CHANGES IN URINE OSMOLALITY AND URINE FLUORIDE CONCENTRATIONS FOLLOWING METHOXYFLURANE ANAESTHESIA

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

SUMMARY

A study of 41 patients receiving methoxyflurane and 8 patients receiving halothane showed that on the first day after exposure to methoxyflurane there was a significant correlation between the reduction of urine osmolality and the dose of methoxyflurane. On the first and second days after exposure to methoxyflurane the patients who received a relatively large dose had significantly lower urine osmolality values than those who received a smaller dose. The patients who were exposed to large doses of methoxyflurane developed significantly decreased urine osmolality values on the second day after exposure compared with patients receiving halothane. In a study of 47 patients exposed to methoxyflurane a significant correlation was found between the dose of methoxyflurane and the urine fluoride concentration on the first and second days after exposure. These findings are taken as further evidence of a causal relationship between renal tubular dysfunction and the increased production of fluoride which follows methoxyflurane anaesthesia.

It has been shown that methoxyflurane anaesthesia is associated with an increase in the serum uric acid concentration (Mazze, Shue and Jackson, 1971; Robertson and Hamilton, 1973) and that the change in serum uric acid concentration is related to the dose of methoxyflurane (Hamilton and Robertson, 1974).

The increase in serum uric acid concentration probably results from a reduced renal tubular ability to clear uric acid, caused by fluoride derived from the metabolic breakdown of methoxyflurane. If there is altered tubular function associated with methoxyflurane, some disturbance of the renal handling of water should be detectable: our initial investigation (Robertson and Hamilton, 1973) did not substantiate the evidence for a methoxyflurane-induced defect in the renal mechanism for concentrating urine (Mazze, Shue and Jackson, 1971). However, in view of the considerable evidence of tubular dysfunction after methoxyflurane anaesthesia, it was decided to assess the effect of methoxyflurane on urine osmolality in patients undergoing relatively minor surgery and who were mildly dehydrated. In addition, a study was undertaken to investigate the relationship between urine fluoride concentrations and the dose of methoxyflurane.

METHOD

Sixty-four patients were studied, all of whom had given permission for the investigation; 41 were included in the osmolality study, 47 in the fluoride study, and 8 were in the control studies. Thirty-two of the patients receiving methoxyflurane were in both the osmolality and the fluoride studies. The patients were to undergo surgery for varicose veins, inguinal hernia, or haemorrhoids, and all received premedication with papaveretum and either hyoscine or atropine, given by intramuscular injection 1 hour before operation. The anaesthetic technique, which was standard, consisted of induction with thiopentone followed by suxamethonium. After endotracheal intubation and throughout the procedure, ventilation was controlled using a Manley ventilator which delivered oxygen 40% in nitrous oxide. Neuromuscular block was maintained with alcuronium.

Groups of patients were given methoxyflurane exposures varying between 0.2% for 15 min and 0.5% for 60 min. The minute volume was standard at 10 litres for all patients, which enabled the total quantity of methoxyflurane vaporized in each group to be calculated. A specially calibrated vaporizer was used and the anaesthetic circuit was flushed with methoxyflurane 0.5% in oxygen 40%/nitrous oxide 60% for 20 min before use in order to equilibrate the rubber components of the circuit with the anaesthetic gas mixture. At the end of the period
of anaesthesia with methoxyflurane, the circuit was replaced by a methoxyflurane-free circuit. A control group (8 patients) received halothane 0.5% for 30 min.

All patients were deprived of fluid from 10 p.m. on the night before operation. During and after surgery no intravenous fluid was administered, and the normal oral intake of fluid was not resumed until at least 24 hours after surgery.

