CHANGES IN KIDNEY AND LIVER FUNCTION AFTER METHOXYFLURANE (PENTHRANE) ANAESTHESIA

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SUMMARY

Three groups of patients receiving methoxyflurane or halothane or pethidine after thiopentone suxamethonium induction were compared. Using multivariate Student t tests with simultaneous confidence intervals, significant differences in the test battery of uric acid, creatinine, blood urea nitrogen and sodium in the methoxyflurane series compared with the other series was found, indicating transient impaired kidney function. Likewise, there was a significant difference between the methoxyflurane and the other series in the s.g.p.t., s.g.o.t., alkaline phosphatase and bilirubin test battery, indicating impaired liver function. This was found after doses less than 16 ml which, so far, had been considered to be without any toxic effects.

The fact that methoxyflurane (Penthrane, Abbott) may cause disturbed renal function seems clearly established as illustrated by many reports in the literature (Crandell, Pappas and MacDonald, 1966; Crandell and MacDonald, 1968; Mazze, Shue and Jackson, 1971). Sporadic reports have appeared also which attempt to link methoxyflurane with disturbed liver function (Cale, Packs and Jenkins, 1962; Durkin, Brick and Schneider, 1966; Klein and Jeffries, 1966; Lischner, MacNabb and Galambos, 1967; Elkington, Goffinet and Conn, 1968; Rosander, 1970; Efundi et al., 1971), although such cases seem to be less frequent. The incidence of nephrotoxicity remains in dispute and opinions seem to be divided between those who believe it to be quite rare, and others who think it may be disturbingly common. A well-controlled study, published by Mazze, Shue and Jackson (1971), has demonstrated a remarkably high incidence of a "high output renal insufficiency syndrome", following the administration of methoxyflurane. In contrast to this, Robertson and Hamilton (1973) have been unable to show any renal effects of methoxyflurane. The manufacturers of methoxyflurane have recorded 101 cases of alleged methoxyflurane toxicity between 1961 and 1971, during which time it has been estimated that 15 million anaesthetics involving the use of this agent have been given (Abbott Laboratories, 1972).

The present study was undertaken to examine evidence of renal or hepatic dysfunction in the period soon after operation in a series of patients receiving only methoxyflurane in doses considered to be safe.

MATERIALS AND METHODS

The study was performed in 76 consecutive patients undergoing elective gynaecological surgery. Patients with known kidney or liver disease or diabetes mellitus, and patients undergoing treatment with corticosteroids, diuretics, anti-hypertensive agents, tetracyclines or known enzyme inducing drugs were excluded, as were those patients who required blood replacement during or after surgery. None of these patients had been subjected to anaesthesia during the previous 6 months.

Premedication consisted of papaveretum and hyoscine approximately 1 hr before operation and supplemented by atropine 0.5 mg given i.v. immediately before the start of anaesthesia.

Anaesthesia was induced with thiopentone 2–5 mg/kg followed by suxamethonium 50 mg i.v. to facilitate endotracheal intubation and thereafter as required. Oxygen 2 litre/min and nitrous oxide 4 litre/min and the volatile anaesthetic agents were delivered to a circle system. Manually controlled ventilation was employed.

Methoxyflurane was administered from a Pentec Vaporizer (Cyprane), initially in a concentration of 0.3%, being reduced to 0.2% within 30 min and discontinued at least 30 min before the expected completion of surgery. Halothane was administered from a Fluotec Vaporizer (Cyprane) in a concentration of 0.5% throughout the anaesthesia. Pethidine 50 mg was given i.v. immediately after induction, and 25 mg thereafter as needed. To estimate the total dose of methoxyflurane or halothane vaporized in each case, the vaporizer was filled with a known volume of the agent and the amount remaining in the vaporizer after each anaesthetic was measured.
Statistical analysis
Multivariate \( t^2 \) tests with simultaneous confidence intervals were used to detect significant differences between the series.

RESULTS
No clinical signs of high output renal failure were found in the course of the study. On the other hand, the blood uric acid concentrations in the methoxyflurane series were increased and there were significant \( (P<0.01) \) differences between the methoxyflurane group and the control series on the 1st and 3rd day. This difference had almost disappeared on the 5th day (table II).

