with normal renal function, similar gentamicin dosage resulted in toxic renal morphologic changes.¹³ There was, however, no evidence of toxic interaction between gentamicin and either halothane or enflurane.

What then is the potential for F^- -induced renal impairment after anesthesia? Dose-related, polyuric, vasopressin-resistant nephropathy following methoxyflurane anesthesia was first reported in 1966, by Crandell *et al.*¹⁴ Subsequent studies showed that F^- , released as a result of methoxyflurane biotransformation, was the cause of the renal lesion,¹⁵⁻¹⁸ and that the severity of nephrotoxicity was proportional to the concentration of serum F^- .^{17,18} In almost all reports, peak serum F^- levels occurred within three days after exposure to methoxyflurane. Patients with the highest levels had the greatest changes in renal function; most patients appeared to recover completely.^{15,18} However, in a case reported by Mazze and

Cousins,¹ the clinical course became atypical after the initiation of gentamicin therapy on the third postoperative day. There was a further increase in serum F^- with the peak value, $250 \mu M$, reached on day 6; blood urea nitrogen and creatinine concentrations increased; creatinine clearance decreased; polyuria occurred, with urinary volumes of as much as 9 l/day. Three months later, creatinine clearance was still reduced by more than 60 per cent compared with preoperative values. Toxic interaction between methoxyflurane and gentamicin in Fischer 344 rats was confirmed by Barr *et al.*² Therapy with gentamicin at the time of exposure to methoxyflurane produced greater renal damage than did treatment with either

gentamicin or methoxyflurane alone. They concluded that methoxyflurane should not be administered to patients likely to need other potentially nephrotoxic drugs.

Studies of renal function following enflurane administration generally have failed to demonstrate abnormalities. Cousins *et al.*³ administered enflurane (mean exposure, 2.7 ± 0.3 MAC hours; mean peak F^- level, $22 \mu M$) to surgical patients and compared postoperative urinary concentrating ability in response to vasopressin administration with that of a control group of patients anesthetized with halothane; there was no difference between the two groups. Mazze *et al.*⁴ administered prolonged enflurane anesthesia (mean exposure 9.6 ± 0.1 MAC hours;

