ENERGY METABOLISM AND ELECTROLYTES DURING THIOPENTONE-MEPERIDINE ANAESTHESIA IN NORMAL MAN

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MOST OF THE STUDIES of the effects of the commonly used inhalational anaesthetic agents on energy metabolism have been made in patients undergoing surgery. Exceptions are those of Oyama and his group¹⁻³ and of Merin and Associates,⁴ who studied effects of anaesthetic agents before the operations began. We have had the opportunity, during pulmonary function studies,⁵⁻⁷ to investigate energy metabolism and electrolyte patterns in healthy volunteers receiving a combination of intravenous agents, uninfluenced by surgical operations. The purpose of this paper is to report our work.

SUBJECTS AND METHODS

Details of Anaesthesia. — The subjects studied were 28 healthy physicians and nurse anaesthetists. All gave written, informed consent. Details of sex, age, weight, and body surface area are shown in Table I.

Before induction of anaesthesia, scopolamine (0.43 mg) was given intravenously to each subject. Anaesthesia was induced with intravenous thiopentone sodium, and the trachea was intubated with a cuffed endotracheal tube (single or double lumen) after intravenous administration of succinylcholine. Maintenance of anaesthesia was by increments of thiopentone sodium (continuous infusion); supplementation was by intermittent doses of meperidine; and the spontaneous respiratory activity was abolished by succinylcholine (continuous infusion). Ventilation was controlled (Bird Respirator; FiO_2 , 0.21); arterial oxygen and carbon dioxide tensions (PaO_2 , PaCO_2) ranged from 80 to 100 mm Hg and from 38 to 46 mm Hg, respectively. An intravenous infusion of dextrose (5 per cent) in water was used as the vehicle for drugs in each subject. Arterial blood pressures and pulse rates were normal throughout.

The dosages of drugs and volumes of intravenous fluids administered (means and ranges) are shown in Table I. Table I also indicates that the subjects were divided into three groups (1, 2, and 3) related to the duration of general anaesthesia, which averaged 3, 2, and 1.5 hours for groups 1, 2, and 3, respectively.

For analysis of blood constituents, arterial blood was drawn into heparinized syringes prior to anaesthesia (groups 2 and 3) or early in the anaesthetic period

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TABLE 1
DETAILS OF SUBJECTS AND ANAESTHETIC MANAGEMENT*

	Groups		
	1	2	3
Subjects			
Sex distribution	4 F 6 M	1 F 9 M	1 F 7 M
Age, years	26 (22 to 31)	28 (23 to 33)	27 (21 to 30)
Weight, kg	68.2 (43.6 to 81.8)	77.3 (60.0 to 97.3)	78.2 (63.6 to 95.4)
Surface area, m ²	1.80 (1.38 to 1.99)	1.94 (1.66 to 2.15)	1.95 (1.75 to 2.15)
Dosages of drugs, mg			
Meperidine	130 (60 to 180)	100 (60 to 120)	90 (70 to 100)
Thiopentone sodium	1,600 (900 to 2,000)	1,550 (1,150 to 2,000)	950 (750 to 1,000)
Succinylcholine	1,100 (700 to 1,600)	1,050 (700 to 1,700)	700 (500 to 1,000)
Intravenous fluids, ml (D5W)	1,290 (850 to 1,725)	1,200 (900 to 1,500)	580 (500 to 750)
Anesthetic duration, min	188 (130 to 210)	115 (91 to 150)	93 (80 to 130)

*All values except for sex distribution, means and ranges.

(group 1), at mid-procedure (groups 1, 2, and 3), and after return of spontaneous respiration and extubation (groups 1, 2, and 3).

Laboratory Procedures. - Blood samples were iced and gas tensions and pH were determined within 10 minutes of collection by appropriate electrodes (Instrumentation Laboratories Inc.) maintained at 37° C. Body temperature changed not more than 1° C, hence correction for body temperature was not done.

