BLOOD GLUCOSE LEVELS DURING METHOXYFLURANE ANAESTHESIA*

JOEL D GOTTlieb, M D , AND ROBERT B SWEET, M D

HYPERGLYCAEMIA has long been recognized as one of the chief responses to the metabolic stress of anaesthesia. Diethyl ether especially will produce increases in the blood sugar of up to 100 per cent during the first half-hour to 45 minutes of anaesthesia and for this reason its effect on carbohydrate metabolism has been studied extensively.¹ Experiments done on dogs in the 1920's seemed to indicate that this hyperglycaemia was related to, or caused by, a profound metabolic acidosis which appeared quite early during the administration of ether.^{2 3 4} This explanation was widely accepted as applying to man until Beecher and his co-workers demonstrated that there is no significant metabolic acidosis during the administration of ether to adults, although some degree of acidosis does occur in children.^{5 6} Prior to Beecher's reports, it had been shown in rabbits that both adrenalectomy and spinal anaesthesia producing a T₄ sensory level would protect against hyperglycaemia during ether anaesthesia.⁷ This observation has been confirmed repeatedly by the use of both local anaesthetics and adrenergic blocking agents.^{8 9} Today, therefore, it is generally concluded that the hyperglycaemia produced by ether anaesthesia is mostly the result of the liberation of catecholamines.¹⁰

Other general anaesthetics are also capable of producing a hyperglycaemic response. Cyclopropane anaesthesia in man elicits an increase in the blood sugar "comparable to that induced by ether" according to Greene.¹¹ Reports concerning the effect of halothane are somewhat divergent. Some studies have shown no effect on blood sugar during halothane anaesthesia, while other evaluations have shown that there is some hyperglycaemic response to halothane.¹² This, however, is not as great as that seen with ether and cyclopropane.^{13 14} It is of interest to note that the hyperglycaemia produced by these agents seems to parallel their effect on sympathetic activity, for it has been shown that both ether and cyclopropane produce a marked increase in the level of circulating catecholamines, while halothane does not.¹⁵

Methoxyflurane combines some of the structural and anaesthetic characteristics of both diethyl ether and halothane, since it is a halogenated methyl ethyl ether. Its effect on carbohydrate metabolism, however, has not yet been studied carefully. In one early report of a clinical trial of methoxyflurane in 206 patients the blood sugar was measured in 6. In 3 of these a moderate rise of about 35 mg % occurred.¹⁶ Another study with dogs indicated that blood sugar was unchanged during spontaneous respiration but decreased with assisted respiration.¹⁷

*From the Department of Anesthesiology, The University of Michigan Medical School, Veterans Administration Hospital, Ann Arbor, Michigan

The present study reports observations concerning the effect of methoxyflurane anaesthesia on blood glucose levels in man in order to determine the drug's effect upon carbohydrate metabolism and sympathetic activity

METHOD

Ten healthy males ranging in age from 28 to 50 years were anaesthetized with methoxyflurane in the following fashion. Three patients received pentobarbital 100 mg and scopolamine 0.4 mg intramuscularly 90 minutes prior to anaesthesia, and anaesthesia was then induced with intravenous thiopentone 280–360 mg. These patients were maintained on methoxyflurane, oxygen, and nitrous oxide. The other seven patients received only scopolamine 0.4 mg for premedication 90 minutes before the study was begun. These patients then received only methoxyflurane and oxygen for induction and maintenance throughout the course of the experiment. In all cases a semi-closed system was used and a total flow of 4 litres per minute was employed (2 litres of oxygen and 2 litres of nitrous oxide, or 4 litres of oxygen alone). Blood samples were drawn just prior to the induction of anaesthesia and at precise 30-minute intervals thereafter. As each blood sample was drawn, the amount of methoxyflurane which had been vaporized in the previous 30 minutes was measured. It has been shown previously that each cubic centimetre of methoxyflurane will produce 209 cc of vapour at room temperature¹⁶. Using this figure and the known flow of diluent gases the average concentration of methoxyflurane administered to the patient over the preceding 30 minutes was calculated. Once anaesthesia was begun all patients exhibited a remarkably stable course, maintaining both pulse and blood pressure well within normal limits. This clinical impression seems to be in accord with other large-scale observations on the effect of methoxyflurane on the circulatory system^{18, 19}. Although the patients were maintained in a light plane of anaesthesia and the concentration of methoxyflurane administered never exceeded 1.6 per cent, respirations were assisted vigorously throughout in order to prevent the development of any degree of respiratory acidosis. Surgical intervention did not begin in these patients until the experiments had been concluded so that in the seven patients who received only methoxyflurane and oxygen we were able to measure the effect of the anaesthetic agent alone.

