Nephrotoxicity from Methoxyflurane Anaesthesia: A 6-Year Retrospective Study*

R. B. Urgena and S. D. Gergis

Summary

Methoxyflurane was administered to 1196 patients during a 6-year period and the records of 1000 patients were reviewed. Two patients developed severe renal insufficiency but survived. There were 17 other patients who showed an inappropriate postoperative diuresis but they did not develop severe renal insufficiency. The records of 1000 patients given general anaesthesia other than methoxyflurane were also studied. None exhibited inappropriate diuresis. The mortality rate from all causes was comparable in the two groups.

During the past three decades many investigators have confirmed that volatile anaesthetics are metabolized and are not biochemically inert, as was previously believed. The organs responsible for the major metabolism of these agents are the liver and kidneys and it is of interest that these organs are primarily affected by the toxic side effects (Van Dyke, 1968). Recently, based on a review of the literature on the problem, the Committee on Anesthesia of the National Academy of Sciences—National Research Council reported that the association of renal tubular dysfunction and methoxyflurane appears to be a distinct entity (Special Report, 1971).

Methoxyflurane has been administered to between 12 and 15 million patients and is in common use by many anaesthetists. Crandell, Pappas and MacDonald (1966), have suggested that a nephrotoxic effect of methoxyflurane is characterized by diuresis (2.5–4 l./day) resulting in dehydration, weight loss, elevation of serum sodium, a relatively fixed specific gravity of the urine and azotaemia. Some reports have suggested that various factors may affect the incidence of this complication, such as the concurrent administration of tetracycline antibiotics (Kuzucu, 1970), the duration of the surgery (Elkington, Goffinet and Conn, 1968), obesity (Panner et al., 1970), and the age (Kuzucu, 1970) of the patient. In those reports in which renal biopsy or postmortem studies were made, a common finding appears to be that of numerous calcium oxalate crystals in the renal tubules (Paddock, Parker and Guadagni, 1964; Kuzucu, 1970; Panner et al., 1970; Frascino, Vanamee and Rosen, 1970). At this time at least two reports (Taves et al., 1971; Mazze, Trudell and Cousins, 1971) have presented convincing evidence that serum inorganic fluoride levels increase among patients who develop methoxyflurane nephrotoxicity and that this may well be responsible for the complication.

In a well-conducted prospective randomized study by Mazze, Shue and Jackson (1971) there was a significantly higher incidence of renal function impairment among the group given methoxyflurane. However, Lowe (1970, personal communication) has made the suggestion that the doses of methoxyflurane used by Mazze, Shue and Jackson were much higher than those in common clinical use.

To be sure, there are reports (Paddock, Parker and Guadagni, 1964; Gauert et al., 1969; Cale, Parks and Jenkins, 1962; Bergeron, 1968) of methoxyflurane anaesthesia being without untoward effects on renal function. In consideration of these reports and that of his own review of 25 patients following closed circuit methoxyflurane anaesthesia, Lowe suggested to us that the administration of methoxyflurane with nitrous oxide rarely entails risk of nephrotoxicity and that the conflicting reports on its incidence are due to an unexplored dose-response relationship.

Our retrospective study attempts to document nephrotoxicity among all patients given methoxyflurane during a 6-year period at the University of Iowa Hospitals. The mode of administration of the...
anaesthetic among our personnel is, with rare exception, quite consistent. The patients are usually premedicated with narcotic (pethidine or morphine) and/or a barbiturate (quinalbarbitone or pentobarbitone) and a drying agent (atropine or hyoscine). Methoxyflurane is vaporized through a Copper Kettle, Pentec or Pentomatic vaporizer with 60–70% nitrous oxide. The usual maintenance dose of methoxyflurane is 0.5% or less. It is seldom given above 1% after the induction period. Neuromuscular blocking drugs are usually employed to provide relaxation during abdominal procedures. More than two-thirds of these patients received an intravenous induction agent which is usually sodium thiopentone, although methohexitone and diazepam have been used also. Perhaps it is accurate to say that with rare exceptions methoxyflurane has been used at the University of Iowa Hospitals “according to clinical custom.”