Haemoglobin concentration and its oxygen saturation were determined by a CO-Oximeter (Instrumentation Laboratories Inc.) Oxygen content was estimated by multiplying haemoglobin concentration (gm/100 ml) by 1.38 and by the fractional oxygen saturation, without regard to oxygen dissolved in plasma. Bicarbonate concentration was read from the Severinghaus slide rule. Plasma sodium and potassium values were determined by flame photometry; magnesium and total calcium values by an atomic absorption spectrophotometer (Perkins-Elmer Inc., Model 303); ionized calcium level by an electrode method;⁸ and inorganic phosphate concentration was determined by an autoanalyzer (Technicon, Inc.). Total plasma protein concentration was determined by electrophoresis on cellulose acetate strips (Gelman Inc.). Concentrations of glucose, lactate, and pyruvate were measured by enzymatic methods⁹ while nonesterified fatty acids (NEFA) were measured by the method of Bierman *et al.*,¹⁰ and total ketone bodies by the method of Bloom.¹¹ Finally, four hormones were determined by radioimmunoassay: parathyroid hormone,¹² immunoreactive insulin,¹³ growth hormone,¹⁴ and luteinizing hormone.¹⁵

Statistical analysis of paired data was by the Student "t" test, comparing concentrations of variables at the middle and end of anaesthesia with the concentra-

FIGURE 1. Changes in mean concentrations of electrolyte: both magnesium and inorganic phosphate concentrations were decreased at mid-anaesthesia; phosphate concentration decreased also at end.

tion present at the beginning (control). Differences in mean levels with P values less than 0.05 were considered significant.

RESULTS

Values (mean $\pm$ SE) for blood gases, electrolytes, and energy substrates and hormones are shown in Tables II through IV and Figures 1 through 3.

Blood Gases. – Oxygen tension, content, and haemoglobin saturation remained normal throughout. In group 2 mean oxygen tension at the end of anaesthesia was lower than that of the control phase, while in group 3 mean oxygen tension was lower than control both at the middle and end of anaesthesia. Mean values for bicarbonate, arterial pH, and P_{CO_2} did not change except in group 3, in which mean P_{aCO_2} increased at the end of anaesthesia, accompanied by a decrease in pH to 7.34.

Electrolytes. – No changes were found in values of plasma sodium, potassium, total and ionized calcium, protein, or parathyroid hormone. The concentration of inorganic phosphate decreased during and at the end of anaesthesia, as did that of magnesium during anaesthesia.

Energy Substrates and Hormones. – Blood glucose concentrations increased in groups 2 and 3 at mid-anaesthesia, and in group 3 also at the end of anaesthesia.

TABLE II
BLOOD GAS VALUES (MEAN $\pm$ SE) AT THREE PHASES OF ANAESTHESIA

Variable	Phase of Anaesthesia					
	Pre-induction		Early		Mid	
	2	3	1	1	2	3
Group	83 $\pm$ 3	94 $\pm$ 3	84 $\pm$ 5	81 $\pm$ 3	92 $\pm$ 3	86 $\pm$ 2*
P _a O ₂ , mm Hg	93 $\pm$ 1	97 $\pm$ 1	95 $\pm$ 1	96 $\pm$ 1	97 $\pm$ 1	96 $\pm$ 1
S ₅₀ , %	18.1 $\pm$ 0.3	18.9 $\pm$ 0.7	16.5 $\pm$ 0.4	16.5 $\pm$ 0.5	17.8 $\pm$ 0.4	18.3 $\pm$ 0.5
Ca ₂₊ , mEq/100 ml	7.43 $\pm$ 0.01	7.43 $\pm$ 0.01	7.39 $\pm$ 0.01	7.40 $\pm$ 0.01	7.39 $\pm$ 0.02	7.41 $\pm$ 0.01
pH	7.42 $\pm$ 1	7.43 $\pm$ 1	7.42 $\pm$ 1	7.41 $\pm$ 1	7.41 $\pm$ 1	7.43 $\pm$ 1
P _a CO ₂ , mm Hg	42 $\pm$ 1	38 $\pm$ 1	42 $\pm$ 1	41 $\pm$ 1	45 $\pm$ 2	38 $\pm$ 1
[HCO ₃], mEq/L	26.8 $\pm$ 0.5	24.7 $\pm$ 1.0	24.8 $\pm$ 0.5	24.8 $\pm$ 0.6	26.2 $\pm$ 0.7	24.2 $\pm$ 0.6
						25.3 $\pm$ 0.6
						25.2 $\pm$ 0.8
						23.5 $\pm$ 0.7

*P < 0.05.

