COMBINED NEPHROTOXICITY OF GENTAMICIN AND METHOXYFLURANE ANAESTHESIA IN MAN

A Case Report

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SUMMARY

The clinical and biochemical findings are described in a patient who developed nephrotoxicity due to the combined effects of methoxyflurane anaesthesia and gentamicin. Following methoxyflurane anaesthesia mild nephrotoxicity occurred which rapidly increased in severity when gentamicin therapy was commenced, suggesting that the nephrotoxicity of these two drugs may be additive.

The inhalation anaesthetic methoxyflurane (Penthane, 2,2-dichloro-1,1-difluoroethyl methyl ether) has caused acute polyuric, vasopressin-resistant, renal insufficiency in man and animals (Crandell, Pappas and Macdonald, 1966; Mazze, Shue and Jackson, 1971; Mazze, Cousins and Kosek, 1972). The lesion is most likely due to toxic accumulation of inorganic fluoride, a metabolite of methoxyflurane, and appears to be dose-related (Mazze, Trudell and Cousins, 1971; Cousins, Nishimura and Mazze, 1972). Oxalic acid, another methoxyflurane metabolite, may contribute to the renal injury. Recent reports suggest that concurrent tetracycline administration may intensify the renal injury caused by methoxyflurane (Kuzucu, 1970; Canadian Food and Drug Directorate, 1971; Proc- tor and Barton, 1971). This report documents a case of methoxyflurane nephrotoxicity, the severity of which increased following administration of the antibiotic, gentamicin sulphate.

CASE REPORT

A 50-year-old man was admitted to the hospital in November 1971 for left radical neck and tonsil dissection, laryngectomy, and left hemimandibulectomy because of recurrent squamous cell carcinoma of the left tonsil fossa. There was no history of cardiovascular, renal or hepatic disease nor had he any allergies. He had received a course of radiation therapy in March and April 1971. Apart from his pharyngeal pathology there were no abnormal physical findings. Blood pressure was 100/60 mm Hg, height 178 cm and weight 71.4 kg. The results of preoperative haematological, urinary and serum biochemical determinations were normal. On November 8, 1971, the patient had direct laryngoscopy and laryngeal biopsy with operative haematological, urinary and serum biochemical determinations were normal. On November 8, 1971, the patient had direct laryngoscopy and laryngeal biopsy with operative day bacteriological cultures from the surgical wound indicated the presence of Pseudomonas aeruginosa infection, resistant to all antibiotics except gentamicin.

The lesion is most likely due to toxic accumulation of inorganic fluoride, a metabolite of methoxyflurane, and appears to be dose-related (Mazze, Trudell and Cousins, 1971; Cousins, Nishimura and Mazze, 1972). Oxalic acid, another methoxyflurane metabolite, may contribute to the renal injury. Recent reports suggest that concurrent tetracycline administration may intensify the renal injury caused by methoxyflurane (Kuzucu, 1970; Canadian Food and Drug Directorate, 1971; Proc- tor and Barton, 1971). This report documents a case of methoxyflurane nephrotoxicity, the severity of which increased following administration of the antibiotic, gentamicin sulphate.

After operation the input of fluids equalled measured losses, plus 700 ml/day for insensible loss. The patient also received intravenously, every 4 hours, sodium methi- cillin, 1 g, sodium cephalothin, 1 g, and aqueous penicil- lin, 2,000,000 units. On the evening of the third postoperative day bacteriological cultures from the surgical wound indicated the presence of Pseudomonas aeruginosa infection, resistant to all antibiotics except gentamicin.

Combined nephrotoxicity of these two drugs may be additive.

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FIG. 1. Preoperative and postoperative uric acid, blood urea nitrogen (BUN), creatinine clearance (CrCl), creatinine (Cr), and serum inorganic fluoride (F⁻). Preoperative values are means for the three days preceding operation.

FIG. 2. Preoperative and postoperative body weight, urine volume and serum and urine osmolality. Preoperative values are means for the 3 days preceding operation.

instilled, with the first dose administered at 9 p.m. on the third day. This treatment was continued as indicated in figure 1.

