RENAL FUNCTION AND METHOXYFLURANE ANAESTHESIA

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Methoxyflurane is a drug that is being used with increasing frequency and reports in the literature have suggested that it is sometimes responsible for post-operative renal dysfunction.[1-6] Thus it seemed prudent to consider the available knowledge concerning effects of methoxyflurane on the kidney, in order to decide the manner of drug usage most likely to avoid any undesirable renal sequelae. The drug was considered with reference to its possible effect on renal enzyme systems, effects on renal function in the intact animal, and the published accounts of methoxyflurane induced renal damage.

Renal Adenosine Triphosphatase Systems

It seemed pertinent to add to the available knowledge of the effects of methoxyflurane on renal function by studying the effect of the drug on renal ATP'ase enzymes.

The studies involved the investigation *in vitro* of enzyme material derived from rabbit renal cortex. After homogenization, a fraction which sedimented at 33,000 G was treated with urea and deoxycholate, then re-suspended in a buffered incubation medium which contained 2.5 mM phosphate, 100 mM Na^+ and 20 mM K^+ at pH 7.15. Enzyme activity was measured by H^+ release which occurred when substrate ATP (10 mM disodium salt) was introduced into the assay system containing 0.03 mgm particulate protein/ml. When required 10^{-4} M ouabain was also present, in order to inhibit that portion of the total ATP'ase reaction which was sensitive to this agent, in a system containing Na:K in a ratio of 5:1. In these experiments between 60–70 per cent of the total ATP'ase activity could be suppressed by this concentration of ouabain. The residual ATP'ase activity was not sensitive to this cardiac glycoside and presumably represents the action of so-called "basic" ATP'ase thought not to be involved in active ion transport. Methoxyflurane solutions were prepared by saturating the buffer system with methoxyflurane. The concentrations were checked by gas chromatography. The saturated solution, which was approximately 10^{-2} M, was diluted as required. The results for 170 mM methoxyflurane were obtained by addition of microlitre amounts of methoxyflurane directly to the mixture. Experimental results are shown in Figure 1. It can be seen that at 10 mM concentration there was depression of enzyme activity. This concentration is within the range of blood levels that could occur during or following deep methoxyflurane anaesthesia, but the concentration likely to occur at the lipo-protein enzyme systems *in vivo* is not known. *In vitro* studies of the kind described are a necessary part of pharmacological investigation, but

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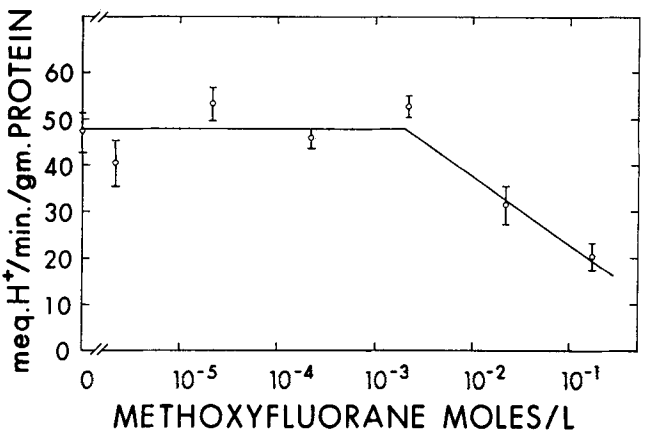

FIGURE 1

in some instances the effects of a direct interaction bear no relationship to events *in vivo*. However, experiments with rabbit kidney slices[7] indicate that the *in vitro* work described here may be closely related to the *in vivo* situation. It is not certain whether the rabbit enzymes isolated here also exist in the human, but the fact that hormone influenced Na^+—K^+ activated ATP'ases exist in other biologic systems make it not unreasonable to suppose that they also exist in the human kidney. Thus these enzyme studies suggest that a direct action on these enzyme systems in the kidney might be added to the multiplicity of factors involved in producing the *in vivo* effect of methoxyflurane on renal function.

RENAL FUNCTION STUDIES

An opportunity existed to perform renal clearances on a group of chronically stressed dogs that had each been subjected to laparotomy and resection of the distal 80 per cent of the small bowel some six to eight weeks prior to the present study. The animals had lost considerable weight and with one exception had moderate diarrhoea. At least some degree of hydration had been maintained by intravenous fluids during this six to eight weeks and serum electrolytes were within a normal range. PAH and inulin clearance measurements were performed on two groups, each of four dogs. Anaesthesia was induced with thiopentone 5.0 mgm/kgm, a cuffed endotracheal tube was introduced, and anaesthesia was maintained with nitrous oxide and oxygen 70:30. The animals were artificially ventilated using a non-rebreathing system and a Harvard variable phase ventilator to maintain the P_{CO_2} within a range of 35–45 mm Hg. D-tubocurarine was injected as required, dosage being approximately 0.5 mgm/kgm body weight. Systemic arterial pressure, monitored intra-arterially, remained between 120–180 mm Hg. Body temperature was monitored by oesophageal thermometer. Preliminary PAH and inulin clearances were measured in the usual manner. A two-hour period of anaesthesia was then commenced, during which the animals received lactated Ringer's solution 12.0 ml/kgm/hour, and D-tubocurarine approximately 0.5 mgm/kgm/hour. One group of dogs received a gaseous mixture