TABLE III
ELECTROLYTE VALUES (MEAN $\pm$ SE) AT THREE PHASES OF ANAESTHESIA

Variable	Phase of Anaesthesia					
	Pre-induction		Early†		Mid	
	3	1	1	1	3	3
Group	...	136 $\pm$ 1	136 $\pm$ 1	138 $\pm$ 1	...	...
Na, mEq/L	...	3.9 $\pm$ 0.1	3.9 $\pm$ 0.1	3.8 $\pm$ 0.03	...	...
K, mEq/L	3.61 $\pm$ 0.29	...	...	...	2.85 $\pm$ 0.24*	2.70 $\pm$ 0.20*
PO ₄ , mEq/100 ml	1.76 $\pm$ 0.03	...	...	...	1.67 $\pm$ 0.04*	1.75 $\pm$ 0.05
Mg, mEq/100 ml	9.3 $\pm$ 0.1	...	...	...	9.2 $\pm$ 0.1	9.2 $\pm$ 0.2
Ca, mEq/100 ml	3.91 $\pm$ 0.08	...	...	...	3.90 $\pm$ 0.09	3.97 $\pm$ 0.09
Total	20.0 $\pm$ 3.9	...	...	...	6.9 $\pm$ 0.19	7.0 $\pm$ 0.21
Ionized	...	...	...	...	22.0 $\pm$ 4.0	30.8 $\pm$ 5.5
Protein, total, gm/100 ml	...	...	...	...	...	...
PTHr, mEq/ml	...	...	...	...	...	...

*P < 0.05.

†Parathyroid hormone.

TABLE IV
ENERGY SUBSTRATE AND HORMONAL VALUES (Mean $\pm$ SE) AT THREE PHASES

Variable	Phase of Anaesthesia											
	Pre-induction			Early			Mid			End		
Group	2	3	3	1	1	1	2	2	3	1	2	3
Glucose, mg/100 ml	90 $\pm$ 10	95 $\pm$ 5	...	...	...	...	165 $\pm$ 11*	189 $\pm$ 8*	...	...	104 $\pm$ 13	135 $\pm$ 9*
Insulin, μ U/ml	13.9 $\pm$ 2.7	3.1 $\pm$ 0.9	...	...	...	...	25.3 $\pm$ 5.2	25.5 $\pm$ 6.5*	...	...	23.7 $\pm$ 4.7	40.2 $\pm$ 9.1*
Lactate, mmole/L	...	...	...	1.12 $\pm$ 0.12	1.15 $\pm$ 0.11	...	...	...	...	1.08 $\pm$ 0.08	...	...
Pyruvate, mmole/L	...	...	...	0.077 $\pm$ 0.077	0.078 $\pm$ 0.007	...	...	...	...	0.062 $\pm$ 0.003*	...	...
Ketone bodies, total, μ g/ml	...	...	...	7.15 $\pm$ 1.32	7.82 $\pm$ 1.00	...	...	...	...	8.20 $\pm$ 0.97	...	...
NEFA†, μ Eq/L	780 $\pm$ 60	...	...	610 $\pm$ 90	560 $\pm$ 30	...	800 $\pm$ 70	...	...	630 $\pm$ 60	...	...
Growth hormone, μ g/ml	7.0 $\pm$ 1.9	7.5 $\pm$ 3.3	...	...	...	...	5.6 $\pm$ 1.0	9.9 $\pm$ 1.9	...	...	8.5 $\pm$ 2.3	6.5 $\pm$ 2.6
Lactinizing hormone, μ g/100 ml	...	8.4 $\pm$ 2.0	...	...	...	...	...	9.9 $\pm$ 1.9	...	...	...	10.3 $\pm$ 2.1

* $P < 0.05$.

†Nonesterified fatty acids.

FIGURE 2. Changes in mean concentrations involved in calcium metabolism: no significant changes during 90 minutes of anaesthesia.

Plasma insulin concentrations increased in group 3 at the middle and end of anaesthesia. Pyruvate concentrations decreased at the end of anaesthesia. Plasma concentrations of lactate, NEFA, total ketone bodies, growth hormone, and luteinizing hormone did not change during anaesthesia.

DISCUSSION

The effects of general anaesthetic agents on energy metabolism have been investigated by a number of workers during the past decade. In 1963, Green¹⁶ reviewed effects of the common inhalational agents on energy metabolism during general anaesthesia. Following the development of more sophisticated methods for analysis of blood for substrates (as lactate, pyruvate, NEFA), hormones (as immunoreactive insulin, growth hormone, 17 hydroxycorticosteroids), and electrolytes (as total and ionized calcium), other reports on this subject have appeared. Using these newer methods, Oyama and his group¹⁻³ have systematically examined the effects of various agents during general anaesthesia. We have examined responses to severe stress during and after cardiac surgery,¹⁷⁻¹⁹ including the changes in fatal cardiogenic shock.²⁰ In contrast to the work on inhalational agents, the work we report in this paper concerns the effects of intravenous agents.