Urine samples were obtained on the day before operation (for urine fluoride estimation only) and on each of the first two days after operation, and these were stored in plastic containers in a deep-freeze. Urine osmolality estimations were carried out using a Fisons Advanced Clinical Osmometer, calibrated before each group of estimations using standard solutions of 100 m.osm/l and 900 m.osm/l. Urine fluoride estimations were carried out using a Model 96-09 Ionalyzer fluoride electrode (Orion Research Inc.) and a Model 23A direct-reading pH meter (Electronic Instruments Ltd). The urinary fluoride reference solution (1.00 mg fluoride/l) was made from a stock solution of sodium fluoride to which was added Total Ionic Strength Urinary Buffer of pH 5.25. This mixture was then diluted with a simulated urine solution containing sodium chloride, dibasic ammonium phosphate, and concentrated sulphuric acid. The preparation of the reference solution and the technique of estimation were conducted according to the method described by Neefus, Cholak and Saltzman (1970).

RESULTS

In calculating the total dose of methoxyflurane delivered to each patient it was assumed that 1 ml of liquid methoxyflurane produces 200 ml of vapour.

The mean urine osmolality values for the patients in each group and the values for the control group are shown in table I. The relationship between urine osmolality and methoxyflurane dose on each of the two days after operation is shown in figures 1 and 2.

Statistical analysis of the results shows that for the first day after operation (day 1) there are no significant differences between any of the means of the groups. However, dividing the methoxyflurane cases into a "low dose" group (1.5–9.0 ml) and a

<table>
<thead>
<tr>
<th>Methoxyflurane dose (ml)</th>
<th>Day 1 Mean</th>
<th>Day 1 SD</th>
<th>Day 2 Mean</th>
<th>Day 2 SD</th>
<th>No. of patients</th>
</tr>
</thead>
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<tr>
<td>1.50–3.0</td>
<td>800</td>
<td>131</td>
<td>589</td>
<td>184</td>
<td>8</td>
</tr>
<tr>
<td>3.75–6.0</td>
<td>849</td>
<td>185</td>
<td>832</td>
<td>235</td>
<td>13</td>
</tr>
<tr>
<td>6.75–9.0</td>
<td>789</td>
<td>176</td>
<td>757</td>
<td>235</td>
<td>11</td>
</tr>
<tr>
<td>11.25</td>
<td>628</td>
<td>313</td>
<td>628</td>
<td>310</td>
<td>4</td>
</tr>
<tr>
<td>15.0</td>
<td>640</td>
<td>209</td>
<td>447</td>
<td>72</td>
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<tr>
<td>LD 1.50–9.0</td>
<td>819</td>
<td>167</td>
<td>745</td>
<td>238</td>
<td>32</td>
</tr>
<tr>
<td>HD 11.25–15.0</td>
<td>635</td>
<td>242</td>
<td>527</td>
<td>219</td>
<td>9</td>
</tr>
<tr>
<td>Halothane</td>
<td>847</td>
<td>190</td>
<td>877</td>
<td>168</td>
<td>8</td>
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"high dose" group (11.25–15.0 ml), the urine osmolality is significantly less in the "high dose" group on day 1 ($t=2.556; P<0.02$). On day 2 also the urine osmolality is significantly less in the "high dose" group ($t=2.405; P<0.05$).

The correlation between reduction of urine osmolality and dose of methoxyflurane is significant on day 1 ($P<0.02; r=-0.375$). The correlation coefficient for day 2 is $-0.251$ which is not significantly different from a zero correlation.

The mean urine osmolality value in the halothane control group on day 1 is equal to the highest osmolality value recorded for any patient who received methoxyflurane, and on day 2 the mean control value is greater than the highest mean value in the methoxyflurane groups (figs. 1 and 2). The difference in mean osmolality values between the halothane group and the group receiving the largest dose of methoxyflurane is highly significant for day 2 (mean difference=350 m.osm/kg; $t=3.44; P<0.01$). The comparable mean difference on day 1 is 212 m.osm./kg (not significant).

The mean urine fluoride concentrations in the different methoxyflurane dose groups and in the halothane control group are shown in table II.

Correlation coefficients were calculated in respect of mean urine fluoride concentrations and the dose of methoxyflurane: for the first and second days after exposure, the correlation coefficients are highly significant ($r=0.380, P<0.01$, on day 1; $r=0.462, P<0.001$, on day 2). The slopes of the regression lines are 1.67 for day 1 ($P<0.01$) and 2.15 for day 2 ($P<0.002$) (figs. 3 and 4).

