RENAL FUNCTION FOLLOWING METHOXYFLURANE ANAESTHESIA

G. W. BLACK AND S. R. KEILTY

SUMMARY

Significant reductions in body weight and increases in plasma uric acid and urea concentrations occurred in the postoperative period in normal children who had inhaled 0.5% methoxyflurane for 60 minutes. In the absence of features such as polyuria, plasma hyperosmolality, hypernatraemia and elevated creatinine levels definite evidence of renal dysfunction is lacking. Also, raised concentrations of plasma uric acid and urea, although less pronounced than with methoxyflurane, were noted following the administration of halothane, an agent which is not prone to induce renal disorder. It is suggested that the present findings resulted from increased metabolism, possibly due to diminished calorie intake. Irrespective of the cause, the changes reported may warrant a reappraisal of the position of methoxyflurane in clinical practice.

Methoxyflurane is particularly useful in paediatric practice since the rather prolonged induction and emergence phases often seen in the adult are largely curtailed, as is the incidence of nausea and vomiting. Also, blood loss during surgery is significantly less than when other agents are employed (Black et al., 1969). Methoxyflurane is widely used in this hospital and concern has been felt because of the possibility of associated renal dysfunction as suggested by reports which have appeared in the literature during the past five years (Crandell, Pappas and Macdonald, 1966; Frascino, Vanamee and Rosen, 1970). There is much evidence to suggest that these may have resulted from relative or absolute overdosage and it was therefore decided to make a controlled study of renal function following methoxyflurane anaesthesia as it is used in ordinary clinical circumstances. In order to make the data more meaningful a comparable study of halothane was also undertaken.

METHODS

Twenty children aged 7–13 years were chosen for the studies. All were healthy boys requiring superficial surgical procedures estimated to last approximately 60 minutes. In all instances the level of haemoglobin concentration was greater than 11 g/100 ml and no child was receiving any form of drug therapy. All preanaesthetic medication was omitted and anaesthesia was induced with intravenous thiopentone 4 mg/kg. This was followed by nitrous oxide (70%) and oxygen (30%) and the volatile anaesthetic under study, using the Magill rebreathing attachment. When surgery required intubation the procedure was facilitated by using intravenous suxamethonium (1 mg/kg) and thereafter respiration was spontaneous and unassisted. Ten of the children were given methoxyflurane from a Pentec vaporizer and ten received halothane from a Fluotec vaporizer, in each case the choice of agent being made on a randomized basis. Higher concentrations of methoxyflurane (1.5–2.0%) were administered initially for 5–10 minutes and then the vapour strength was reduced to 0.5%. With halothane a concentration of 1.5% was given continuously during the operation.

Immediately following the induction of anaesthesia 20 ml of venous blood was withdrawn for the determination of plasma uric acid, urea, creatinine, osmolality and electrolytes. All these measurements were repeated at 24-hour and 48-hour intervals following surgery.

Plasma uric acid and urea concentrations were measured with the Technicon Auto Analyzer 12/60 and sodium, chloride and potassium determinations with the 60/60 Analyzer. Plasma creatinine levels were estimated with the Jaffe reaction after absorption on to Lloyd's reagent, and plasma osmolality was determined with the Fiske Osmometer (Advanced Instruments Inc.).

The volumes of urine voided in the 48-hour period after operation were collected and measured.

All the children were weighed under standard conditions before surgery and again 48 hours afterwards. Two hours after return to the ward each child received 20 ml water by mouth and this was repeated as required. The following day a light fluid diet was instituted.
### TABLE I. Changes in body weight, plasma uric acid, urea, creatinine, osmolality and sodium concentration, following methoxyflurane anaesthesia.