The creatinine concentration was increased in the methoxyflurane group and the difference between the methoxyflurane and the control series was significant \( (P<0.05) \). This was especially marked on the 3rd day after operation (table II).

Blood urea nitrogen and sodium values did not show any significant differences (table II).

On the 5th day following surgery there was no significant difference between the methoxyflurane series and the control series.

S.g.p.t. measurements showed a significantly greater \( (P<0.01) \) increase in the methoxyflurane group than in the control series on the 1st day after operation.

### Table I. Age and duration of anaesthesia in the compared series, and type of surgery performed (mean values ± SD)

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (yr)</th>
<th>Duration of anaesthesia (hr)</th>
<th>Type of surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methoxyflurane</td>
<td>50 ±14</td>
<td>1.71 ±0.6</td>
<td>Hysterectomy</td>
</tr>
<tr>
<td>( n = 31 )</td>
<td></td>
<td></td>
<td>Ovarian cysts</td>
</tr>
<tr>
<td>Controls</td>
<td>48 ±12</td>
<td>1.90 ±0.7</td>
<td>Tubal-reconstruction</td>
</tr>
<tr>
<td>( n = 45 )</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table II. Concentration and changes in concentration of uric acid, creatinine, urea and sodium (m-mol/litre; mean±SD).

There are statistically significant differences between the two groups on 1st and 3rd day after operation. For details, see text.

<table>
<thead>
<tr>
<th></th>
<th>Uric acid (mg/100 ml)</th>
<th>Creatinine (mg/100 ml)</th>
<th>Urea (mg/100 ml)</th>
<th>Sodium (m-mole/litre)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Methoxyflurane</td>
<td>Controls</td>
<td>Methoxyflurane</td>
<td>Controls</td>
</tr>
<tr>
<td></td>
<td>3.8 ±0.9</td>
<td>3.8 ±0.8</td>
<td>0.84 ±0.1</td>
<td>0.85 ±0.1</td>
</tr>
<tr>
<td>1st post-operative day</td>
<td>4.0 ±1.2</td>
<td>3.4 ±1.0</td>
<td>0.83 ±0.03</td>
<td>0.80 ±0.12</td>
</tr>
<tr>
<td>3rd post-operative day</td>
<td>4.2 ±1.0</td>
<td>3.6 ±0.9</td>
<td>0.93 ±0.20</td>
<td>0.82 ±0.12</td>
</tr>
<tr>
<td>5th post-operative day</td>
<td>3.7 ±1.1</td>
<td>3.6 ±0.9</td>
<td>0.80 ±0.12</td>
<td>0.80 ±0.12</td>
</tr>
</tbody>
</table>

*Value before operation. Remaining values on respective days are (value before operation + mean of individual changes from that value).
RENAL AND HEPATIC EFFECTS OF METHOXYFLURANE

TABLE III. Concentrations and changes in concentrations (m-mol/litre; mean ± SD) for s.g.p.t., s.g.o.t., alkaline phosphatase and bilirubin. The two groups differ significantly only on the 1st day after operation. For details, see text

<table>
<thead>
<tr>
<th></th>
<th>Methoxy-</th>
<th>Controls</th>
<th>Methoxy-</th>
<th>Controls</th>
<th>Methoxy-</th>
<th>Controls</th>
<th>Methoxy-</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>flurane</td>
<td></td>
<td>flurane</td>
<td></td>
<td>flurane</td>
<td></td>
<td>flurane</td>
<td></td>
</tr>
<tr>
<td>S.g.p.t.</td>
<td>15.5 ± 7.3</td>
<td>14.7 ± 5.0</td>
<td>15.3 ± 5.2</td>
<td>13.2 ± 3.7</td>
<td>4.3 ± 1.6</td>
<td>3.9 ± 1.7</td>
<td>0.30 ± 0.20</td>
<td>0.32 ± 0.17</td>
</tr>
<tr>
<td>S.g.o.t.</td>
<td>32.7 ± 12.6</td>
<td>20.6 ± 12.8</td>
<td>25.8 ± 20.5</td>
<td>20.6 ± 13.2</td>
<td>3.6 ± 1.3</td>
<td>3.6 ± 1.4</td>
<td>0.60 ± 0.25</td>
<td>0.62 ± 0.26</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>22.7 ± 18.6</td>
<td>18.5 ± 8.6</td>
<td>19.3 ± 17.3</td>
<td>15.5 ± 6.0</td>
<td>4.1 ± 1.4</td>
<td>3.8 ± 1.6</td>
<td>0.50 ± 0.26</td>
<td>0.52 ± 0.22</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>26.5 ± 19.2</td>
<td>19.8 ± 15.7</td>
<td>20.6 ± 18.8</td>
<td>15.3 ± 8.9</td>
<td>4.3 ± 1.3</td>
<td>4.2 ± 1.6</td>
<td>0.40 ± 0.25</td>
<td>0.52 ± 0.22</td>
</tr>
</tbody>
</table>