also containing 0.56 per cent methoxyflurane delivered from a calibrated vaporizer. At the termination of the two hour period PAH and inulin clearances were repeated. The plasma concentrations of methoxyflurane were measured with an F & M Model 402 gas chromatograph and averaged for the group receiving the drug. The animals were lightly anaesthetized. At the beginning of the final renal function tests the values were 2.13 ± 0.15 moles/L.

The results of the renal function tests appear in Table I. All clearance values obtained as units of ml/min were divided by the body weight of the dog to yield approximately normalized values expressable as ml/min/kgm. The columns headed Δ represent the difference in clearance between the second and first tests. These values varied considerably within each group of animals. The slight reduction of PAH and inulin clearance in the methoxyflurane group is consistent with the results of other workers, but it is noteworthy that in one dog clearance values may have improved. Inulin clearance values increased in excess of a 15 per cent error of measurement in three of the control animals and PAH clearance also improved. There was no statistical difference between the changes in PAH clearance of the two groups at the end of the two-hour period, but there was a difference between the changes in inulin clearance which occurred. Although a difference in cardiovascular haemodynamics could be suggested as an explanation for the difference between the two groups, perhaps of greater importance is the fact that four out of the eight dogs from the two groups apparently had an improved inulin and PAH clearance after the two-hour period of anaesthesia. This is attributed to the administration of fluids during this time.

TABLE I

Thiopentone $N_2O:O_2$	Inulin clearance ml/min/kg			PAH clearance ml/min/kg		
Dog	Test 1	Test 2	Δ	Test 1	Test 2	Δ
1	2.39	2.29	−0.10	5.51	5.76	+0.25
4	2.86	3.35	+0.49	5.53	6.79	+1.26
7	2.54	4.23	+1.69	7.45	8.04	+0.59
8	0.018	0.139	+0.12	0.017	0.49	+0.47
$\bar{x}$	1.95	2.50	0.550	4.63	5.27	0.642
SD	±1.30	±0.76	±0.798	±3.20	±3.32	±0.435
2	3.20	2.53	−0.67	7.64	5.23	−2.41
3	1.88	1.94	+0.06	3.63	3.89	+0.26
5	2.76	2.60	−0.16	8.14	6.84	−1.30
6	3.27	2.45	−0.82	5.88	4.89	−0.99
$\bar{x}$	2.78	2.38	−0.398	6.32	5.21	−1.11
SD	±0.639	±0.30	±0.416	±2.04	±1.22	±1.10

Discussion

Clinical and laboratory investigations of renal function during methoxyflurane anaesthesia have shown a reduction in glomerular filtration rate, renal blood flow, water and electrolyte excretion.[8–11] Clinical assessments of renal function in the postoperative period have also been reported.[12,13] The results obtained by Pad-

dock and his colleagues were considered by them to exonerate the drug as a cause of renal pathology in healthy patients, though the results of the study of patients with severe preoperative renal damage were inconclusive and the authors indicated the need for additional investigation. North and Stephen concluded from a random series of patients that methoxyflurane showed no evidence of renal toxicity greater than any other anaesthetic drug.

A lack of detrimental effect on healthy kidney is supported by the histological studies of a number of workers,[12,14–17] who failed to find significant pathological changes under normal circumstances. Histological changes, when reported,[14,18] were demonstrated in laboratory animals and occurred in association with blood gas and circulatory abnormalities.

The first clinical reports attributing a syndrome of postoperative increasing azotemia and high urinary output to methoxyflurane anaesthesia appeared in the period 1964–1966. Crandall[1] described 17 cases of high output renal failure. Paddock[12] and his colleagues reported three cases, and Pezzi[2] reported twenty cases with the proviso that a serious medical or surgical complication had to be present for so-called methoxyflurane toxicity to manifest itself. At that time Vandam,[19] in an editorial comment, drew attention to the problem of determining the true cause of postoperative renal complications. The fact was emphasized that if the clinical use of a drug was to be incriminated, more evidence than just guilt by association was necessary. The published reports did not present sufficient data to indicate a specific methoxyflurane nephrotoxicity. Since then additional case reports have appeared,[3–6] but these also fail to satisfy the criteria suggested by Vandam and others concerned with drug toxicity. In fact a striking thing about these frequently quoted case reports is the paucity of relevant data. Perhaps the time has come for published reports of impaired physiological function associated with drug administration to assume an established format with a title consistent with the evidence presented for a specific drug toxicity. However, though the methoxyflurane case reports fail to provide conclusive evidence that methoxyflurane is a specific nephrotoxic agent, they do provide information regarding the circumstances under which methoxyflurane has been associated with postoperative renal problems. The vast majority of patients were middle aged or elderly. The surgery performed was usually of a major nature, often prolonged, and considerable reliance seems to have been placed on methoxyflurane as a muscle relaxing drug. Details of intravenous fluid therapy during surgery were often not included.

