METHOXYFLURANE NEPHROTOXICITY - A REVIEW AND A CASE REPORT

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METHOXYFLURANE (1,1 difluoro, 2,2 dichloro ethyl methyl ether) was first investigated as an anaesthetic in dogs by Van Poznak and Artusio, and, subsequently in 1960, Artusio *et al.*[1] reported on the clinical use in man. It is estimated that since that time, approximately 15 million methoxyflurane anaesthetics have been administered. The clinical advantages of its use have been found in its association with adrenaline, for it does not sensitize the myocardium to catecholamines,[2] in the management of phaeochromocytoma,[3] in eye surgery and as an analgesic in obstetrics.

The first report of nephrotoxicity appeared in 1964. Paddock *et al.*[4] mentioned three cases, two of whom died in uraemia with calcium oxalate crystals in the renal tubules. They also reported on a personal communication from Artusio of three patients with increased urinary output, rising blood urea-nitrogen and creatinine, following methoxyflurane, which resolved in seven to nine days. Their subsequent investigation of 40 healthy males receiving methoxyflurane anaesthesia of not less than one hour duration, failed to detect any changes in renal function as measured by creatinine clearance, blood urea-nitrogen levels and fluid balance. They therefore exonerated methoxyflurane as a cause of nephrotoxicity in healthy subjects. They also found that 20 out of 200 autopsy specimens of kidneys contained calcium oxalate, none of the patients having received methoxyflurane, but all having had renal disease.

In 1966, Crandell, Pappas and MacDonald,[5] writing from White River Junction, Vermont, reported on 94 patients receiving methoxyflurane, of whom 16 (17 per cent) developed toxic nephropathy with urine of low specific gravity, negative fluid balance, clinical dehydration and hypernatraemia, developing in the first postoperative day following methoxyflurane anaesthesia lasting from three to six hours. The syndrome continued for six to ten days. They utilized fluid deprivation, rapid intravenous fluid infusion and antidiuretic hormone administration to differentiate between nephropathy and ADH insufficiency but noticed that the patients who recovered early were those who had received high fluid intake early in the postoperative period. The relationship between methoxyflurane and nephrotoxicity was attributed to absence of antidiuresis and inadequate response to ADH, methoxyflurane being the only common factor in all the cases. A follow-up[6] reported no further cases at that hospital, since the use of methoxyflurane had been discontinued three years previously.

Pezzi *et al.*,[7] 1966, found a syndrome in postoperative patients consisting of rising blood urea-nitrogen, increased urinary output, low urinary specific gravity, hypernatraemia, dehydration and mental confusion. In 180 methoxyflurane anaes-

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thetics over an eight-month period, of which 123 were abdominal cases, 20 patients (16 per cent) showed the syndrome, of which six died. All had complications post-operatively which may have exacerbated the effects of methoxyflurane.

Lebowitz,[8] in 1969, reported two cases of high output renal failure. The first was a 48-year-old male with chronic relapsing pancreatitis, mild diabetes, and partial common bile duct obstruction, for whom a pancreatico-jejeunostomy was performed which lasted six hours. Preoperatively, the serum creatinine was normal. On the second post-operative day a diuresis of 4–5 litres was noticed with dehydration, hypernatraemia and urine of low specific gravity. On the eighth post-operative day an osmolality challenge test showed lack of concentrating power. The patient subsequently improved and one year later there was no evidence of renal defect. The second patient was a 24-year-old male for laryngectomy. The operation lasted four hours and vital signs were stable throughout. Over the next few days the urinary output was 3–4 litres/day on an intake of 2–3 litres/day. On the fifth day the patient was dehydrated, with serum creatinine of 2.3 mg per cent. There was no response to water deprivation or vasopressin but one month later polyuria had ceased. There was no common factor in these two cases except methoxyflurane, and only one patient had antibiotics (penicillin and streptomycin).

Kuzuci in 1970[9] described the administration of methoxyflurane to 115 patients for major abdominal or thoracic surgery, lasting longer than two hours. Seven received tetracycline, of whom three elderly and obese patients died after elevation of blood urea-nitrogen, calcium oxalate crystals being found in the renal tubules. Two had rising blood urea-nitrogen and recovered and two had no change in renal function. Of the other 108 none had rising BUN and those who died had no calcium oxalate in the renal tubules. Another 40 patients who received spinal anaesthesia and tetracycline together showed no impairment of renal function. The conclusion drawn was that methoxyflurane and tetracycline together may impair renal function, which may be aggravated by renal arteriolar sclerosis in the elderly. It was noticeable, however, that two of the three patients who died had no diuresis.