RESULTS

We observed that after 30 minutes of anaesthesia the blood glucose level was approximately 85 mg % and it generally remained near this level throughout the remainder of the experiment (Fig 1). No difference could be detected between the patients who received pentobarbital and thiopentone prior to anaesthesia and those who did not. Variations in the concentrations of methoxyflurane administered were not great in any one patient and did not seem to have any effect on the blood glucose level (Table I).

FIGURE 1 Average values of blood glucose determinations in 10 patients receiving methoxyflurane anaesthesia. The bars indicate the range of values in each time interval

TABLE I

BLOOD GLUCOSE LEVELS IN 10 PATIENTS RECEIVING METHOXYFLURANE ANAESTHESIA

(The first three were premedicated with pentobarbital and received thiopentone for induction, the others received only scopolamine and methoxyflurane)

Patient	Control, blood sugar, mg %	30 minutes		60 minutes		90 minutes		120 minutes		150 minutes	
		Blood sugar, mg %	% MOF adm	Blood sugar, mg %	% MOF adm	Blood sugar, mg %	% MOF adm	Blood sugar, mg %	% MOF adm	Blood sugar, mg %	% MOF adm
1	68	86°	1 3	87	0 7	86	1 0	87	1 0		
2	87	85	0 8	84	0 8	85	0 7	90	0 8		
3	75	83	1 2	82	1 2	85	1 0	91	1 2		
4	71	81	1 6	82	1 0	81	1 2	87	1 2	83	1 2
5	90	83	1 6	78	1 2	79	1 0	83	1 0		
6	64	82	1 6	81	1 0	81	0 7	80	1 0		
7	88	93	1 5	89	1 0	93	1 0	91	0 7		
8	71	81	1 6	80	1 3	84	0 7	85	1 0	87	1 0
9	77	88	1 6	91	0 8	89	0 8	88	0 8	84	1 0
10	68	78	1 6	76	1 5	78	1 0	77	1 0		

DISCUSSION

The obvious conclusion from these results is that methoxyflurane anaesthesia does not produce any change in blood glucose levels. This negative observation has, however, some interesting and important positive corollaries. The first and most obvious of these is that methoxyflurane in clinically applicable concentrations produces no detectable alteration in carbohydrate metabolism in so far as such alterations would be reflected in the blood glucose level. While we have not measured other intermediary metabolites it has been found that changes in these metabolites most frequently parallel the changes seen in the blood sugar level, at least during ether anaesthesia.¹⁰ The second corollary to our observation is that methoxyflurane probably does not produce any significant increase in the circulating catecholamines, for as we have said, such an increase is usually reflected in an increased rate of glycogenolysis. Of course, a variety of other explanations have been offered for hyperglycaemia during general

anaesthesia other than an increase in sympathetic activity. Studies involving the administration of insulin during ether anaesthesia and *in vitro* observations on brain tissue seem to indicate that ether may block or uncouple oxidative phosphorylation processes.^{20 21} Had we observed an increase in blood sugar during methoxyflurane anaesthesia, we might find it difficult to choose between these explanations as a cause for it. In the absence of any such increase it seems safe to conclude that methoxyflurane does not alter sympathetic tone appreciably, does not produce an increase in glycogenolysis, and does not interfere with oxidative phosphorylation processes.

SUMMARY

Blood glucose levels were observed at 30-minute intervals in ten healthy male patients anaesthetized with methoxyflurane. It was found that the blood glucose level was approximately 85 mg % throughout these anaesthetics. It is concluded that methoxyflurane does not interfere with carbohydrate metabolism or alter sympathetic tone in the normal patient.

RÉSUMÉ

La plupart des anesthésiques généraux augmentent la glycémie. Ceci est vrai surtout de l'éther et du cyclopropane. Le fluothane, cependant, est moins susceptible de le faire. On a démontré que l'élévation du sucre dans le sang est causée par une augmentation du tonus sympathique. Chez 10 malades du sexe masculin qui avaient reçu du méthoxyflurane comme anesthésique, on a mesuré le taux du sucre dans le sang, sans observer d'élévation. Les concentrations de méthoxyflurane administré allaient de 0.5 à 1.6%. On peut conclure que le méthoxyflurane ne trouble pas le métabolisme des hydrates de carbone et qu'il n'est pas sympathicotonique.

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