Report on Methoxyflurane

The publication in this issue of the Journal of the report by W. B. Crandell et al. on Nephrotoxicity Associated with Methoxyflurane Anesthesia represents, for several reasons, somewhat of an editorial departure. We have printed an article that is bound to cause controversy—one which some of the reviewers believe does not prove beyond doubt all that the authors proclaim. Both the authors and the Editorial Board have availed themselves of the best consultative opinion on renal function. We agreed that it would be best to present the findings in Anesthesiology accompanied by an editorial that would also set forth the ideas of the dissenters. The facts are here in considerable detail for the reader’s consideration.

Essentially what is described is an unusual nephropathy occurring after the administration of methoxyflurane. The syndrome, if it can be so designated, is characterized by inappropriate diuresis in the postoperative period, with development of dehydration and a rise in serum osmolality. That this may be a tubular defect is implied by loss of concentrating and dilutional ability, and lack of responsiveness to exogenous antidiuretic hormone. A more generalized renal lesion is suggested by a rise in the BUN in many of the reported cases, although it is recognized that the filtrating function of the glomerulus and the osmotic regulatory activities of the distal portion of the nephron may modify each other. Biopsy and postmortem specimens of the kidney, few in number, fail to show a specific lesion, but morphological changes as detected by light microscopy need not be present in a disturbance of probable molecular nature. Although causative factors can be implicated in one case or another the only common denominator seems to be methoxyflurane.

The authors do us and our patients a service in bringing these cases to light and they point out, rightly, that this is a most unusual occurrence even if it were present in only a few instances. As a matter of fact a similar picture has hitherto not been described. There is a rare hereditary type of vasopressin resistant diabetes insipidus. Isothemeruria may also be present in the recovery phase of acute tubular necrosis, in azotemia, hypokalemia, hypercalcemia, sickle cell disease, water-losing nephritis and post-obstructive uropathy.

What is puzzling is the occurrence of so many cases in one institution and that, until recently, no other group had made similar observations. This alone should not cast doubt on the findings, for after the introduction of new drugs it is common for adverse reactions to pass unnoticed for considerable periods. Prior to its use in man methoxyflurane had not undergone the closest scrutiny so far as renal effects were concerned, but there were hints of renal involvement in some of the early clinical reports. Moreover, a recent letter to the Lancet 1 describes an identical syndrome in somewhat higher incidence originating from a hospital in Pennsylvania.

From the standpoint of experimental design, however, the results should be challenged. The patients to whom methoxyflurane was given were a highly selected group, chosen because halothane, in the light of then current opinion, was considered hazardous in the presence of certain pathophysiological conditions. Not all of the cases in Group I fit the pattern closely enough to satisfy all criteria, and the retrospective discovery of a second group of cases does not diminish the possibility of bias in selection of patients. Indeed, in Group II the evidence in at least half the cases is not nearly so convincing and many essential details of clinical management are perforce lacking; these were complicated surgical problems in exceedingly ill patients with a fairly high mortality. The vasopressin challenge test was applied to only eight cases as controls, all having received halothane. Some contend that the dosage of vasopressin is rather small; the vagaries of the test are well known and normal values admittedly not established. Lastly, the retrospective selection of a seemingly comparable group of cases all given halothane and the failure to discover
nephropathy does not eliminate the possibility that bias in selection could have led to a concealed common denominator in those given methoxyflurane.

More information is required before methoxyflurane can be indicted as a harmful drug. The National Halothane Study provides an apt analogy. Even if there are cases of nephropathy associated with methoxyflurane, the incidence and severity should be weighed against the reputed usefulness of the anesthetic and the overall morbidity and mortality as compared to other agents. If methoxyflurane is worth having and its usage is extensive, a carefully planned randomized prospective study should answer most of the questions posed here. Some of the questions raised concerning the overall safety of the anesthetics scrutinized in the National Halothane Study remain unanswered today despite a carefully conducted, large scale retrospective analysis.

The problems posed here are common to all adverse drug reactions. It is apparent that the most detailed laboratory studies should be conducted before a drug is introduced to clinical practice. Even so, findings in the laboratory animal may not presage the effects in man. Once a drug is suspect, carefully designed studies should be conducted as early as possible to refute or establish a cause and effect relation. Finally, there is a need for continual scrutiny of the newer drugs and the reporting of unusual responses to a central agency such as the A.M.A. Registry on Adverse Drug Reactions.

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REFERENCE


RENAL FUNCTION The influence of nitrous oxide-Halothane anesthesia of 30 to 45 minutes average duration on excretion of aldosterone, sodium, potassium and cortisol was investigated in 15 female patients with normal cardiovascular and renal status. There was a significant reduction in urinary excretion of sodium, on the day of anesthesia, which returned to normal on the following day. Since aldosterone levels were perfectly normal, this oliguria and sodium retention are believed to be due to a hemodynamic and intrarenal reaction. No significant influence on cortisol secretion was demonstrated. (Stark, G.: The Influence of Anesthesia on the Excretion of Aldosterone, Cortisone, Sodium and Potassium, Der Anaesthesist 15: 4 (Jan.) 1966.)

ETHYL ALCOHOL Forearm motor nerve conduction time was measured in awake normal human beings both before and after the injection of 135 to 195 ml. of whiskey. When temperature was not controlled, the ingestion of alcohol was followed by an increase in skin temperature of 4.6° C. This was accompanied by a decrease in the conducting time of 0.71 msee. If skin temperature was kept constant, no change in conduction time was observed. The effect of warming the extremity alone without ingesting alcohol was to reduce the conduction time 0.95 msee. It is concluded that ethyl alcohol (blood levels of 50–130 mg./100 ml.) has no significant effect on motor nerve conduction provided skin temperature does not change. (Peiris, O. A., and others: The Action of Ethyl Alcohol on the Peripheral Nerves, Amer. J. Med. Sci. 251: 207 (Feb.) 1966.)