For the first 3 postoperative days urine volume averaged 2.5 L. day. Urine osmolality gradually decreased to 213 mOsm/kg despite a slight increase in serum osmolality to 288 mOsm/kg. Serum uric acid increased from 3.8 to 8.2 mg/100 ml and serum inorganic fluoride from 2 to 175 µM/L. These values were consistent with methoxyflurane-induced nephrotoxicity (Mazze, Shue and Jackson, 1971; Mazze, Cousins and Kosek, 1972) though it was possible that polyuria was due to vigorous postoperative hydration. To establish a definite diagnosis a programme of fluid restriction followed by vasopressin infusion was instituted beginning 4 p.m. on the third postoperative day. Frequent determinations of serum and urine osmolality were carried out and urine flow rate was continuously monitored to ensure that the patient would not become excessively dehydrated.

During the initial 18 hours of fluid restriction there were no changes in urine flow rate or osmolality. However, from the 18th to 24th hour urine flow rate increased despite an increase in serum osmolality to 299 mOsm/kg (fig. 3). Vasopressin, 40 mU administered intravenously in 1 min, followed by 1 mU/min for the next 90 min, was not accompanied by significant changes in urine flow rate or osmolality.

From this time, despite attempts to maintain fluid balance, urine output exceeded fluid input. The patient complained of thirst and appeared to be confused on the sixth and seventh postoperative days when dehydration was most severe. Urine volume was 5.7 L. on the seventh day despite serum osmolality of 319 mOsm/kg. Peak 24-hour urine volume of 9.3 L. was attained on the ninth postoperative day after serum osmolality had started to fall.
in response to vigorous fluid therapy. Creatinine clearance reached a low of 36 ml/min on the twelfth postoperative day and three months later was 43 ml/min. Urine osmolality following overnight dehydration was 277 mOsm/kg, three months after surgery. Repeated postoperative urinalyses were normal except for specific gravity which was consistently in the range of 1.010. Postoperative serum inorganic fluoride, uric acid, urea nitrogen and creatinine concentrations and creatinine clearance are shown in figure 1. Urine volume, serum and urine osmolality, and body weight are shown in figure 2.

**DISCUSSION**

In 1966 Crandell, Papper and Macdonald first reported nephrotoxicity following administration of methoxyflurane anaesthesia. This was characterized by polyuria, hypernatraemia, increased serum osmolality, elevated blood urea nitrogen level, excessive weight loss, and inability to concentrate urine following administration of vasopressin. Subsequent clinical studies confirmed these findings with the degree of nephrotoxicity proportional to serum concentration of inorganic fluoride resulting from the metabolism of methoxyflurane (Mazze, Trudell and Cousins, 1971; Cousins, Nishimura and Mazze, 1972; Taves et al., 1970). Increased urinary excretion of oxalic acid also resulting from methoxyflurane biodegradation has been noted, though oxalic acid is thought to be of secondary importance in causing the renal lesion associated with methoxyflurane administration (Mazze, Cousins and Kosek, 1972; Mazze, Trudell and Cousins, 1971; Frascino, Vanamee and Rosen, 1970). Studies with Fischer 344 rats have shown nephrotoxicity to be related to the total dose of methoxyflurane and to the serum concentration of its metabolite, inorganic fluoride; injection of inorganic fluoride, produced a functionally and histologically similar dose related renal lesion (Mazze, Cousins and Kosek, 1972). Recently, it has been claimed that tetracycline intensifies the nephrotoxicity produced by methoxyflurane administration (Kuzucu, 1970; Canadian Food and Drug Directorate, 1971; Proctor and Barton, 1971). Kuzucu (1970) noted renal impairment in 5 of 7 patients given tetracycline immediately before or after surgery with methoxyflurane anaesthesia. No changes in renal function were observed in 180 patients anaesthetized with methoxyflurane who received an antibiotic other than tetracycline or no antibiotics at all (Kuzucu, 1970).

The present report documents exacerbation of methoxyflurane nephrotoxicity following administration of the aminoglycoside antibiotic, gentamicin. Renal function studies during the 3 days following methoxyflurane anaesthesia and prior to gentamicin therapy showed mild polyuria due to impaired concentrating ability with no changes in blood urea nitrogen, serum creatinine or creatinine clearance. In previously reported cases of methoxyflurane nephrotoxicity, peak serum fluoride levels occurred no later than 3 days postoperatively and coincided with the greatest changes in renal function. Therefore, during the first 3 postoperative days all features of this case were consistent with the diagnosis of mild methoxyflurane nephrotoxicity, with full recovery anticipated.