**DISCUSSION**

The results of this investigation show that in 41 patients undergoing relatively minor surgery without the intravenous infusion of fluid, there is a significant relationship between the dose of methoxyflurane and the reduction in urine osmolality on the first day after exposure to methoxyflurane, and that on the first and second days after exposure the urine osmolality is significantly reduced in patients receiving a "high" dose of methoxyflurane as compared with those receiving a "low" dose. There is also a significant correlation on both the first and second days after surgery between the concentration of fluoride in the urine and the dose of methoxyflurane delivered in a group of 47 patients. By contrast, patients given halothane show practically no

![Fig. 3. Relationship between urine fluoride concentration and methoxyflurane dosage (47 cases) on the first day after exposure.](https://academic.oup.com/bja/article-abstract/46/2/153/259174/)

<table>
<thead>
<tr>
<th>Methoxyflurane dose (ml)</th>
<th>Preoperative</th>
<th>Postoperative</th>
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<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
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<td></td>
<td></td>
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<tr>
<td>1.50–3.0</td>
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<td>6.75–9.0</td>
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<td>0.93</td>
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<td>11.25</td>
<td>0.65</td>
<td>0.13</td>
</tr>
<tr>
<td>15.0</td>
<td>1.64</td>
<td>1.09</td>
</tr>
<tr>
<td>Halothane controls</td>
<td>0.81</td>
<td>0.34</td>
</tr>
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</table>
change in urine fluoride concentration. The mean urine osmolality values in the halothane control group probably represent the normal response to moderate dehydration and surgery.

The results contrast with the urine osmolality values found in our initial comparative study (Robertson and Hamilton, 1973), in which the fluid replacement regime was designed to produce a normal fluid balance. While there were no statistically significant differences in urine osmolality when groups of patients receiving methoxyflurane, halothane or phenoperidine were compared, it is noteworthy that the mean urine osmolality values in the methoxyflurane group were remarkably similar to those found in the present study. Also in our previous study it was found that the patients exposed to methoxyflurane had the lowest mean urine osmolality values on the first and second days after anaesthesia.

The physiological changes in the renal handling of water after surgery have been described as being very similar to those following the administration of vasopressin (Hayes and Goldenberg, 1963). The changes include a marked increase in urine osmolality, a decrease in serum osmolality, and a reduction of urine volume. Deutsch and his colleagues (1969) have described similar changes, but they considered the state of anaesthesia itself to be a sufficient stimulus to account for any increase in urine osmolality.

In the circumstances of our study, it would be expected that the combination of dehydration, surgery and anaesthesia would result in the production of concentrated urine in the early days after operation. The results show that patients receiving halothane or small doses of methoxyflurane develop a high urine osmolality (greater than 750–800 m.osm/kg) on the first day after operation, but patients exposed to larger doses of methoxyflurane fail to produce urine of high osmolality.

The impaired physiological response to surgery and dehydration shown here is similar to the impaired response to infused vasopressin which has been described in cases of nephrotoxicity following methoxyflurane (Crandell and Macdonald, 1968; Elkington, Goffinet and Conn, 1968; Lebowitz, 1969; Proctor and Barton, 1971). These case reports referred to patients receiving either very prolonged exposures to methoxyflurane or other therapy which could have accounted for a degree of renal dysfunction. The prospective studies reported by Mazze, Shue and Jackson (1971) and by Merkle and colleagues (1971) are of greater importance, although large doses of methoxyflurane appear to have been used. These workers found significant reductions of urine osmolality and impaired responses to vasopressin in patients exposed to methoxyflurane.

In a comparative study of women in labour receiving either methoxyflurane or nitrous oxide analgesia, Rosen, Latto and Asscher (1972) found no evidence of renal dysfunction associated with methoxyflurane. In particular, they found no significant differences between the groups in respect of serum osmolality and urine/serum osmolality ratios, but the study failed to take account of the dramatic decline in the ability to excrete a water load during pregnancy, particularly at full term (Hyttén and Klopper, 1963). In late pregnancy the normal reduction of serum osmolality which follows a water load does not occur, and it may be that osmoreceptors adjust to preserve a lower serum osmolality during pregnancy (Hyttén and Leitch, 1971). Thus measurements of serum and urine osmolality during the first week after parturition would be influenced by several factors which could obscure an effect of methoxyflurane.
A recent study (Hetrick et al., 1973) indicated that in patients exposed to “light” methoxyflurane anaesthesia, there was a significant reduction in urine osmolality, but the reduction was not significantly different from that in a control group; it was concluded that fluoride derived from methoxyflurane might inhibit antidiuretic hormone as a dose-related phenomenon.