North and Stephen, in 1966,[10] published results of a study of two large groups of patients. The first group of 190 patients received methoxyflurane. Of these, 38 had rising BUN. The second group of 213 patients received halothane and 30 of this group had rising BUN. The difference between the two groups was not statistically significant with regard to methoxyflurane nephrotoxicity, and none of the patients had excessive diuresis.

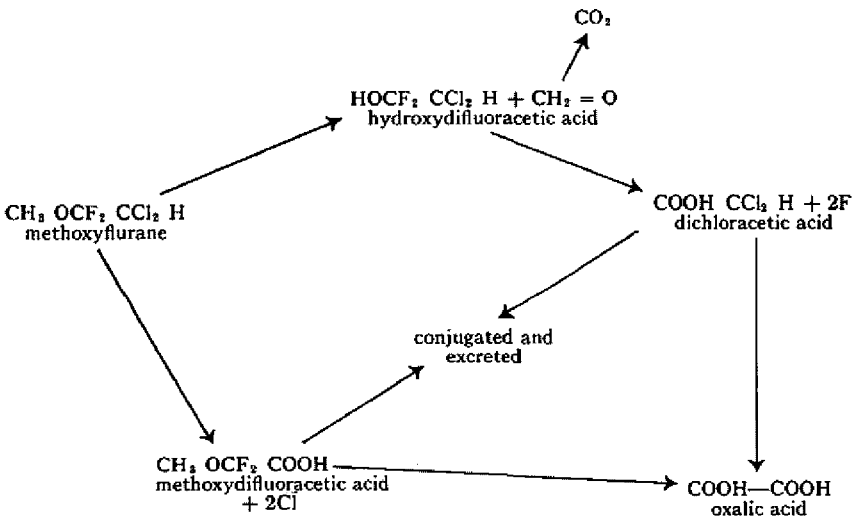
In 1969, Gauert *et al.*[11] published data from 23 patients receiving methoxyflurane anaesthesia. Ages ranged from 19 to 78 years. Length of anaesthesia was 1–4 hours and concentrations of inspired methoxyflurane from 0.2–2 per cent in semi-closed circuits with CO_2 absorption. Three patients had previous renal disease. Hypotension was avoided and large volumes of intravenous dextrose were given during the procedures. No nephrotic effect or high ouput azotaemia was demonstrated by Hippuran I^{131} tests, although the three patients with previous renal disease had some suppression of renal function, to be expected with any agent.

Panner *et al.*[12] reported on two fatal cases, both obese and receiving methoxyflurane for more than four hours. Both showed high levels of BUN and large volumes

of urine within 24 hours of surgery. One received tetracycline but only after the onset of polyuria. Both showed calcium oxalate crystals in renal tubules post-mortem.

Taves *et al.*,[13] 1970, following up one of the cases of Panner found that that patient showed a serum inorganic fluoride of 275 micromoles eight days after the operation, this being ten times that found in patients with an uneventful post-operative course. The serum and urine fluorides were still elevated 19 days after operation. Inorganic fluoride clearance from the blood was 5.8 ml/min or 10 per cent of normal, with a creatinine clearance of 6 ml/min. The organic fluoride after anaesthesia was much higher than the inorganic, except in the urine sample, and the renal clearance of organic fluoride was low, implying considerable metabolism. Inorganic fluoride of more than 200 micromoles has been shown indirectly to be nephrotoxic from the work of Goldemburg[14] (diabete insipidus fluorique) who used sodium fluoride intravenously, the estimated serum levels of 200 micro moles being much less than the 275 micromoles of Panner's case. Taves *et al.*[13] felt the liklihood of the syndrome developing depended on duration of anaesthesia, retention of methoxyflurane in the body relative to obesity, and rate of clearance of inorganic and organic fluoride. They suggested limitation of anaesthesia for obese patients and those of patients with impaired renal function, and an increased urinary flow rate to dilute the fluoride in the kidney.

The metabolism is thought to be as follows:[15]



Holaday[16] labelled methoxyflurane with ^{14}C in in the methoxy position and showed that degradation occurred immediately and continued for 9–12 days. Thirty per cent was exhaled unaltered, 10–20 per cent underwent cleavage at the ether linkage to give CO_2, fluoride and dichloracetic acid. Forty per cent is dechlorinated and oxidized to give methoxy difluoracetic acid, excreted by the kidneys.

Frascino *et al.*[17] in eleven cases of exposure to methoxyflurane of from 2.75 to 7.5 hours duration, in patients with previously normal serum creatinine, reported the occurrence in seven patients of calcium oxalate crystals in the renal tubules and raised urinary oxalates of 96–400 milligrams/24 hours (normal 5–45 milligrams/24 hours). These authors divided the patients into three groups depending on the serum creatinine levels, but could not relate these to duration of exposure. The extent of oxalate crystallization could not adequately explain renal failure. Some of their patients may have developed renal failure due to urogenital surgery or hypotension, with the hyperoxaluria of methoxyflurane superimposed and prolonging the renal failure.