TABLE 2. Laboratory Results

	Experimental Day								
	14 Preop- erative	62	73	77	79	83	98	126	154
		Gentamicin					Post-gentamicin		Sacrifice
Urinary osmolality (mOsm/kg)									
Group 1, control-saline	1977 ± 60	1064 ± 109	942 ± 95	1008 ± 107	914 ± 81	1172 ± 134	658 ± 80	616 ± 84	571 ± 87
Group 2, control-gentamicin	2193 ± 124	798 ± 78	836 ± 109	765 ± 97	799 ± 73	819 ± 100	547 ± 57	536 ± 29	489 ± 23
Group 3, halothane-saline	2166 ± 103	834 ± 62	899 ± 79	923 ± 73	897 ± 89	699 ± 66	642 ± 48	507 ± 45	516 ± 34
Group 4, halothane-gentamicin	2008 ± 96	806 ± 52	820 ± 77	871 ± 83	743 ± 58	780 ± 70	679 ± 84	546 ± 83	534 ± 65
Group 5, enflurane-saline	2099 ± 150	909 ± 42	954 ± 61	959 ± 28	952 ± 39	1109 ± 53	762 ± 39	558 ± 43	477 ± 30
Group 6, enflurane-gentamicin	2179 ± 42	855 ± 82	874 ± 53	841 ± 52	784 ± 52	739 ± 37	649 ± 31	515 ± 34	466 ± 27
Serum urea nitrogen (mg/100 ml)									
Group 1, control-saline	20.4 ± 1.3	35.4 ± 1.5	39.2 ± 3.1	36.8 ± 3.5	39.3 ± 3.5	37.8 ± 3.4	49.7 ± 5.9	63.6 ± 9.8	79.0 ± 16.6
Group 2, control-gentamicin	19.8 ± 1.2	40.1 ± 4.1	44.0 ± 3.7	42.4 ± 4.5	47.2 ± 3.9	44.9 ± 2.9	52.8 ± 5.0	71.2 ± 8.4	109.1 ± 32.9
Group 3, halothane-saline	20.2 ± 1.6	39.4 ± 1.5	40.3 ± 2.7	40.4 ± 2.7	38.5 ± 1.9	39.9 ± 1.8	54.6 ± 4.8	76.5 ± 7.3	148.1 ± 52.7
Group 4, halothane-gentamicin	19.0 ± 1.4	37.1 ± 1.0	42.7 ± 3.9	39.4 ± 2.5	43.8 ± 2.4	39.7 ± 3.0	49.9 ± 4.6	66.5 ± 7.7	65.7 ± 16.9
Group 5, enflurane-saline	20.1 ± 1.1	34.0 ± 1.4	36.3 ± 0.7	36.7 ± 0.8	39.8 ± 2.4	35.5 ± 0.9	46.6 ± 2.3	65.9 ± 4.1	75.7 ± 6.7
Group 6, enflurane-gentamicin	21.9 ± 1.3	38.3 ± 1.4	46.5 ± 2.2	41.8 ± 2.2	45.0 ± 2.5	45.5 ± 3.2	53.5 ± 3.8	72.2 ± 8.9	108.5 ± 19.9
Creatinine clearance (ml/min/100 g)									
Group 1, control-saline	0.27 ± 0.01	0.24 ± 0.01	0.21 ± 0.01	0.23 ± 0.01	0.23 ± 0.02	0.22 ± 0.02	0.23 ± 0.03	0.17 ± 0.03	0.15 ± 0.03
Group 2, control-gentamicin	0.27 ± 0.02	0.23 ± 0.01	0.21 ± 0.01	0.23 ± 0.02	0.20 ± 0.02	0.20 ± 0.02	0.22 ± 0.02	0.16 ± 0.03	0.12 ± 0.02
Group 3, halothane-saline	0.27 ± 0.04	0.23 ± 0.01	0.22 ± 0.01	0.19 ± 0.02	0.23 ± 0.03	0.21 ± 0.01	0.22 ± 0.01	0.15 ± 0.02	0.09 ± 0.02
Group 4, halothane-gentamicin	0.31 ± 0.02	0.22 ± 0.02	0.23 ± 0.01	0.23 ± 0.02	0.19 ± 0.01	0.21 ± 0.02	0.21 ± 0.02	0.16 ± 0.02	0.15 ± 0.03
Group 5, enflurane-saline	0.27 ± 0.01	0.23 ± 0.01	0.23 ± 0.01	0.26 ± 0.01	0.23 ± 0.01	0.21 ± 0.01	0.24 ± 0.01	0.17 ± 0.03	0.13 ± 0.01
Group 6, enflurane-gentamicin	0.27 ± 0.02	0.25 ± 0.02	0.20 ± 0.01	0.22 ± 0.01	0.19 ± 0.01	0.20 ± 0.01	0.21 ± 0.01	0.13 ± 0.02	0.10 ± 0.01

FIG. 3. Serum creatinine concentrations during the experiment. After operation values increased in all groups but were relatively stable during the period of gentamicin and anesthetic treatments. There was a marked increase in creatinine values in all groups on days 126 and 154. Two gentamicin-halothane-treated animals died of renal failure prior to day 154. The day 154 data point for that group, 1.6 ± 0.4 mg/100 ml, is not included in the figure. The area within the box is enlarged and shown as figure 6, below.