*Value before operation. Remaining values on respective days are (value before operation + mean of individual changes from that value).

operation (table III). Higher values of s.g.p.t. in the methoxyflurane group were seen also on the 3rd and 5th day following surgery, but they did not differ significantly from those in the control series. In the other liver tests no significant differences were seen (table III).

Comparison of the simultaneous changes in s.g.p.t., s.g.o.t., alkaline phosphatase and bilirubin between the methoxyflurane group and the control series showed a significantly (P<0.05) greater change in the methoxyflurane group than in the control series on the 1st day after operation, mostly as a result of changes in s.g.p.t., but not on the 3rd and 5th day.

DISCUSSION

In this postoperative study there was no major difference in age distribution, type of surgery and duration of anaesthesia between patients belonging to the methoxyflurane group and the control series. All patients were assigned randomly to the different groups. The measurement of the vaporized amount of the methoxyflurane was reasonably accurate. No patient received more methoxyflurane than the dose advised by the manufacturer: 16 ml. Before surgery, no patient was treated with drugs known to be nephrotoxic or to induce enzymes to enhance the biodegradation of methoxyflurane. No factor that would systematically influence the results could be traced. Thus, the patient material and the procedures were well standardized, which should allow comparison of the results obtained in the different series.

The nephrotoxic syndrome as described by Mazze, Shue and Jackson (1971) is characterized by polyuria, lack of responsiveness to infusion of vasopressin, marked weight loss, serum hypernatraemia, serum hyperosmolality, increased blood urea nitrogen concentrations, increase in serum creatinine and serum uric acid concentrations and a decrease in uric acid clearance. In this study only the serum concentrations of sodium, creatinine, blood urea nitrogen and uric acid have been measured. Of these the uric acid and the creatinine concentrations were influenced by methoxyflurane anaesthesia, but not the serum concentrations of urea nitrogen and sodium. As no nephrotoxic or "inducer" drugs or recent anaesthesia had been given, these changes were likely to be a result of exposure to methoxyflurane.

These results are in agreement with those reported by Robertson and Hamilton (1973), who emphasize the apparent specific effect of the drug on the excretion of uric acid. Mazze, Shue and Jackson (1971) have shown that the occurrence of renal dysfunction is dose-related. Oxalic acid and inorganic fluoride appear to be the major metabolites of methoxyflurane. Inorganic fluoride exhibits a nephrotoxic effect at mean peak serum concentrations greater than 75 μmole/litre (Abbott Laboratories, 1972). Taves and colleagues (1970) have shown that the lowest delivered total dose of methoxyflurane, associated with a mean peak value of 75 μmole/litre, is 16 ml. If this is a threshold dose, it might be true concerning the clinically recognized high output renal failure. Our results seem to indicate, however, that renal impairment was still evident with doses less than 16 ml. An increasing dysfunction correlating with the vaporized amount of methoxyflurane/patient is thus to be expected.

Methoxyflurane anaesthesia was followed by a significantly more marked increase in s.g.p.t. than that seen after halothane or pethidine anaesthesia, indicating a liver impairment after methoxyflurane anaesthesia. The greater standard deviation seen in the methoxyflurane series was not correlated with age, dose or duration of exposure, and was probably a result of an individual sensitivity reaction to methoxyflurane and its metabolites. Case reports by Durkin, Brick and Schneider (1966), Klein and Jeffries (1966) Elkington, Goffinet and Conn (1968),
and Rosander (1970), and a prospective study in dogs by Cale, Packs and Jenkins (1962), indicate that after methoxyflurane anaesthesia signs of liver damage may occur, similar in histopathology to "halothane hepatitis". The s.g.p.t. and s.g.o.t. values reported in these papers were, however, increased markedly.