Mazze *et al.*[15] presented a randomized study of 12 methoxyflurane and 10 halothane anaesthetics. Induction was with these agents and maintenance was with oxygen and the agent concerned. Six patients on methoxyflurane showed impaired ability to conserve body water and increasing serum osmolality, which failed to respond to vasopressin and led to polyuria, hypernatraemia and dehydration. Increases in serum and urinary inorganic fluoride and urinary oxalic acid were found in all patients anaesthetized with methoxyflurane, being greater in the patients with the clinical syndrome. Patients anaesthetized with halothane had only slight increases in urinary inorganic fluoride excretion, and no change in oxalic acid excretion. A correlation was found between elevated serum inorganic fluoride, urinary oxalic acid and renal dysfunction. Oxalic acid has been shown to be nephrotoxic by Hockaday,[18] but produces oliguric failure.

Lowe, however, in a personal communication[19] pointed out that in the cases reported by Mazze and Jackson high inspired concentrations of methoxyflurane were used for induction, fluid and electrolyte losses were not adequately replaced, and that overnight dehydration could have contributed to the problem.

More recently, Mazze *et al.*[20] confirmed the opinion of Lowe, by their study of patients undergoing cardiac surgery with low dosage of methoxyflurane anaesthesia (MAC less than 0.16). The serum inorganic fluoride concentration and urinary inorganic fluoride excretion were approximately one third of that found in the patients they described previously with renal dysfunction, and on this occasion no patients showed renal dysfunction.

Silverberg *et al.*[21] showed after methoxyflurane anaesthesia that oxalic acid excretion rose markedly in the first postoperative day to a range of 148 to 698 milligrams/day (normal less than 55 milligrams/day). No other alteration in renal function tests was noticed and no polyuria developed. Their deduction was that renal function impairment is multifactorial and that the hyperoxaluric state may play a part.

Several reports on high output renal failure in relation to nonspecific injury are of interest. Torpey, from his Vietnam experience[22] stated that most cases of renal failure from nonspecific injury were not oliguric, Torin[23] reported a case resulting from administration of dimethylchlortetracycline and Baxter[24] reported association with general anaesthesia with agents other than methoxyflurane.

Cale[25] gave high doses of methoxyflurane for five hours to dogs with concomitant hypoxia and hypercapnia and found no significant histological changes in the kidneys.

Case Report

A white male, aged 63, weight 168 lbs, but not obese, presented for removal and reconstruction of the larynx. No past history of renal disease was evident and physical examination was normal.

Anaesthesia was induced with halothane, nitrous oxide and oxygen and maintained with methoxyflurane, nitrous oxide and oxygen at an inspired concentration of 0.5 per cent for seven hours, with spontaneous ventilation. Three units of blood, 500 mls of normal saline, and 900 mls of lactated Ringer's solution were administered during the procedure. No hypotension or hypoxia occurred. Postoperatively the patient received cephaloridine, cloxacillin and carbenicillin.

Eight days postoperatively the patient was drowsy and confused, with a blood urea-nitrogen of 95 mg per cent. No obvious polyuria was noted after the third postoperative day, but the fluid balance measurements were unsatisfactory because of the patient's confused state.

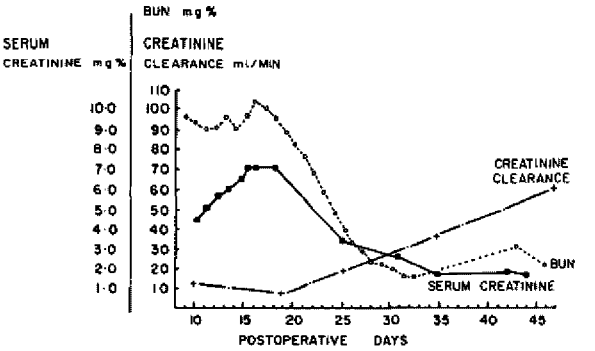


Figure 1

Figure 1 shows the changes in BUN, serum creatinine and creatinine clearance in this patient. While the creatinine clearance did not return to accepted normal limits, it probably represents a reasonable value for an individual of this age.

A renal biopsy done on the 18th postoperative day revealed doubly refractile casts in the renal tubules, and scattered peritubular inflammatory cells. Urinary oxalate excretion on the 28th postoperative day was normal.