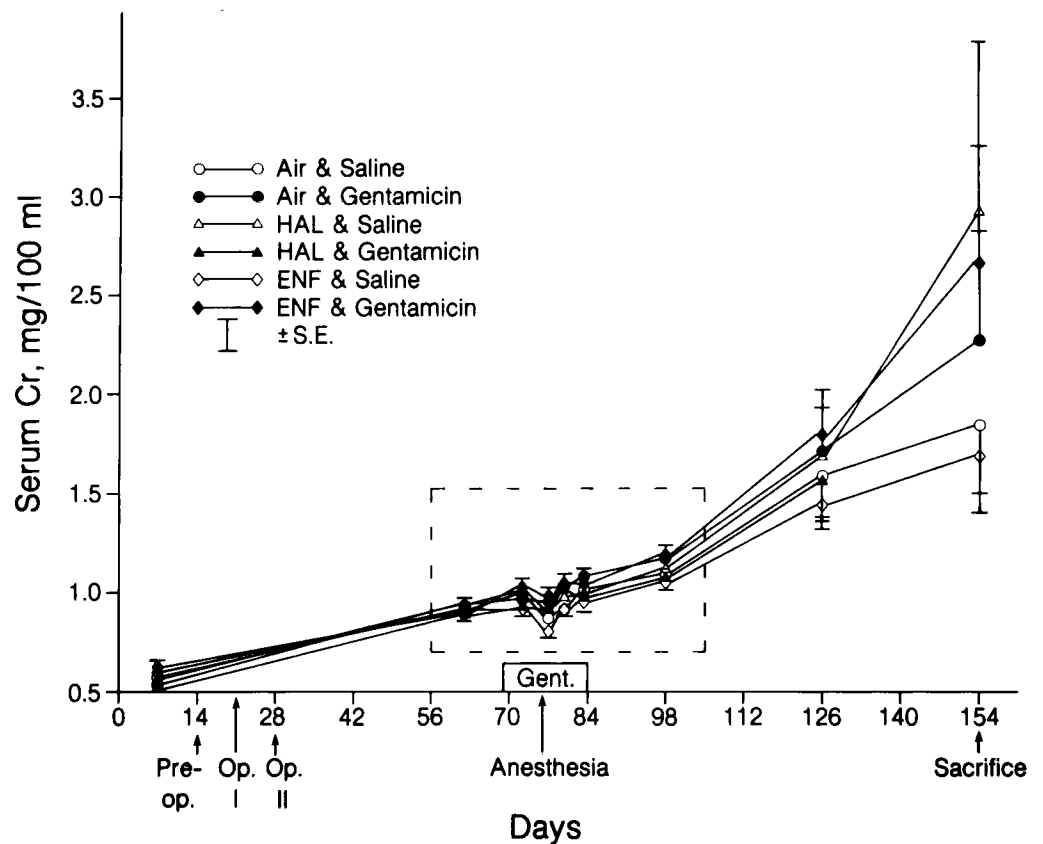
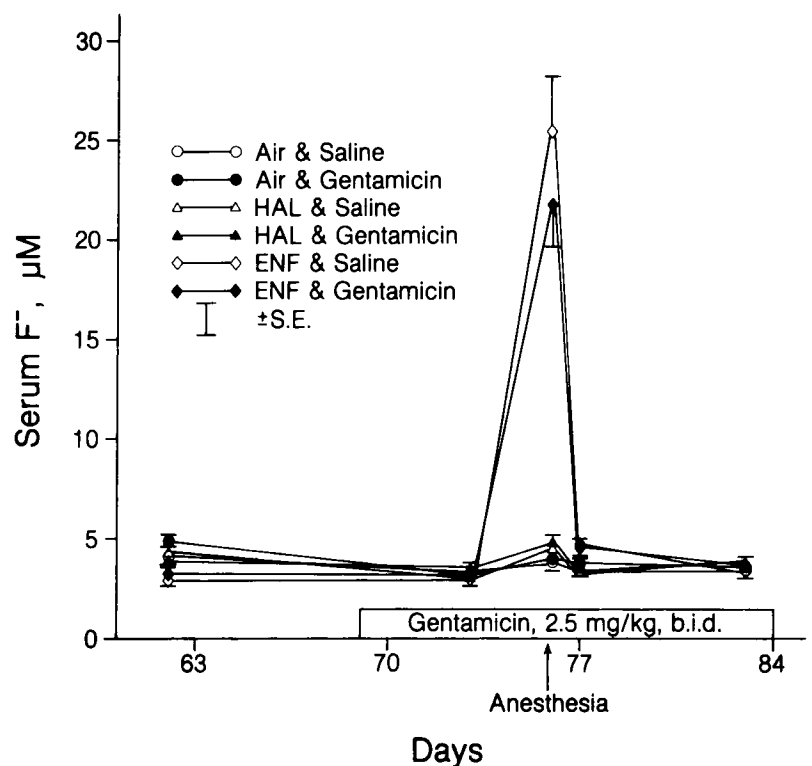


FIG. 4. Serum fluoride values during the experiment. There was no difference between the gentamicin-enflurane (ENF)-treated group and the saline-enflurane-treated group. Rats anesthetized with halothane had no increase in F^- .



