oxide on oxygen cannot be relied upon to produce a clinically significant increase in arterial oxygenation.

REFERENCES


Possible Nephrotoxicity from Enflurane in a Patient with Severe Renal Disease

ROBERT W. LOEHNING, M.D., PH.D.,* AND RICHARD I. MAZZE, M.D.†

Enflurane (Ethane,\textsuperscript{1} 2-chloro-1,1,2-trifluoroethylfluoromethyl ether) is metabolized to inorganic fluoride, but to a lesser extent than methoxyflurane.\textsuperscript{1,2} Renal dysfunction associated with its administration has not been reported in man. This report describes deterioration of renal function following enflurane anesthesia in a patient who several years earlier had received a kidney transplant.

REPORT OF A CASE

A 24-year-old woman was admitted to the University of Oregon Hospital for insertion of a saphenous-vein arteriovenous shunt in an arm in preparation for nephrectomy and a new allograft transplant. History revealed chronic glomerulonephritis, initially diagnosed at the age of 14 years, leading to transplantation of a cadaver kidney at the age of 22 years. Following transplantation the patient had been admitted to the hospital three times for episodes of rejection. Six months prior to the present admission she had received an Austin Moore hip prosthesis because of aseptic necrosis of a femoral head. Halothane anesthesia had been administered on that occasion without complication, BUN varying between 25 and 33 mg/100 ml during the postoperative period. In the following months renal function had stabilized at levels which indicated minimal reserve. At the time of the present admission, laboratory values included BUN 54 mg/100 ml, serum creatinine 5.6 mg/100 ml, and creatinine clearance 11.5-17.5 ml/min. Urinary volumes ranged from 1,300 ml/day to as much as 2,600 ml/day following treatment with furosemide. Drug treatment included azathioprine, prednisone, furosemide, chloral hydrate, meperidine, and propoxyphene.

On December 1, 1972 following premedication with meperidine and atropine, anesthesia was induced with thiopental and 3.0 per cent enflurane with oxygen and nitrous oxide. Enflurane concentrations during the procedure, which lasted 3 hours and 45 minutes, ranged from 0.5 to 0.8 per cent. Both operation and anesthesia were uncomplicated. During the first two postoperative days, urinary output averaged 1,900 ml/day, exceeding fluid intake by 500 ml/day. This resulted in a fluid deficit of approximately 1,500 ml/day, including insensible losses. BUN increased to 105
mg/100 ml and creatinine clearance decreased slightly, to 9.4 ml/min. Because of this acute deterioration in renal function, a renal biopsy was done on the fourth postanesthetic day, using local anesthesia. During the next two weeks bio-chemical measurements of renal function showed values that gradually returned toward preoperative levels.

Histologic examination of the kidney biopsy specimen showed changes typical of chronic allograft rejection, including hyperplasia of glomerular and capillary epithelium with thickening of basement membranes and replacement of capillary loops by fibrosis, narrowing of the lumens of arteries and arterioles, endothelial hyperplasia, and in some areas, replacement of the media with fibrous tissue beneath the internal elastic membrane. Tubular atrophy, interstitial fibrosis, and infiltrates of mature lymphocytes were also seen. However, there were also atypical changes in some of the proximal convoluted tubules, including swelling and vacuolization of cytoplasm, as well as several areas of markedly damaged tubular epithelium. The latter changes suggest acute renal damage. Oxalate crystals were not seen.

The recently-introduced saphenous-vein shunt had clotted, so a silastic arteriovenous shunt was inserted on December 28, 1972. Since the kidney was already irreversibly diseased, the patient's permission to administer enfurane for this operation and subsequent nephrectomy was obtained. Following the shunt procedure, which lasted an hour and 45 minutes, urinary output again exceeded input by about 800 ml/day during the first two days. However, there was no change in BUN or creatinine clearance. Peak serum inorganic fluoride, occurring eight hours postanesthesia, was 16 μM/l (Fig. 1). On January 8, 1973, a nephrectomy was carried out, the procedure lasting 2 hours and 20 minutes. Peak serum inorganic fluoride following this procedure, occurring 12 hours postanesthesia, was 19 μM/l. Microscopic examination of renal tissue from the nephrectomy specimen showed changes consistent with chronic rejection without the histologic features of acute renal damage seen in the biopsy specimen.

**DISCUSSION**

Enflurane and methoxyflurane are both fluorinated methylethyl ethers. Enflurane is less soluble than methoxyflurane in all tissues, particularly blood and fat, and is chemically more stable. At equivalent anesthetic dosage there is less metabolism of enflurane to inorganic fluoride. In fact, the highest post-enflurane serum inorganic fluoride level we have measured was 38 μM/l, following enflurane anesthesia at 1 MAC for 7 hours (Mazze; unpublished data); serum inorganic fluoride levels following comparable methoxyflurane anesthesia would be in the range of 120 μM/l. In man and animals following anesthesia with methoxyflurane, serum inorganic fluoride levels of approximately 50 μM/l have been associated with minimal nephrotoxicity. In a study in Fischer 344 rats, in which 1 MAC enflurane was administered for as long as 10 hours, transient polyuria associated with peak serum inorganic fluoride levels of 44–56 μM/l developed. Since Fischer 344 rats metabolize fluorinated anesthetics 30–50 per cent more than does man, this suggests that nephrotoxic fluoride levels will not result from enflurane administration under usual clinical circumstances.
The present case represents an unusual clinical circumstance, in which enflurane may have contributed to the deterioration of renal function due to the presence of severe renal disease. Although this relationship is by no means clear-cut, the contributory role of the anesthetic is suggested by: 1) the occurrence of polyuria following the first two procedures, accompanied in one instance by increased BUN; 2) the atypical renal histologic biopsy findings, which suggested superimposition of an acute nephrotoxic process on chronic allograft rejection; 3) the absence of acute histologic changes in the nephrectomy specimen when exposure to enflurane and its metabolites was of short duration due to the absence of postoperative exposure.

If enflurane did contribute to deterioration of renal function in this case, it may have been because the presence of renal disease prevented excretion of fluoride ion. Fluoride clearance is usually half of creatinine clearance, which in the present case was only 15 per cent of normal. Also it is possible that the threshold of fluoride nephrotoxicity in a diseased transplanted kidney may be lower than that in normal kidneys; serum inorganic fluoride levels were 16 and 19 μM/l after the second and third anesthetics, respectively and probably no more than 30 μM/l after the first, longer anesthesia.

The contributory role of enflurane is by no means certain. It is possible that insufficient postoperative fluid administration led to dehydration and in turn decreased renal blood flow and glomerular filtration rate. This is more apt to occur in patients with severe renal disease because of their inability to concentrate urine and conserve extracellular water. Also, the low serum inorganic fluoride levels and the difficulty in diagnosing acute renal damage in pathologic specimens manifesting chronic allograft rejection further contribute to the uncertainty of the diagnosis.

In weighing the evidence, we believe that enflurane contributed to the deterioration of renal function in this patient. We question whether enflurane should be used in the presence of severe renal disease or for renal transplantation, for donor or recipient. A newly transplanted kidney seldom functions normally, and should it ultimately become nonfunctional, it would be difficult to identify the cause. We feel that the addition of another variable in determining the cause of malfunction following transplantation is unwarranted. The same contraindications apply to the use of methoxyflurane: renal damage following its use for kidney transplantation already has been documented.

REFERENCES