CHANGES IN SERUM URIC ACID RELATED TO THE DOSE OF METHOXYFLURANE

W. F. D. HAMILTON AND G. S. ROBERTSON

SUMMARY

In a study of 59 patients subjected to minor general surgical procedures under methoxyflurane anaesthesia, a significant correlation was obtained between the elevation of serum uric acid and the dose of methoxyflurane administered. These results are compared with those from a control group of 8 patients anaesthetized with halothane. The mechanism of uric acid excretion is reviewed briefly, and it is suggested that the estimation of serum uric acid is a sensitive test of distal tubular function following methoxyflurane. A dose-response relationship for the elevation of serum uric acid is consistent with the findings of other workers in respect of changes in serum and urine fluoride after methoxyflurane anaesthesia, and supports the hypothesis that methoxyflurane nephrotoxicity is caused by the action of fluoride on distal tubular function.

During the past 10 years there have been numerous reports, mainly in the American literature, describing high-output renal failure after methoxyflurane (Penthane) anaesthesia (Crandell, Pappas and Macdonald, 1966; Pezzi, Frobose and Greenberg, 1966; Merkle et al., 1971). Inevitably these reports were retrospective and lacked control investigations. Mazze, Shue and Jackson (1971) published the results of a randomized prospective clinical comparison of the effects of methoxyflurane and halothane anaesthesia on renal function. They concluded that an increase in the urine volume, the serum concentrations of urea, sodium and uric acid and the serum osmolality in the patients receiving methoxyflurane indicated that "methoxyflurane anaesthesia produced high-output renal insufficiency" and that this resulted from a lesion of the distal nephron.

In several respects Mazze's study does not reflect the customary use of methoxyflurane in the United Kingdom. In particular, high inspired concentrations of methoxyflurane were used for long periods of time and the total dose of methoxyflurane administered was substantial. Recently we attempted to evaluate the changes in renal function associated with methoxyflurane used in a manner which is similar to that of most anaesthetists in the United Kingdom (Robertson and Hamilton, 1973). We found no significant changes in the serum concentrations of sodium, urea and creatinine, and the serum and urine osmolality after methoxyflurane anaesthesia. The main finding was a significant increase in serum uric acid concentration, which did not occur after anaesthesia with either halothane or pheneridine.

A relationship between methoxyflurane administration and renal dysfunction has been suggested in both animals and man by various investigators (Lapointe and Bele-Binda, 1970; Vandam, 1970). In the light of case reports of renal dysfunction following exposure to large doses of methoxyflurane (Crandell, Pappas and Macdonald, 1966; Mazze, Shue and Jackson, 1971; Merkle et al., 1971), and an absence of alterations in renal function following exposure to small doses of methoxyflurane (Bergeron et al., 1968; Cousins, Nishimura and Mazze, 1972; Rosen, Latto and Asscher, 1972), the present study was designed to determine whether the increase in serum uric acid concentration is related to the dose of methoxyflurane.

METHOD

Sixty-seven patients undergoing minor general surgical procedures were studied. All had given permission for the investigation. There were 18 operations for varicose veins, 29 for inguinal hernia repair, and 20 anal, orthopaedic or plastic surgery operations. Each patient was allocated to one of 13 groups depending on the estimated duration of surgery. Patients with the following conditions were excluded: renal disease; diabetes mellitus; corti-

costeroid, diuretic or tetracycline therapy; obstructive airways disease.

Premedication was with papaveretum and either hyoscine or atropine, given by intramuscular injection 1 hour before the operation. The anaesthetic technique was standard and consisted of a sleep dose of thiopentone followed by suxamethonium. After endotracheal intubation, and throughout the procedure, ventilation was controlled with a Manley ventilator which delivered oxygen 40% in nitrous oxide. After recovery from suxamethonium, alcuroonium 10 mg was given. To each of 12 groups (a total of 59 patients) different concentrations of methoxyflurane were administered for different periods of time. A control group (8 patients) received halothane 0.5% for 30 minutes. Using a standard minute volume of 10 1. for all patients, the total dose of liquid methoxyflurane vaporized in each group could be calculated.

Attempts were made to ensure that the total dose of methoxyflurane administered to each patient was predictable to a high degree of accuracy. Expired methoxyflurane was not measured because, in the clinical situation it is preferable to consider the total dose delivered to the patient rather than the dose taken up. It has been shown that the rubber components of an anaesthetic system can absorb a significant quantity of methoxyflurane (Eger and Brandstater, 1963). Accordingly, the anaesthetic circuit was vented with methoxyflurane 0.5% in oxygen 40% in nitrous oxide for 20 minutes immediately before use. At the end of the accurately timed period of anaesthesia with methoxyflurane, the circuit was disconnected at the catheter mount and anaesthesia was continued using a methoxyflurane-free circuit. The vaporizers for methoxyflurane and halothane were specially calibrated for this study.

No intravenous fluids were given during or following surgery. A venous blood sample was taken on the day before operation, and on each of the first 2 days after operation for the measurement of serum uric acid concentrations. This was measured with an AutoAnalyzer I (Technicon Instruments Co. Ltd) using the phosphotungstate/cyanide method. The serum, obtained by centrifugation of the samples, was frozen to allow a large number of samples to be analysed following each calibration of the AutoAnalyzer.