<table>
<thead>
<tr>
<th>No.</th>
<th>Age (yr)</th>
<th>Duration Anaesthesia (min)</th>
<th>Weight (kg)</th>
<th>Uric Acid (mg/100ml)</th>
<th>Urea (mg/100ml)</th>
<th>Creatinine (mg/100ml)</th>
<th>Osmolality (mOsm/kg)</th>
<th>No. (m.eq/ml)</th>
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<tbody>
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<td>9.0</td>
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<td>4.6</td>
<td>11.3</td>
<td>11.8</td>
<td>31</td>
</tr>
</tbody>
</table>

Mean: 10.8 | 62.0 | 36.3 | 34.5 | 4.4 | 8.6 | 7.8 | 30.6 | 46.2 | 40.0 | 0.6 | 0.56 | 0.57 | 290 | 292 | 293 | 141 | 140 | 142

S.D.: 1.8 | 6.7 | 8.1 | 7.9 | 0.7 | 2.1 | 2.1 | 4.1 | 6.5 | 7.8 | 0.06 | 0.05 | 0.05 | 6.1 | 9.0 | 7.3 | 2.2 | 2.8 | 3.6

S.E.: 2.1 | 2.6 | 2.5 | 0.2 | 0.6 | 0.6 | 1.3 | 2.0 | 2.5 | 0.02 | 0.02 | 0.02 | 1.9 | 2.9 | 2.3 | 0.7 | 0.8 | 1.1

* P < 0.001
(a) P < 0.001
(b) P < 0.001
(c) P > 0.001
(d) P > 0.001
(e) P > 0.001
(f) P > 0.001
(g) P > 0.001
(h) P > 0.001
(i) P > 0.001
(j) P > 0.001
(k) P > 0.001
(l) P > 0.001
(m) P > 0.001
(n) P > 0.001

* Denotes significant difference

Column 1 denotes data at 0 hours, column 2 data after 24 hours and column 3 data after 48 hours

(a) Indicates significance of difference between columns 1 and 2

(b) Indicates significance of difference between columns 1 and 3

### TABLE II. Changes in body weight, plasma uric acid, urea, creatinine, osmolality and sodium concentration, following halothane anaesthesia.

<table>
<thead>
<tr>
<th>No.</th>
<th>Age (yr)</th>
<th>Duration Anaesthesia (min)</th>
<th>Weight (kg)</th>
<th>Uric Acid (mg/100ml)</th>
<th>Urea (mg/100ml)</th>
<th>Creatinine (mg/100ml)</th>
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<th>No. (m.eq/ml)</th>
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<td>4.8</td>
<td>7.1</td>
<td>6.2</td>
<td>30</td>
</tr>
</tbody>
</table>

Mean: 10.5 | 65.0 | 34.6 | 34.6 | 4.2 | 6.2 | 4.9 | 28.0 | 37.2 | 34.0 | 0.60 | 0.60 | 0.60 | 292 | 291 | 292 | 139 | 138 | 140

S.D.: 1.3 | 11.8 | 5.4 | 5.7 | 0.8 | 1.7 | 1.3 | 7.4 | 9.2 | 9.1 | 0.06 | 0.06 | 0.06 | 7.6 | 6.0 | 5.6 | 3.7 | 3.1 | 1.8

S.E.: 0.4 | 3.7 | 1.7 | 1.8 | 0.2 | 0.5 | 0.4 | 2.3 | 2.9 | 2.9 | 0.02 | 0.02 | 0.02 | 2.4 | 1.9 | 1.8 | 1.2 | 1.0 | 0.5

* P = 1
(a) P < 0.001
(b) P > 0.001
(c) P > 0.001
(d) P > 0.001
(e) P > 0.001
(f) P > 0.001
(g) P > 0.001
(h) P > 0.001
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(p) P > 0.001
(q) P > 0.001
(r) P > 0.001
(s) P > 0.001
(t) P > 0.001
(u) P > 0.001
(v) P > 0.001
(w) P > 0.001
(x) P > 0.001
(y) P > 0.001
(z) P < 0.001

* Denotes significant difference

Column 1 denotes data at 0 hours, column 2 data after 24 hours and column 3 data after 48 hours

(a) Indicates significance of difference between columns 1 and 2

(b) Indicates significance of difference between columns 1 and 3
RESULTS

The changes in body weight, plasma uric acid, creatinine, osmolality and sodium following the administration of methoxyflurane and halothane are summarized in tables I and II respectively. The mean values of these parameters (± 1 SD) are shown in figure 1.