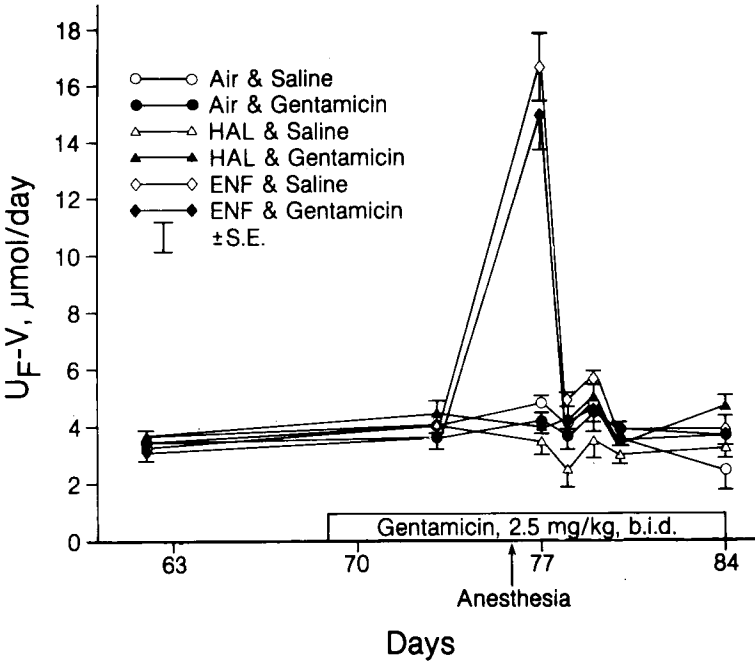


FIG. 5. Urinary fluoride excretion during the experiment. There was no difference between the gentamicin–enflurane-treated group and the saline–enflurane-treated group.

mean peak F^- level, $33.6 \mu\text{M}$) to normal volunteers and studied its effect upon urinary concentrating ability. A transient but consistent reduction in urinary osmolality, to an average of 264 mOsm/kg from a mean preanesthetic value of 1034 mOsm/kg , was observed one day after anesthesia. This is a clinically insignificant impairment of urinary concentrating ability. Volunteers exposed to halothane had a slight increase in concentrating ability. It may be concluded from these data that surgical patients with normal renal function will not have clinically significant urinary concentrating defects following enflurane anesthesia.

These studies, however, did not address the question of whether individuals with preexisting renal disease might be harmed by exposing their already damaged kidneys to a F^- load. There have been three case reports to suggest that this might occur.⁵⁻⁷ Hartnett *et al.*⁵ described a 42-year-old woman with

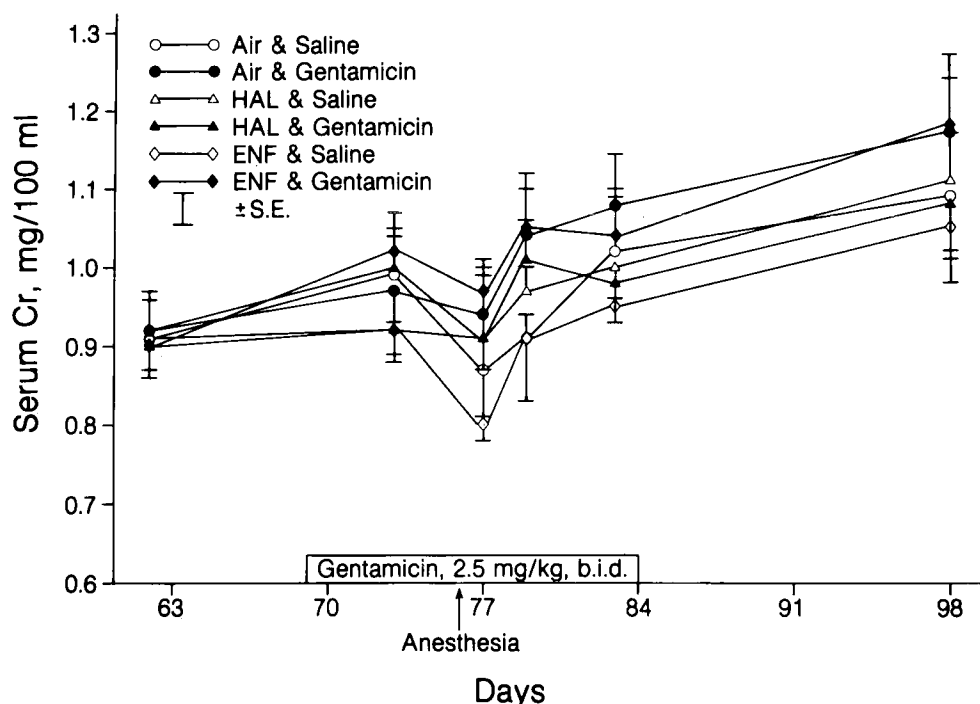
a low preoperative creatinine clearance (55 ml/min) in whom nonoliguric renal insufficiency developed after a three-hour exposure to enflurane; F^- levels were not documented. She had a period of mild intraoperative hypotension and was treated during and after operation with several potentially nephrotoxic antibiotics. Loehning and Mazze⁶ reported the case of a patient in whom enflurane anesthesia may have been a factor in the deterioration of function of a transplanted kidney. In this case, insufficient perioperative fluid replacement probably contributed to the problem. Peak F^- concentration was only $16 \mu\text{M}$. The authors suggested that the threshold of F^- nephrotoxicity might be lower in diseased or transplanted kidneys, although they presented no evidence to support this view. The third case was reported by Eichhorn *et al.*,⁷ who described a patient who had renal failure following a six-hour exposure to enflurane for creation of an ileal loop urinary diversion. The patient's postoperative course was unusual in two respects: first, anuria developed on the second day, suggesting that he may have had complete urinary tract obstruction; second, serum F^- was $96 \mu\text{M}$ on day 2 after operation, and required two weeks to return to normal values. All of these reports, therefore, are equivocal in their indictment of enflurane as the cause of postoperative renal failure.