RESULTS

The exposure groups ranged from 0.2% methoxyflurane for 15 min to 0.5% for 60 min. The total dose of liquid methoxyflurane delivered ranged from 1.5 ml to 15.0 ml. In calculating these values, it was assumed that 1 ml of liquid methoxyflurane produces 200 ml of vapour.

The mean serum uric acid concentration values for the patients in each group and the values for the control patients are shown in Table I. The regression lines for the relationship of change of serum uric acid concentration to dose of methoxyflurane on each of the two postoperative days are shown in figs. 1 and 2. Table II shows the mean serum uric acid concentration values for the same patients in four larger dose groups.

These tables and figures show that in all groups the serum uric acid concentration was increased on the first day after operation as compared with before operation and this increase appears to be related to the dose of methoxyflurane. On the second day after operation, in the higher dose groups, the increase in serum uric acid concentration is either

### Table I. Mean concentrations of serum uric acid for each group of patients.

<table>
<thead>
<tr>
<th>Group</th>
<th>Methoxyflurane dose (ml)</th>
<th>Number of patients</th>
<th>Before opn.</th>
<th>After opn. Day 1</th>
<th>Day 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.5</td>
<td>5</td>
<td>5.10</td>
<td>6.22 5.40</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2.25</td>
<td>5</td>
<td>5.46</td>
<td>6.16 5.30</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3.0</td>
<td>5</td>
<td>4.38</td>
<td>5.36 4.66</td>
<td></td>
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<td>4</td>
<td>3.75</td>
<td>5</td>
<td>5.08</td>
<td>6.54 5.40</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>4.5</td>
<td>5</td>
<td>5.08</td>
<td>6.80 5.46</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>4.5</td>
<td>5</td>
<td>4.44</td>
<td>5.42 4.88</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>6.0</td>
<td>5</td>
<td>5.26</td>
<td>6.38 5.66</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>6.75</td>
<td>5</td>
<td>5.72</td>
<td>7.28 6.84</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>7.5</td>
<td>4</td>
<td>4.43</td>
<td>5.80 5.15</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>9.0</td>
<td>5</td>
<td>4.76</td>
<td>6.98 6.54</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>11.25</td>
<td>5</td>
<td>6.08</td>
<td>8.02 8.66</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>15.0</td>
<td>5</td>
<td>4.99</td>
<td>7.32 8.0</td>
<td></td>
</tr>
<tr>
<td>Control (halothane 0.5% for 30 min)</td>
<td>8</td>
<td>5.40</td>
<td>6.24 5.55</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table II. Mean concentrations of serum uric acid for four methoxyflurane dose ranges.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Number of patients</th>
<th>Methoxyflurane dose range (ml)</th>
<th>Before opn.</th>
<th>After opn. Day 1</th>
<th>Day 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3</td>
<td>15</td>
<td>1.5–3.0</td>
<td>4.98</td>
<td>5.90 5.12</td>
<td></td>
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<tr>
<td>4-6</td>
<td>15</td>
<td>3.75–4.5</td>
<td>4.43</td>
<td>5.62 5.25</td>
<td></td>
</tr>
<tr>
<td>7-9</td>
<td>14</td>
<td>6.0–7.5</td>
<td>5.23</td>
<td>6.61 6.11</td>
<td></td>
</tr>
<tr>
<td>10-12</td>
<td>15</td>
<td>9.0–15.0</td>
<td>5.27</td>
<td>7.44 7.73</td>
<td></td>
</tr>
</tbody>
</table>
sustained or increased further. The absolute increase on the first day after operation was calculated for each patient and was plotted against the dose of methoxyflurane. The correlation coefficient is 0.621 which represents a significant difference from a zero correlation (P<0.001). The slope of the regression line relating the change in serum uric acid concentration to the dose of methoxyflurane is 0.2035. This is significant (t=7.00; P<0.001).

Similar calculations were made in respect of serum uric acid concentration values on the second day after operation. The correlation coefficient is 0.764 (P<0.001) and the slope of the regression line is significant (t=6.218; P<0.001).

Similar calculations were performed on the results from the halothane group. The mean increase in serum uric acid concentration on the first day after operation was 0.84 mg/100 ml (P<0.05). On the second day the mean increase was 0.15 mg/100 ml which is not statistically significant. If the control group mean values and the regression lines calculated for methoxyflurane are compared, the first and second day increases in the control group are equivalent to a dose of about 3.5 ml and 2.5 ml methoxyflurane respectively.

**DISCUSSION**

Hyperuricaemia is an easily detected and common clinical abnormality. Uric acid is filtered freely by the glomeruli, and 98% of this is reabsorbed by the proximal tubules. At least 80% of uric acid excretion occurs at the distal tubules (Berliner et al., 1950; Gutman, Yu and Berger, 1959; Steele, 1971).