METHOD

The name and clinical record number of patients who were given methoxyflurane anaesthesia at our University Hospitals from January 1, 1965 to December 31, 1970 were obtained from the operating room records. For control, the name and clinical record number of 1000 patients who were given various types of general anaesthesia other than methoxyflurane during the same period were obtained by a random sampling method. The clinical records of these patients were requisitioned and reviewed by the authors. A study sheet was completed for each clinical record. Among the data recorded on this sheet were a pre- and postoperative evaluation of renal function, preoperative medications with special attention to antibiotics, the occurrence of significant hypotension during the surgery (more than 25% drop of systolic arterial pressure) as well as the kind of surgery performed. Postoperative data also included details of fluid intake and output, and plasma electrolyte estimations. Postmortem results were included if the patient died in the postoperative period. The clinical records of those patients who showed inappropriate diuresis after the second operation. The incidence of inappropriate diuresis in this series is shown in tables I and II as related to the type of operation and duration of the anaesthesia.

RESULTS

A total of 1196 patients were given methoxyflurane during the 6-year period between January 1, 1965, and December 31, 1970. The clinical records of 1000 patients were available for review (83.6%). In this group there are fairly accurate intake and output records. Methoxyflurane was used for all types of surgery except those involving the use of cardio-pulmonary bypass. Among the 1000 patients given methoxyflurane anaesthesia during the 6-year period we were able to document only two cases of methoxyflurane nephrotoxicity (0.2%) which proceeded to severe renal insufficiency. There were 17 other patients who showed an inappropriate postoperative diuresis but their course did not progress to a stage of severe renal insufficiency. Seven of these 17 patients had surgery which lasted for more than 4 hours and 1 had a radical jaw and neck dissection which lasted for more than 6 hours. None of these patients became critically ill and all were discharged in good health. Tetracycline was not given to any of these patients during the perioperative period.

Forty-two patients (4.2%) who received methoxyflurane died during the period from January 1, 1965 to December 31, 1970. None of these deaths could be directly related to the anaesthetic agents or anaesthetic management. Among those who died within 6 weeks after surgery, 3 were the subjects of autopsies. There were no remarkable findings in their kidneys.

A total of 14 patients had multiple exposures to methoxyflurane; 13 had two exposures and 1 had three exposures. Among those who had two exposures, 1 exhibited inappropriate diuresis after the second operation. The incidence of inappropriate diuresis in this series is shown in tables I and II as related to the type of operation and duration of the anaesthesia.

The types of anaesthetic used on the patients in the control group is shown in table III. As a general rule the patients in this control group were premedicated and anaesthesia induced in a manner similar to the methoxyflurane group except when nitrous oxide was the main anaesthetic (1 and 2) in which case morphine and hyoscine were used for premedication. In the control group 40 patients died during the study period which is a comparable mortality rate of 4%.  

* Copies can be obtained from the authors.
The incidence of inappropriate diuresis following methoxyflurane anaesthesia related to the type of surgery as compared to control.

<table>
<thead>
<tr>
<th>Type of operation</th>
<th>Methoxyflurane</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>%</td>
<td>No. of cases</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>849</td>
<td>12</td>
</tr>
<tr>
<td>Thoracoabdominal</td>
<td>151</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>1000</td>
<td>19</td>
</tr>
</tbody>
</table>

The relation of duration of operation to the development of inappropriate diuresis in methoxyflurane and control groups.