Following initiation of gentamicin therapy the clinical course became atypical: urine flow rate nearly doubled during the last 6 hours of water restriction despite increasing serum osmolality; creatinine clearance progressively declined and
serum creatinine and blood urea nitrogen levels continued to increase; serum inorganic fluoride levels continued to rise, reaching a peak on the sixth postoperative day; and maximum weight loss, serum hyperosmolality and polyuria occurred between the seventh and ninth days. This further impairment in renal function and the permanent damage that resulted appeared to be due to the combined effect of two nephrotoxins.

Despite an incidence of nephrotoxicity following gentamicin administration of 2–7%, there are few descriptions of the clinical features of this condition (Wilfert et al., 1971; Falco, Smith and Arcieri, 1969). Reversible azotaemia is said to occur but polyuria has not been reported. The lesion is thought to be related to prolonged treatment with high doses of the antibiotic; toxicity has rarely been described before the fifth day of treatment (Wilfert et al., 1971). By contrast, this patient’s renal function markedly deteriorated within 24 hours after the beginning of gentamicin treatment. A second course of gentamicin therapy at reduced dosage, 40 mg t.i.d., was started on the twelfth day when inorganic fluoride level was 40 μM/L, well below toxic levels. Blood urea nitrogen and serum creatinine levels increased after several days of treatment but returned to pretreatment values when gentamicin was discontinued (fig. 1). This episode was typical of gentamicin nephrotoxicity and was unlike the response following the initial course of antibiotic therapy.

Though methoxyflurane administration preceded initial gentamicin therapy by 3 days, there is no doubt that molecular methoxyflurane was present when antibiotic treatment was instituted. Methoxyflurane is highly fat-soluble and may persist in the body for more than a week following its administration (Holaday, Rudofsky and Treuhaft, 1970). This results in a depot of drug being available for prolonged postoperative metabolism, with as much as 50% of an administered dose undergoing catabolism (Holaday, Rudofsky and Treuhaft, 1970). In fact, inorganic fluoride levels have been reported to be markedly elevated for as long as 10 days following methoxyflurane anaesthesia (Mazze, Trudell and Cousins, 1971). Thus, even if overt methoxyflurane nephrotoxicity has not occurred there may be subclinical impairment of tubular function and the potential for additional damage if other nephrotoxic agents are subsequently administered. Another possible explanation for the deterioration of renal function following gentamicin administration is suggested by the delayed rise in serum inorganic fluoride concentration. In animal studies (Barr et al., 1973) we have shown that gentamicin interferes with inorganic fluoride excretion. This could result in higher and even more toxic inorganic fluoride concentrations accumulating in the blood. A third explanation for the development of severe nephrotoxicity is that the initially appropriate gentamicin dose, 80 mg t.i.d. (3.4 mg/kg/day), became toxic as renal impairment occurred and gentamicin excretion was reduced. The decrease in creatinine clearance from 104 to 36 ml/min was evidence that this could have occurred (Gyselynck, Forrey and Cutler, 1971).

In addition to the above report, we have been consulted on two additional cases and are aware of others in which renal insufficiency followed treatment with both methoxyflurane and gentamicin (Deutsch, unpublished data; Canadian Food and Drug Directorate, unpublished data). Also, there are several reports of fatal nephrotoxicity in patients receiving methoxyflurane and kanamycin (Canadian Food and Drug Directorate, unpublished data; Hollenberg et al., 1972), another antibiotic of aminoglycoside structure. We suspect additive nephrotoxicity may be a factor in all these cases. Finally in support of the concept of additive nephrotoxicity, Fischer 344 rats treated with both methoxyflurane and gentamicin develop greater renal functional and histological abnormalities than rats treated with either drug alone (Barr et al., 1973). Therefore, in addition to the contraindications previously enumerated (Mazze and Cousins, 1973) we recommend that methoxyflurane should not be administered to surgical patients who are likely to require antibiotic therapy in the postoperative period.

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REFERENCES


**NEPHROTOXICITE COMBINEE DE GENTAMYCINE ET ANESTHESIE AU METHOXYFLURANE CHEZ L'HOMME: DESCRIPTION D'UN CAS**

**SOMMAIRE**

Les auteurs décrivent les observations cliniques et biochimiques chez un patient, qui développa une néphrotoxicité due aux effets combinés de l'anesthésie au méthoxyflurane et de la gentamicine. Une légère néphrotoxicité se manifesta après l'anesthésie au méthoxyflurane; elle devint rapidement plus grave lorsqu'on débuta le traitement à la gentamicine, ce qui suggère que la néphrotoxicité de ces deux médicaments pourrait être additive.