An increasing azotemia and high urinary output have for many years been associated with other pathology such as soft tissue trauma, burns, and head injuries. The relationship between gall bladder surgery and renal dysfunction has recently been reviewed by Dawson.[20] Attention has also been drawn to the effects of inadequate metabolism of radio opaque substances,[21] while certain drugs such as tetracycline have been associated with renal damage. Thus the difficulty in establishing a specific methoxyflurane toxicity is great. The term toxicity can refer to unwanted reversible effects on function as well as irreversible effects. It appears from the laboratory evidence available that reversible effects of methoxyflurane on function might persist into the postoperative period if large doses of

the drug have been administered. It is not suggested that this has a causal influence on the syndrome of toxicity associated by some authors with methoxyflurane. However, in the absence of knowledge concerning the significance of methoxyflurane metabolites and the concentrating effect of the kidney on these it appears unreasonable to assume that other toxic effects of methoxyflurane, be they temporary derangement of function or permanent damage, are not dose related.

In conclusion, for the practical purpose of clinical anaesthesia, users of methoxyflurane should bear in mind the high fat solubility of the drug, the pharmacological effects persisting into the postoperative period, and the unknown effects of metabolites. It is suggested that only the very small quantities of methoxyflurane necessary to depress the motor and autonomic responses of the surgical patient be administered. If, in addition, muscle relaxation or abolition of upper respiratory tract reflexes is required then reliance should primarily be placed on the judicious use of neuromuscular blockers, analgesics,[22] or topically applied local anaesthetic drugs.

Summary

The intermittent appearance of clinical reports associating methoxyflurane with renal toxicity indicated the necessity of considering the manner of drug usage most likely to avoid such sequelae. Evidence is presented that methoxyflurane may have a depressant effect on adenosine triphosphatase systems in the kidney. Evidence is presented that very light methoxyflurane anaesthesia reduces inulin and PAH clearances in the intact dog. These and other reports indicate that undesirable effects on renal function may persist into the postoperative period if deep methoxyflurane is employed. The clinical reports of renal toxicity are briefly reviewed and it is noted that the surgery performed was usually of a major nature, often prolonged, and considerable reliance seems to have been placed on methoxyflurane as a muscle relaxing drug. It appears reasonable to assume that other toxic effects attributed to methoxyflurane may be dose related, particularly in the absence of knowledge concerning the significance of methoxyflurane metabolites. It is suggested that only minimal quantities of methoxyflurane be used to maintain anaesthesia and if in addition muscle relaxation or abolition of upper respiratory tract reflexes is required then reliance should be placed primarily on neuromuscular blockers and analgesics.

Résumé

L'apparition occasionnelle de rapports cliniques associant le méthoxyflurane à une toxicité rénale indique la nécessité d'étudier le mode d'emploi qui serait le plus susceptible d'éviter de telles séquelles. Certains prétendent que le méthoxyflurane exercerait un effet dépresseur sur les systèmes à adénosine triphosphatase du rein. On prétend également qu'une anesthésie très légère au méthoxyflurane diminue la clearance de l'inuline et PAH chez le chien. Ces rapports laissent entendre que, au cours de la période post-opératoire, ces effets indésirables sur la fonction rénale pourraient continuer à exister si l'on a administré une anesthésie profonde au méthoxyflurane. Nous faisons une brève revue des rapports

sur la toxicité rénale et nous observons que, bien souvent, la chirurgie était importante, prolongée et que l'on comptait beaucoup sur le méthoxyflurane comme myorésolutif. Il semble juste d'assumer que d'autres effets toxiques attribués au méthoxyflurane seraient proportionnels à la dose donnée, particulièrement si l'on ignore la signification des métabolites du méthoxyflurane. Nous suggérons d'utiliser seulement des quantités minimes de méthoxyflurane pour maintenir l'anesthésie et s'il faut, de plus, un relachement musculaire ou l'abolition des réflexes des voies respiratoires supérieures, il est à conseiller alors de compter surtout sur les myorésolutifs et les analgésiques.

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