There was no difference in the data of the two groups after 48 hours.

**Creatinine.** There were no significant changes in plasma creatinine following the use of either agent.

**Osmolality.** No change of significance was noted after the use of methoxyflurane or halothane.

**Electrolytes.** No changes of importance were detected and all determinations of plasma sodium concentrations were within normal limits. Measurements of plasma chloride and potassium levels were also made but no significant alterations were observed.

**Urine volume.** There was great variation in the total volume of urine passed in the 48-hour period following anaesthesia, although there was no evidence of polyuria associated with the use of either agent (see table III).

<table>
<thead>
<tr>
<th>TABLE III</th>
</tr>
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<tbody>
<tr>
<td>TOTAL URINE VOLUME (ml) IN THE 48 HOURS FOLLOWING ANAESTHESIA</td>
</tr>
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<td>METHOXYFLURANE</td>
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<tr>
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</tr>
<tr>
<td>1390</td>
</tr>
<tr>
<td>640</td>
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<td>1120</td>
</tr>
<tr>
<td>MEAN</td>
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<tr>
<td>1117</td>
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</table>

DISCUSSION

During the past few years several reports have appeared in the literature which suggest that the administration of methoxyflurane might be followed by renal tubular dysfunction in the postoperative period (Crandell and Macdonald, 1968; Austin and Villandry, 1967). The clinical picture observed is one of high output renal failure, polyuria with low urinary specific gravity being associated with elevated serum osmolality and plasma sodium and uric acid levels, together with decreased uric acid clearance and loss of weight.

Work by Mazze, Trudell and Cousins (1971) showed that serum and urinary inorganic fluoride concentrations were markedly elevated in patients who developed clinical signs of renal dysfunction associ-
ated with the inhalation of methoxyflurane. They forwarded the hypothesis that increased plasma fluoride concentrations may well be the causative factor because this substance inhibits many enzyme systems in the body and can cause polyuric renal insufficiency in rats. They substantiate this in further studies (Mazze, Cousins and Kosek, 1972) which indicate that in rats the injection of inorganic fluoride produces changes in renal function and histology similar to those seen after the administration of methoxyflurane.

Many of the cases of renal dysfunction which have been reported followed the use of high concentrations of methoxyflurane for prolonged periods and the complication may well indicate a dose-related response. As an example, in the studies of Mazze, Trudell and Cousins (1971) methoxyflurane, the sole agent used for induction and maintenance, was often administered for 3 hours or longer. Also, since preanaesthetic medication, nitrous oxide and muscle relaxants were omitted, it is probable that higher vapour concentrations were consequently required.

It is now known that concentrations of inhaled methoxyflurane much lower than previously used are adequate and indeed desirable for satisfactory clinical use. Also, it would seem logical to suggest that the incidence of postoperative renal dysfunction could be reduced by using only minimal vapour strengths. In this regard it is of interest that Rosen, Latto and Asscher (1972) found no evidence of renal disorder after methoxyflurane analgesia (0.35%) during labour.

It is the practice in this hospital to limit the administration of high concentrations of methoxyflurane (1–3%) to a 15-minute period, following which maintenance levels of 0.3–0.5% are given for a maximum of 60 minutes, after which time anaesthesia is continued solely with nitrous oxide and oxygen. The continuous inhalation of concentrations in excess of 0.5% is avoided in order to reduce the possibility of circulatory and respiratory depression, and postoperative renal dysfunction.

The present study shows that the inhalation of low concentrations of methoxyflurane (0.5%) for relatively short periods of time (60 minutes) results in significant reductions in body weight and increases in plasma uric acid and urea levels. Features such as polyuria, elevated plasma osmolality and sodium concentration which have been noted in other reports were not observed and, in the absence of these, renal tubular dysfunction cannot be incriminated as a cause of the above findings. Further, it is unlikely that impairment of glomerular function was a factor because plasma creatinine levels were unaltered.