Several recent reports conclude that fluoride is responsible for the nephrotoxicity of methoxyflurane: Cousins, Nishimura and Mazze (1972) found that patients having “low dose” exposures to methoxyflurane did not show evidence of nephrotoxicity, but there were significant changes in tests reflecting the metabolism of methoxyflurane. The changes were considerably less than in the earlier work reported by Mazze, Trudell and Cousins (1971) in patients receiving larger doses of methoxyflurane. These workers interpreted their results as suggesting a relationship between dose of methoxyflurane and blood concentration of fluoride. The presumed relationship was confirmed in a study using rats (Mazze, Cousins and Kosek, 1972), although there was not a significant correlation between urine fluoride concentrations and dose of methoxyflurane. The nephrotoxicity of fluoride was clearly demonstrated in rats following intraperitoneal injection of sodium fluoride, and Mazze and his colleagues concluded that fluoride probably interfered with the renal sodium pump mechanism by acting on cellular energy-transfer systems.

The infusion of fluoride in dehydrated dogs has been shown to cause a marked reduction of urine osmolality and an increase in urine volume by Frascino et al. (1972), who remarked upon the similarity between their experimental model and the clinical condition of dehydration after surgery. Our investigation shows that there is wide variation in the urine fluoride concentrations within dose groups (figs. 3 and 4), suggesting that the amount of methoxyflurane eliminated by metabolic breakdown, as distinct from simple exhalation, depends upon the proportion of the agent retained within the body. Because of the high fat solubility of methoxyflurane it is likely that obese patients will retain a greater proportion of methoxyflurane for subsequent biodegradation than will lean patients. Taves and colleagues (1970) noted that a patient who developed nephrotoxicity and increased blood fluoride concentrations was very obese, whereas two other patients with lower blood fluoride concentrations and without nephrotoxicity, despite receiving similar exposures to methoxyflurane, were not obese.

Lapointe and Bele-Binda (1970) reported five patients with methoxyflurane nephrotoxicity, four of whom were very obese. In our study, one patient developed urine fluoride concentrations of 102.4 μg/ml and 105.0 μg on day 1 and day 2 respectively after receiving 9.0 ml of methoxyflurane. These concentrations are very high; it is noteworthy that the patient weighed 107 kg and was the heaviest in the series.

The role of oxalate as distinct from fluoride in the causation of renal dysfunction after methoxyflurane anaesthesia is uncertain (Frascino, Vanamee and Rosen, 1970; Silverberg et al., 1971), but Mazze, Trudell and Cousins (1971) while finding increased oxalic acid excretion in patients who had received methoxyflurane, considered that oxalate had little to do with the renal dysfunction in their patients. They stated that oxalate intoxication normally resulted in an anuric or oliguric type of renal failure rather than the polyuric type seen after methoxyflurane. This conclusion is in agreement with the earlier opinion of Taves and associates (1970) that oxalate would be expected to cause oliguric renal failure.

The correlation between the dose of methoxyflurane and urine concentrations of fluoride shown in our study is strong evidence that fluoride is the cause of the dose-related changes in urine osmolality. Previous work has indicated a dose-related increase in serum uric acid after exposure to the relatively modest doses of methoxyflurane used in the present study (Hamilton and Robertson, 1974). The changes in serum uric acid were attributed to a reduced ability of the renal tubules to clear uric acid, and the demonstration of a disorder of an entirely different aspect of renal tubular function in the present investigation substantiates the conclusion that the dose-related changes may be explained as an effect of fluoride derived from biodegradation of methoxyflurane.

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REFERENCES