In the only clinical study of enflurane anesthesia in surgical patients with abnormal renal function, Carter *et al.*¹⁹ examined fluoride kinetics after enflurane administration in healthy and anephric patients, and in patients with poor renal function. They

TABLE 3. Serum Gentamicin

	Serum Gentamicin ($\mu\text{g/ml}$)			
	Day 72 Trough	Day 73 Peak	Day 79 Peak	Day 83 Peak
Group 2, control	1.4 ± 0.1	8.5 ± 1.0	9.9 ± 1.2	8.1 ± 0.6
Group 4, halothane	1.2 ± 0.1	8.6 ± 0.5	8.7 ± 2.1	9.1 ± 2.1
Group 6, enflurane	1.4 ± 0.1	8.9 ± 1.2	9.4 ± 1.7	8.6 ± 1.2

FIG. 6. Serum creatinine values from days 62–98 of the experiment. Beginning on day 77, serum creatinine in the three gentamicin-treated groups was significantly higher than that in the three saline-treated groups, but the difference was not maintained after day 83.



were unable to demonstrate any clinically or statistically significant difference among the groups with respect to maximum serum F^- concentration or the rate of reduction of serum F^- after anesthesia. They concluded that enflurane was not contraindicated for surgical patients with preexisting renal disease.

Should the results of the present study be extrapolated to the clinical situation? Fischer 344 rats have been used by us and others for several years as animal models for investigation of the nephrotoxicity of both the fluorinated inhalational anesthetic agents and gentamicin.^{2,11–13,16,17,20,21} The renal lesions associated with methoxyflurane administration are similar in rats²² and man.²³ They are characterized by proximal tubular dilatation and focal necrosis, with interstitial fibrosis and oxalate crystal deposition present in cases that have progressed beyond the acute stage. The gentamicin-induced lesion is characterized by formation of proximal tubular lysosomal cytogrosgesomes, many of which contain myeloid bodies.¹³ Functionally, methoxyflurane,¹⁷ sodium fluoride,^{16,20,21} and gentamicin^{2,13} produce polyuric, vasopressin-resistant renal insufficiency. The renal lesion associated with the animal model in this study is characterized initially by loss of renal mass and then by a glomerular lesion resembling glomerulonephritis; functionally, it is a high-output renal insufficiency.¹² The morphologic components of these lesions are not in all cases similar, but animal models in renal failure research have only occasionally resembled their human counterpart. What is significant is that the functional changes have

correlated well with the responses of humans to these agents. For this reason and because of the absence of well-documented cases of adverse renal effects following enflurane anesthesia in surgical patients, we believe this study has clinical relevance. We postulate that further deterioration of already impaired renal function is not likely to occur following exposure to enflurane, and, when indicated, enflurane may be used with safety for surgical patients who have minimal or moderate renal disease. Furthermore, concurrent therapy with gentamicin does not appear to contraindicate the use of enflurane.

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