<table>
<thead>
<tr>
<th>Duration of surgery (hr)</th>
<th>Methoxyflurane</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>%</td>
<td>No. of cases</td>
</tr>
<tr>
<td>Below 2</td>
<td>588</td>
<td>7</td>
</tr>
<tr>
<td>2-4</td>
<td>324</td>
<td>5</td>
</tr>
<tr>
<td>4-6</td>
<td>63</td>
<td>4</td>
</tr>
<tr>
<td>Above 6</td>
<td>25</td>
<td>3*</td>
</tr>
<tr>
<td>Total</td>
<td>1000</td>
<td>1000</td>
</tr>
</tbody>
</table>

* Two patients developed severe renal insufficiency (case reports).

Type of anaesthetic used among the cases in the control group.

| 1. Nitrous oxide and tubocurarine | 107 |
| 2. Nitrous oxide and thiopentone and/or narcotic | 50 |
| 3. Cyclopropane | 63 |
| 4. Fluoroxyde and nitrous oxide | 49 |
| 5. Ether and nitrous oxide | 40 |
| 6. Innovar and nitrous oxide | 10 |
| 7. Halothane and nitrous oxide | 681 |
| Total | 1000 |

About an hour before induction of anaesthesia he was given morphine sulphate 10 mg and hyoscine 0.4 mg for premedication. The preoperative blood pressure was 130/90 mm Hg and during the operation it was maintained at 95-105 mm Hg systolic/60 mm Hg diastolic. Two units of blood completely cross-matched, (540 ml each) were transfused without any apparent complication. The course during the immediate postoperative period proceeded uneventfully until the 4th day when his temperature rose to 101°F (38°C) and a chest radiogram revealed an elevated right hemidiaphragm and right lung atelectasis. The respiratory care management was intensified and he was given the following antibiotics: streptomycin, penicillin, erythromycin and gentamicin (the last was given only for 2 days and was immediately discontinued when the blood urea nitrogen was found to be elevated). At this time, and while still on intravenous alimentation, the amount of urine output increased to 1700-2500 ml but water balance remained positive as the input was at 2.5-3.2 l. There was a mild weight loss and serum electrolytes showed Na 136, K 4.5, Cl 101 m.equiv/l.

A more severe diuresis was noted from the 12th postoperative day (urine volume 2700-3500 ml) which resulted in a progressive weight loss (88.6-82.5 kg) over a 10-day period. The blood urea nitrogen and creatinine levels were then found to be markedly elevated (144 and 3.4 mg/100 ml) but the serum electrolytes were within normal limits. The urine specific gravity was no higher than 1.008.

By the 20th day after operation, the urine output decreased but the azotaemia and the weight loss continued and after another 10 days the serum electrolytes were as follows: b.u.n. 151 mg/100 ml, creatinine 5.1 mg/100 ml, Na 154, K 3.3, and Cl 117 m.equiv/l. During this time the surgical wound had also become infected and the wound had to be debrided twice. The antibiotics being used at this time were unipen and chloromycin.

Some improvement in the clinical and laboratory pictures started after the 35th postoperative day. The patient started gaining weight and the electrolyte picture was almost normal upon discharge. Two months after admission, the patient was being fed through a gastric tube. Unfortunately, the patient appeared to be well during this time and was being fed through a gastric tube. Unfortunately, the electrolytes were not checked at this time and the weight was not measured. On the 4th day of hospitalization he became slightly confused. Upon examination of serum electrolytes, the following results were found: creatinine 2.4 mg/100 ml, b.u.n. 73 mg/100 ml, Na 162, K 5.3, and Cl 124 m.equiv/l. The patient weighed 79.5 kg at this time.

Gastric tube feeding was discontinued and intravenous fluid was started and close attention paid to fluid balance, serum electrolyte values and urine specific gravity. The patient's general condition improved when the daily fluid intake was increased to 3000-4000 ml. However, the urine...
output continued to be high, 2100–4100 ml up to the 13th postoperative day. He now weighed 75.5 kg. The electrolyte picture also improved gradually during this period. The urine specific gravity was 1.005–1.008 and a concentration test brought it up to only 1.016. On the 14th day, the serum electrolytes were close to normal: b.u.n. 14 mg/100 ml, creatinine 1.9 mg/100 ml, Na 147, K 3.9. C1 106 m.equiv/l. The general condition improved further and he started gaining weight. When discharged, his urine output was still fairly high (1500–2000 ml per day), but his serum electrolytes were normal.