In another prospective well-controlled study in rats subjected to a short exposure to methoxyflurane, Efundi and colleagues (1971) have found, 1.5 hr after the exposure, statistically significant increases in lactate dehydrogenase, maltate dehydrogenase, creatinine phosphokinase and fructose-1,6 phosphate aldolase. On the 1st day after the exposure to methoxyflurane the authors found that s.g.p.t. was increased also. Furthermore, there was shown a fatty infiltration in the liver decreasing simultaneously with the enzymatic changes towards the 5th day. Efundi and colleagues stated that moderate metabolic changes occur as seen with certain histochemical analysis, reaching the maximum within a day after anaesthesia with methoxyflurane and disappearing after 2–5 day in the heart and liver, whereas in the kidneys these changes were observed for more than 5 day.

An impairment of liver function is most likely to be a result of the fact that methoxyflurane is metabolized to a large extent, the main metabolites being inorganic fluoride and oxalic acid (Van Dyke and Chenoweth, 1965; Holaday, Rudofsky and Treuhaft, 1970; Mazze and Cousins, 1974). This biodegradation might overload or inhibit the enzymes the latter as a result of the fluoride ion described by Wiseman (1970), Kosek, Mazze and Cousins (1972), Mazze, Cousins and Kosek (1972) and Mazze and Cousins (1973).

Although case reports mentioned previously showed a broad similarity to "halothane hepatitis", these reported cases might be the fulminant stage of a hepatic impairment, occurring in a very early form also after clinically uncomplicated anaesthetics. There seems to be a dose-related toxic response in the liver as well as in the kidneys.

CONCLUSION

The results of the present study indicate that a mild, transient impairment of kidney and liver function occurs even after light methoxyflurane anaesthesia, after doses less than 16 ml, which so far have been considered to be without any toxic effects.

ACKNOWLEDGEMENTS

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RENAL AND HEPATIC EFFECTS OF METHOXYFLURANE

VARIATIONS DANS LES FONCTIONS HEPATIQUES ET RENALES APRES ANESTHESIE A LA METHOXYFLURANE (PENTHRANE)

RESUME
On a compare trois groupes de patients auxquels on avait administré soit de la méthoxyflurane soit de l'halothanej soit de la pethidine après induction par le thiopentone succinylicholine. A l'aide du test $t$ de Student à variantes multiples avec des intervalles de confiance simultanés, on a trouvé des différences importantes dans la batterie de tests sur l'acide urique, la créatinine, l'azote de l'urée du sang et le sodium dans la série relative à la méthoxyflurane et ce par rapport aux autres séries, ce qui indique une altération transitoire de la fonction rénale. Il y a également eu des différences importantes entre la méthoxyflurane et les autres séries de batteries de tests sur la s.g.p.t. (transaminase glutamo-pyruvique sérique), la s.g.o.t. (transaminase glutamo-oxalique sérique), la phosphatase alcaline et la bilirubine, indiquant une altération de la fonction hépatique. On a découvert ce qui précède après administration de doses inférieures à 16 ml, qui avaient jusqu'à présent été considérées comme n'ayant aucun effet toxique.

CAMBIOS EN LA FUNCION DEL HIGADO Y DEL RINON DESPUES DE LA ANESTESIA DE METOXIFLURANO (PENTRANO)

SUMARIO
Se compararon tres grupos de pacientes que recibieron metoxifurano, halotano o petidina después de una inducción por succinilcolina de tiopentona. Mediante el uso de un test multivario $t$ de Student con intervalos de confianza simultánea, se encontró una diferencia significativa en la batería de prueba de acido úrico, creatinina, constituyente nitrogenado de urea en la sangre y sodio, en la serie de metoxifurano comparada con las otras series, lo que indicó una función defectuosa pasajera del riñón. Asimismo, hubo una diferencia significativa entre el metoxifurano y las otras series en el s.g.p.t., s.g.o.t., fosfatasa alcalina y la batería de prueba de bilirubina, que indicaba mal funcionamiento del higado. Esto se encontró después de dos dosis menores de 16 ml que, hasta ahora, se pensaba no tenían efectos tóxicos.