If loss of fluid is excluded as a cause of the reduction in body weight then tissue breakdown has to be considered. The findings of this study could have resulted from metabolic derangements and since there were no detectable alterations in body fluid it is conceivable that reduced calorie intake in the postoperative period could have contributed to the loss of body weight and the increase in plasma uric acid and urea which followed the use of methoxyflurane.

In support of such a concept is the fact that significant increases in plasma uric acid and urea were found to follow halothane anaesthesia, an agent not prone to induce renal dysfunction. It seems reasonable to postulate that the changes observed following the use of both anaesthetics were largely due to increased metabolism. The absence of loss of weight and the less pronounced rises in plasma uric acid and urea associated with the use of halothane suggest the catabolic process was much less pronounced with this agent than with methoxyflurane.

Since accurate fluid intake data were not obtained in these studies it is not possible to determine if postoperative calorie intake differed in the two groups. However, vomiting was minimal in all cases and all the children were given a comparable fluid regime. Another possibility is that methoxyflurane per se causes a greater degree of catabolism than halothane.

Irrespective of the cause, the present findings indicate that increases in plasma uric acid and urea levels may be associated with methoxyflurane anaesthesia in the absence of the definite renal dysfunction which has been demonstrated in other studies.

In view of such results, what should the policy be regarded the continued use of methoxyflurane in clinical practice? It was the opinion of the Committee in Anesthesia of the National Academy of Science (U.S.A.) (1971) that the agent should continue to be made available until the results of further prospective studies were known.

One is forced to conclude that the findings of this investigation, although apparently not directly attributable to renal dysfunction, emphasize that the position of methoxyflurane in clinical practice should be carefully re-evaluated.

ACKNOWLEDGMENTS

It is a pleasure to acknowledge the willing advice given by Dr M. G. McGeown and Dr J. D. Merrett. We also wish to express our grateful thanks to Mr T. D. Lavery, Sister M. I. Jamieson and Sister L. McLain for their cooperation.
RENAL FUNCTION FOLLOWING METHOXYFLURANE ANAESTHESIA

REFERENCES

FONCTION RENALE APRES ANESTHESIE AU METHOXYFLURANE

SOMMAIRE
Des réductions significatives du poids corporel et des augmentations de l'acide urique plasmatique et des concentrations d'urée sont survenues lors de la phase postopératoire chez des enfants normaux qui avaient inhalé 0,5% de méthoxyflurane pendant 60 minutes. En absence de signes tels que polyurie, hyperosmolalité plasmatique, hypernatrémie et taux élevés de créatinine, la preuve d'une dysfonction rénale fait défaut. Des concentrations élevées de l'acide urique et urée plasmatiques, mais moins prononcées qu'avec méthoxyflurane, ont également été observées après l'administration d'halothane, une substance qui ne tend pas à causer des troubles rénaux. Il est suggéré que les observations faites résultant d'un métabolisme accru, peut-être dû à une ingestion calorique réduite. Quelle que soit la cause, les modifications rapportées peuvent justifier à réévaluer la place du méthoxyflurane en pratique clinique.

NIERENFUNKTION NACH NARKOSE MIT METHOXYFLURANE

ZUSAMMENFASSUNG

FUNCION RENAL SIGUIENTE A UNA ANESTESIA CON METOXIFLURANO

RESUMEN
Reducciones considerables del peso corporal y aumentos del ácido úrico y concentración de la urea en el plasma ocurrieron durante el periodo postoperatorio en niños normales, que habian inhalado un 0,5% de metoxiflurano durante 60 minutos. En ausencia de signos tales como poliuria, hiperosmolaridad del plasma, hipernatremia y niveles altos de creatinina, no existe una evidencia exacta de una mala función renal. Aunque menos pronunciadas que cuando se usa el metoxiflurano, unas mayores concentraciones de ácido úrico en el plasma y de la urea se observaron a consecuencia de la administración de fluotano, un agente que no es propenso a inducir trastornos renales. Se sugiere que los hallazgos presentes resultaron de un metabolismo aumentado, posiblemente debido a una disminución de la administración de calorías. Independientemente de esta causa, los cambios referidos anteriormente pueden garantizar una nueva evaluación de la posición del metoxiflurano en la práctica clínica.