CHANGES IN SERUM URIC ACID CONCENTRATIONS AFTER CAESAREAN SECTION USING METHOXYFLURANE

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

SUMMARY
In a study comparing the changes in serum uric acid concentration after methoxyflurane anaesthesia in 10 patients subjected to either Caesarean section or minor general surgical procedures, a significantly greater increase in serum uric acid concentration occurred in those patients undergoing Caesarean section. These results were compared with results from a control group of five patients undergoing Caesarean section, anaesthetized without methoxyflurane and with a second control group of five patients having uncomplicated spontaneous deliveries. Reasons are presented to suggest that although obstetric patients are unlikely to be more vulnerable to methoxyflurane nephrotoxicity, those with pre-eclamptic toxaemia may be more at risk.

Methoxyflurane anaesthesia causes an increase in the serum uric acid concentration (Mazze, Shue and Jackson, 1971; Robertson and Hamilton, 1973), and the change is related to the dose of methoxyflurane (Hamilton and Robertson, 1974). Dose-related changes in urine osmolality and urine fluoride concentrations after methoxyflurane anaesthesia provide additional evidence of a causal relationship between renal tubular dysfunction and an increased production of fluoride from the metabolic breakdown of methoxyflurane (Robertson and Hamilton, 1974).

An increase in the serum uric acid concentration occurs during labour and in the post-partum period (Crawford, 1939), and in pre-eclampsia the concentration is much increased (Schaffer, Dill and Cadden, 1943; Chesley and Williams, 1945; Seitchik, 1953). The serum uric acid concentration in normal pregnancy is within the normal non-pregnant range but this is achieved by a high renal uric acid clearance (Boyle et al., 1966). As methoxyflurane is used in obstetric anaesthesia and analgesia, it seemed important to establish whether it influenced the serum uric acid concentration in obstetric patients and to compare any changes with those occurring in non-obstetric patients.

METHOD
Twenty patients were studied, all of whom had given permission for the investigation. The patients formed four groups: Group A: normal spontaneous delivery; Group B: Caesarean section with methoxyflurane anaesthesia; Group C: Caesarean section under anaesthesia without methoxyflurane; Group D: minor general surgical procedures with methoxyflurane anaesthesia. The mean age in the four groups was 20, 29, 27 and 59 years respectively. The mean parity in the obstetric Groups A, B and C was 0, 1.7 and 2.0 respectively. Patients with renal disease, diabetes mellitus, and pre-eclampsia were excluded. In addition, patients receiving corticosteroid, diuretic or tetracycline therapy were excluded.

The anaesthetic technique for patients in Groups B and D was standard and consisted of the induction of anaesthesia with thiopentone followed by the i.v. injection of suxamethonium. After endotracheal intubation, and throughout the procedure, ventilation was controlled using a Manley ventilator which delivered oxygen 40% in nitrous oxide at a minute volume of 10 litres. Neuromuscular block was maintained with alcuronium. Patients in these two groups were each given a total dose of methoxyflurane equivalent to 3 ml of liquid agent: Group B patients received 0.1% methoxyflurane for 60 min and Group D patients received 0.2% methoxyflurane for 30 min. 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. A specially calibrated vaporizer was used and the anaesthetic circuit was flushed with methoxyflurane 0.5% in oxygen 40% and nitrous oxide 60% for 20 min before use in
order to equilibrate the rubber components of the circuit with the anaesthetic gas mixture. The control Group A had no anaesthetic, receiving only pethidine for analgesia during labour. The control Group C received a standard anaesthetic in which the technique was similar to that administered to Groups B and D, apart from the substitution of pethidine and perphenazine i.v. for methoxyflurane; anaesthesia lasted 60 min. None of the patients studied required blood transfusion.

Venous blood samples were taken before the operation or the onset of labour and on each of the first 2 days following operation or delivery, for the determination of the serum uric acid concentration, which 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 all the samples to be analysed following one calibration of the AutoAnalyzer.