Discussion

The association between methoxyflurane and renal dysfunction appears to be established despite reports which appear to deny the relationship, such as the papers of Paddock,[4] North,[10] Gauert[11] and Cale.[25] The sporadic nature of the condition may be the result of variable dosage, predisposing factors, and perhaps prevention by adequate intravenous therapy. It is probable that the mechanism of action is an effect of fluoride ion on the distal renal tubule, which renders it unresponsive to antidiuretic hormone.

The work of Lowe[26] at the University of Chicago states that whole body anaesthetic requirement is a linear function of the square root of time.

$$Q\,\text{an} = 1.3\,MAC \times \lambda B \times \dot{Q} \times \sqrt{t}$$

Q an	— total anaesthetic dose
$\dot{Q}$	— cardiac output in decilitres
$\sqrt{t}$	— square root of time in minutes
1.3 *MAC*	— the clinically effective alveolar concentration
λB	— the blood gas partition coefficient

Lowe has derived a nomogram which allows delivery of methoxyflurane on a weight basis with 50 per cent N_2O to maintain an alveolar gas concentration of 0.1 per cent and states it may be used clinically without risk of overdose.

Animal models for testing methoxyflurane induced renal sensitivity have been so far unsuccessful but Mazze[27] has suggested that the Fisher Rat metabolizes methoxyflurane in a way similar to man and the effects on kidney function are similar.

In the meantime caution should be observed in methoxyflurane administration with regard to the following:

1. *Age.* Creatinine clearance tends to fall in the elderly and reflects overall kidney function.

2. *Obesity.* Methoxyflurane is retained in fat, the total amount being related to the quantity of adipose tissue present. In all probability, the incidence of toxicity will be shown to be related to the total amount retained.

3. *Pre-existing renal disease.* Kidneys with diminished function are more susceptible to exogenous toxins.

4. *Tetracycline.* The combination of tetracycline administration with methoxyflurane anaesthesia appears to markedly increase the tendency for the latter to affect the kidney.

5. *Hypotension and hypoxia.* These factors render the kidney more susceptible to exogenous toxins and methoxyflurane should be avoided if they can be foreseen.

6. *Prolonged anaesthesia.* Like obesity this increases the total amount of methoxyflurane retained by the body.

7. *Inadequate fluid intake.* From the literature it seems that a postoperative fluid intake which maintains a high urinary output has a protective effect on the kidneys by diluting the metabolic products of methoxyflurane.

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Résumé

Nous passons en revue certains articles publiés sur la néphrotoxicité du méthoxyflurane et nous rapportons un nouveau cas de défaillance rénale à la suite d'une anesthésie au méthoxyflurane.

L'association méthoxyflurane et troubles rénaux semble assez bien établie, même si certains rapports nient toute relation de cause à effet entre l'un et l'autre. L'apparition sporadique de ces ennuis peut être due au résultat d'un dosage différent, à des facteurs prédisposants et, aussi, à une certaine prévention de tels incidents faite par une thérapie endoveineuse adéquate. Il est probable que le mécanisme soit l'action d'un ion fluor sur le tubule rénal distal, rendant celui-ci inapte à répondre à l'hormone antidiurétique.

En attendant que la lumière se fasse sur le sujet, il faut apporter, lors de l'anesthésie au méthoxyflurane, une attention toute particulière aux facteurs suivants:

(1) L'âge: La clearance de la créatinine a tendance à diminuer chez les vieillards et donne une idée de la fonction rénale en général.

(2) L'obésité: Le méthoxyflurane est retenu dans les graisses; la quantité totale retenue est variable selon la quantité de tissu gras en cause. Selon les probabilités, la fréquence de la toxicité variera selon la quantité totale retenue.

(3) Les maladies rénales pré-existantes : Les reins dont la fonction est diminuée sont plus susceptibles aux toxines exogènes.

(4) La tétracycline: L'administration concomittante de la tétracycline et du méthoxyflurane semble favoriser l'atteinte du rein par le méthoxyflurane.

(5) L'hypotension et l'hypoxie: Ces facteurs rendent le rein plus susceptible aux toxines exogènes et, si l'on prévoit une telle éventualité, il faudrait éviter l'usage du méthoxyflurane.

(6) L'anesthésie prolongée: Tout comme l'obésité peut le faire, l'anesthésie prolongée peut augmenter la quantité totale de méthoxyflurane retenue dans l'organisme.

(7) Une fluidthérapie inadéquate: D'après ce que nous lisons dans la littérature, il semble qu'une quantité de fluides qui maintient le débit urinaire élevé au cours des suites opératoires exercerait une certaine protection sur les reins en diluant les produits du métabolisme du méthoxyflurane.

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