Hyperuricaemia may be secondary to increased production of uric acid or to decreased renal clearance. Several factors influence reabsorption and secretion, including intravenous infusions of glucose and saline (Skeith, Healey and Cutler, 1967), diuretic drugs (Steele and Oppenheimer, 1969) and the circulating level of catecholamines (Cannon et al., 1966). Certain disorders appear to have a specific effect on distal tubular handling of uric acid. Lead nephropathy and beryllium intoxication are associated with hyperuricaemia because they cause
a decrease in excretion. Whilst many retrospective
and prospective studies of methoxyflurane nephro-
toxicity suggest both a glomerular and a tubular
defect, our previous study (Robertson and Hamil-
ton, 1973) suggested that a small total dose of
methoxyflurane caused a significant rise in serum
uric acid only, probably reflecting an effect on the
distal tubular secretion. In agreement with others
(Mazze, Shue and Jackson, 1971; Laird and Chrys-
tal, 1972) we concluded that serum uric acid con-
centration is the most sensitive test for renal dys-
function associated with methoxyflurane anaesthesia.

A recent investigation in rats (Mazze, Cousins
and Kosek, 1972) demonstrated convincingly that
the changes in renal function after methoxyflurane
anaesthesia were dose-related, and there is consider-
able circumstantial evidence that this applies in man.
Lapointe and Bele-Binda (1970) reported that
methoxyflurane nephrotoxicity was rare but that it
appeared to be related to prolonged anaesthesia.
Laird and Chrystal (1972) investigating a small
group of burned patients reported that all their
patients had an increase in serum acid concentration
after methoxyflurane anaesthesia, and that there was
a direct relationship between the percentage in-
crease in serum uric acid concentration and the
"methoxyflurane factor" (vaporizer setting X
minutes of exposure). Cousins, Nishimura and
Mazze (1972) showed that, in 10 patients having
surgery requiring cardiopulmonary bypass, there
were significant changes in measurements which
reflected methoxyflurane metabolism as distinct
from toxicity and they made assumptions regarding
the levels of metabolites in earlier patients with
evidence of renal impairment associated with meth-
oxylflurane, suggesting that these renal lesions might
be dose-related.

Mazze and Cousins (1973) claim to have demon-
strated a relationship between nephrotoxicity, the
dose of methoxyflurane and the serum inorganic
fluoride concentration in man. Their study was
conducted on a small number of patients and details
of the method of evaluating renal dysfunction have
not been published.

The present study demonstrates that, after rela-
tively short exposure to methoxyflurane there is a
significant correlation between the elevation of
serum uric acid concentration and the dose of
methoxyflurane. It is not possible to draw firm
conclusions regarding the clinical significance of
these findings since it is likely that transient mild
or moderate hyperuricaemia, which is an "almost
physiological" feature in women during labour
(Crawford, 1939), is not harmful. However, we be-
lieve that the finding of a dose-response relationship
is important.

The inhalational anaesthetics, regarded for many
years as inert, are now known to be degraded in the
body to some extent. It was considered possible
that biotransformation of methoxyflurane in man
results in a metabolite which is toxic to the renal
tubule and it has been shown that the principal
metabolic products of the biotransformation of
methoxyflurane are oxalic acid (Frascino, Vanamee
and Rosen, 1970) and fluoride (Taves et al., 1970;
Mazze, Trudell and Cousins, 1971). Both sub-
stances have been incriminated in nephrotoxicity.
The characteristics of oxalic acid intoxication differ
from those of methoxyflurane nephrotoxicity, and
oxalic acid affects glomerular function to a much
greater extent than it affects tubular function
(Mazze, Trudell and Cousins, 1971). Fluoride ion
is known to inhibit several enzyme systems, and
chronic ingestion has been shown to produce both
clinical and histological evidence of renal tubular
damage (Wiseman, 1970). In addition, the serum
and urinary concentrations of fluoride are particu-
larly high following methoxyflurane anaesthesia
(Taves et al., 1970; Mazze, Trudell and Cousins,
1971). Mazze, Cousins and Kosek (1972) injected
inorganic fluoride into rats and produced changes
in renal function and renal histology similar to those
seen after the administration of methoxyflurane.
They concluded that methoxyflurane produced a
lesion of the renal tubule because of the production
of fluoride. While there is evidence that methoxy-
flurane itself can cause direct depression of enzyme
activity in animal preparations (McIntyre and Rus-
sell, 1971), the amount of methoxyflurane required
to produce this effect is equivalent to that required
for deep anaesthesia in man, and there is no evi-
dence that methoxyflurane can produce histological
changes in the kidney except by means of its
metabolic products.

Our study produces clear evidence of a dose-
related increase in serum uric acid, presumably re-
flecting a dose-related change in distal tubular func-
tion following methoxyflurane anaesthesia in man.
The available evidence indicates that the cause of
the tubular dysfunction is fluoride derived from the
breakdown of methoxyflurane.

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REFERENCES


6TH WORLD CONGRESS OF ANAESTHESIOLOGISTS

On account of the successful journey to the World Congress of Anaesthesiologists in Japan in 1972, the Belgian Professional Association of Anaesthetists will be organizing three different tours on the occasion of the 6th World Congress to be held in Mexico in April, 1976.

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