RESULTS

Table I shows the mean serum uric acid concentrations and the blood losses for the patients in each group of five patients; in all groups the serum uric acid concentration was increased on the 1st and 2nd days after operation or delivery. Blood loss was not measured in Group D patients, but as the group comprised four patients subjected to herniorrhaphy and one patient who underwent stripping of varicose veins, blood loss was assumed to be negligible. The inter-group comparisons (table II) show that the increase in serum uric acid concentration in patients undergoing Caesarean section using methoxyflurane was significantly greater than in the other groups on the 2nd day, and was significantly greater than that observed in patients undergoing Caesarean section without methoxyflurane on the 1st and 2nd days.

There was no significant difference between the increases in serum uric acid concentration in patients undergoing Caesarean section without methoxyflurane when compared with those patients having normal spontaneous deliveries.

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 the increased production of uric acid or to decreased renal clearance. In normal pregnant patients the serum uric acid concentrations lie within the normal range during late pregnancy (Boyle et al., 1966), but these authors have shown also that there is a much greater renal loss of uric acid. They concluded that the high renal uric acid clearance is necessary to clear the maternal blood of the increasing amounts of uric acid produced by the foetus. Crawford in 1939 studied the serum uric acid concentration during labour and in the post-partum period in 67 patients. He noted an increase in serum uric acid concentration during labour, in both normal patients and patients with pre-eclampsia, which was proportional to the length and severity of labour; it was postulated that the increased serum uric acid concentration was the result of starvation, oliguria and increased muscle exertion during labour.

After methoxyflurane anaesthesia, it is now well established that there is a relationship between renal tubular dysfunction and the production of fluoride from the metabolic breakdown of methoxyflurane, and that the changes are dose-dependent (Mazze, Shue and Jackson, 1971; Mazze, Cousins and Kosek, 1972; Mazze and Cousins, 1973;

<table>
<thead>
<tr>
<th>Group</th>
<th>Methoxyflurane dose (ml)</th>
<th>Blood loss (ml)</th>
<th>Mean serum uric acid concentration (mg/100 ml)</th>
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<tr>
<td></td>
<td></td>
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<td>Before operation or labour</td>
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<td>Mean</td>
</tr>
<tr>
<td>A. Normal spontaneous delivery</td>
<td>-</td>
<td>206</td>
<td>86</td>
</tr>
<tr>
<td>B. Caesarean section</td>
<td>3</td>
<td>440</td>
<td>114</td>
</tr>
<tr>
<td>C. Caesarean section</td>
<td>-</td>
<td>590</td>
<td>270</td>
</tr>
<tr>
<td>D. Minor general surgical procedures</td>
<td>3</td>
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Because of the increased production of uric acid in normal pregnancy and labour it is likely that any impairment of distal tubular function following exposure to methoxyflurane would result in higher serum uric acid concentrations in obstetric as opposed to general surgical patients. The results of the present study support this conclusion. Transient mild or moderate hyperuricaemia is unlikely to be harmful and normal obstetric patients exposed to methoxyflurane are probably no more vulnerable to nephrotoxicity than any other group of patients. There is no indication that parity affects the renal handling of uric acid, and the differences in blood loss within the obstetric groups is unlikely to alter uric acid clearance in the absence of arterial hypotension; in the most important comparison, between Groups B and C, the blood losses were remarkably similar.

The hyperuricaemia of pre-eclampsia has attracted considerable study. It has been established that the increased serum uric acid concentrations in pre-eclamptic patients are the result of diminished uric acid clearance rather than increased production of urate (Chesley and Williams, 1945). As the glomerular abnormality in pre-eclampsia is minimal (Pollack and Nettles, 1960) it is difficult to explain the reduced uric acid clearance on the basis of impaired glomerular filtration. There is, however, a considerable amount of evidence to support the hypothesis that renal cortical ischaemia, secondary to the reduced renal blood flow demonstrated in pre-eclampsia, is a more important factor (Seitchik, 1953; Altchek, 1964; Simanowitz, MacGregor and Hobbs, 1973). These authors conclude that the primary cause of hyperuricaemia is an increased reabsorption or decreased secretion of uric acid by the kidney tubules rather than decreased glomerular filtration. There have been no reports of renal dysfunction after methoxyflurane anaesthesia or analgesia in obstetric patients. Nevertheless in patients with pre-eclampsia, in whom impaired tubular function may be present already, it would seem desirable to exercise caution in the use of methoxyflurane which is known to have dose-related effects on distal tubular function.