DISCUSSION

Methoxyflurane was administered to 1196 patients during a 6-year period. We were able to document only two cases of methoxyflurane nephrotoxicity among 1000 patients whose records were available for study. The information obtained from those records was fairly accurate, considering the large number of cases reviewed and the inevitability of having missing or incomplete data. The two cases were of elderly patients subjected to prolonged anaesthesia and surgery. There was no episode of significant hypotension during the surgery, nor were they given tetracycline in the perioperative periods; both factors have been implicated in the causation of renal damage. Marked diuresis together with negative water balance developed in the postoperative period. These 2 patients also showed a slow but progressive improvement although function had not returned to preoperative levels a few months later. Seventeen other patients developed postoperative diuresis in the range of 2.5–4 l./day, with negative fluid balance, for at least 4 days during the first 2 weeks after surgery. The postoperative course of these 17 patients was otherwise unremarkable as their renal function did not show significant change. These findings are similar to the clinical picture described by Canel, Pappas and MacDonald (1966). Our data indicated that the incidence of inappropriate diuresis after methoxyflurane anaesthesia is greater among patients subjected to thoracoabdominal procedures (table I) and that the incidence increases with the duration of anaesthesia (table II). The overall incidence of inappropriate diuresis in our series is very low (1.9%) in comparison to other reports. In keeping with Lowe’s suggestion that methoxyflurane nephrotoxicity may be dose-related, our routine use of nitrous oxide and frequent use during abdominal surgery of muscle relaxants may be responsible for this low incidence because it entails using less volatile anaesthetic agent.

The control group consisted of 1000 patients comparable in age, type and duration of operation but subjected to anaesthesia with different agents. The records were reviewed but did not reveal any data that would suggest renal insufficiency or inappropriate diuresis that could be attributed to the anaesthetic. There were instances of diuresis in the postoperative period but they always matched the fluid intake, which was sometimes generous because those patients were maintained on intravenous fluid and alimentation. The mortality rate from all causes in both the methoxyflurane and control group were comparable.

REFERENCES


NÉPHROTOXICITÉ DE L’ANESTHÉSIE AU METHOXYFLURANE: UNE ÉTUDE RETROSPECTIVE COUVRANT 6 ANS

SOMMAIRE
Méthoxyflurane a été administré à 1196 patients en 6 ans et les dossiers de 1000 malades ont été revus. Deux patients ont développé une sévère insuffisance rénale mais ont survécu. On observa chez 17 autres patients une diurèse postopératoire insatisfaisante mais sans développement d'une insuffisance rénale sévère. Les dossiers de 1000 malades, ayant reçu une anesthésie autre que méthoxyflurane, ont également été étudiés. Une diurèse insatisfaisante ne s'observa dans aucun cas. Le taux de mortalité, quelle que soit la cause, était comparable dans les deux groupes.

UNIVERSITY OF LIVERPOOL

NÉPHROTOXICIDAD POR LA ANESTESIA CON METOXIFLUARANO: UN ESTUDIO RETROSPECTIVO DE 6 ANOS

RESUMEN
Se administró metoxiflurano a 1196 pacientes durante un periodo de seis años y han sido revisados los historiales clínicos de 1000 pacientes. Dos de estos desarrollaron una insuficiencia renal grave, pero sobrevivieron. Hubo otros 17 pacientes que mostraron una diuresis postoperatoria anormal, pero no desarrollaron insuficiencia renal grave. También fueron estudiados los historiales clínicos de otros 1000 pacientes que recibieron anestesia con otros compuestos. En ninguno de ellos se produjo una diuresis anormal. La tasa de mortalidad por diversas causas fue comparable en ambos grupos.