ACKNOWLEDGEMENTS

We wish to thank Professor I. MacGillivray, Mr P. F. Jones, Mr J. Kyle and Mr I. F. K. Muir, Aberdeen Teaching Hospitals, for permission to study patients under their care. We thank also Professor S. C. Frazer, Department of Chemical Pathology, University of Aberdeen, for advice and assistance with the carrying out of biochemical estimations and Dr G. Hems, Department of Statistics, University of Aberdeen, for assistance with the statistical analysis.

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absorption of uric acid: normal pregnancy and abnor-

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<tr>
<th>TABLE II.</th>
<th>Inter-group comparisons of serum uric acid concentrations subjected to t-tests of the differences of group means.</th>
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<tbody>
<tr>
<td></td>
<td>Post-op Day 1/ Pre-op</td>
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<tr>
<td>A v. B</td>
<td>t</td>
</tr>
<tr>
<td></td>
<td>-1.9987</td>
</tr>
<tr>
<td>C v. B</td>
<td>t</td>
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<tr>
<td></td>
<td>-2.6874</td>
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<tr>
<td>D v. B</td>
<td>t</td>
</tr>
<tr>
<td></td>
<td>-1.6939</td>
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<tr>
<td>A v. C</td>
<td>t</td>
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<td>0.7276</td>
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n.s. = not significant.
CHANGEMENTS AFFECTANT LA CONCENTRATION D'ACIDE URIQUE DU SERUM APRES LA CESARIENNE AU METHOXYFLURANE

RESUME
Dans une étude portant sur la comparaison des changements affectant la concentration d'acide urique du sérum après l'anesthésie au méthoxyflurane chez 10 patientes subissant soit une césarienne, soit des interventions chirurgicales générales de caractère mineur, une augmentation nettement plus élevée de la concentration d'acide urique du sérum s'est produite chez les patientes subissant une césarienne. Ces résultats ont été comparés aux résultats obtenus avec un groupe de contrôle de cinq patientes subissant une césarienne et anesthésiées sans méthoxyflurane et à ceux d'un second groupe de contrôle de cinq patientes ayant un accouchement spontané sans complications. On présente certaines raisons suggérant que, bien qu'il soit peu probable que les patientes en obstétrique soient plus vulnérables à la néphrotoxicité du méthoxyflurane, celles atteintes de toxémie pré-éclamptique courent sans doute un risque plus marqué.

CAMBIOS DE CONCENTRACION DE ACIDO URICO DEL SUERO DESPUES DE SECION CESAREA AL ANESTESIA CON METOXIFLURANO

SUMARIO
En un estudio comparando los cambios de concentración de ácido úrico del suero después de anestesia con metoxiflurano en 10 pacientes sujetos bien a sección cesárea o procesos quirúrgicos menores de tipo general, tuvo lugar un aumento mucho mayor de la concentración de ácido úrico del suero en aquellos pacientes que soportaron la sección cesárea. Se compararon estos resultados con los resultados de un grupo testigo de 5 pacientes en los que se realizó la sección cesárea, anestesiados sin metoxiflurano y con un segundo grupo testigo de cinco pacientes que tenían partos espontáneos sin complicaciones. Se presentaron motivos para sugerir que a pesar de que no es posible que los pacientes obstétricos sean más vulnerables a la nefrotoxicidad del metoxiflurano, aquellos con toxemia pre-éclámptica puede que tengan un mayor peligro.