Energy production in fasting anaesthetized patients undergoing major surgery is subjected to influences that are different from those in the awake person with regular food intake. There are three main areas of difference: (1) the disease pro-

FIGURE 3. Changes in mean concentrations of energy substrates: increases in blood glucose noted in both groups during anaesthesia (due to dextrose infusion) and in one group also at end; plasma insulin was increased in one group during and at end of anaesthesia.

cess itself, which may alter metabolic patterns; (2) alteration of nutritional balance during the operative and postoperative period, when the patient receives insufficient carbohydrate, so that fat and protein are utilized for production of adenosine triphosphate;²¹ and (3) the major operation, which activates the body's response to stress, as exemplified by increases in 17-hydroxycorticosteroid,²² growth hormone,¹⁸ and the catecholamines,²³ that have potent effects on fat and carbohydrate metabolism. Increased concentrations of catecholamines also inhibit insulin release from the pancreas and stimulate fat mobilization.²⁴

All these interrelated factors make it difficult to elucidate metabolic effects of anaesthetic agents themselves by studying patients during operation. Even investigation of patients immediately prior to operation is complicated by the fear and worry that are inevitably present. Thus any discussion of the effects of anaesthesia on energy metabolism, electrolytes, and hormonal substances must take the complexity of these various factors into consideration.

Energy Metabolism.—In the present study, since glucose was infused as a vehicle for the anaesthetic agents we cannot comment on endogenous changes. In groups 2 and 3 (dextrose given, approximately 60 gm and 30 gm), arterial blood glucose increased significantly during the study. There appeared to be no obvious inhibition of insulin release (Fig. 3) since it increased in one group in response to the glucose load, as described previously by others.²⁵ The increase in group 2 did not achieve

statistical significance. The magnitude of increase in insulin concentration was approximately the same as that found by Merin *et al.*⁴ in intravenous glucose tolerance tests during halothane and methoxyflurane anaesthesia. The insulin response in his patients during anaesthesia with these volatile agents was less than in the same patients given glucose awake, late in the postoperative period. Such a smaller increase in blood insulin concentration after a glucose load is defined as glucose intolerance.

It appears, therefore, that at best some degree of glucose intolerance may have occurred during anaesthesia with nonvolatile agents in our patients. One cause of glucose intolerance would be depression of insulin release by increased catecholamine activity.²³ We did not determine catecholamines but we did measure growth hormone, which behaves in a manner similar to the catecholamines in response to stress. We found no increase in concentrations of growth hormone; this suggests that catecholamine concentrations also did not rise. Hence, if glucose intolerance did occur, either there was some other mechanism or there was no glucose intolerance.

In contrast to our previous findings in patients having abdominal²¹ or cardiac operations,¹⁷⁻²⁰ the concentrations of neither fatty acids nor ketone bodies increased in this study. We believe that the degree of stress in the subjects of this study was small, as indicated by the failure of growth hormone concentration to increase; therefore lipid mobilization was not stimulated.

Thiopentone and nitrous oxide appear to be good anaesthetic agents for diabetic patients owing to their minimal effect on glucose and energy metabolism. Studying the effects of thiopentone-nitrous oxide anaesthesia, Oyama *et al.*³ found no change in the plasma concentration of plasma growth hormone or insulin before the start of the operation. However, they also found that growth hormone did increase during anaesthesia but before operation with methoxyflurane¹ and ether.² In their study, ether anaesthesia produced a significant increase in blood glucose concentration. Halothane and methoxyflurane are also associated with increased concentrations of glucose and fatty acid, findings that suggest sympathetic stimulation.⁴

The lack of change in luteinizing hormone in our relatively short study is consistent with other studies. Charters and co-workers²⁶ found no changes in patients anaesthetized with nitrous oxide and either meperidine or halothane for orthopaedic or general surgical operations that lasted 3 hours; and Ryan and associates²⁷ found no change in luteinizing hormone during an awake control period of 6 hours, though they did observe increases after convulsive electroshock treatment of patients managed with general anaesthesia and muscle paralysis.

Mineral Metabolism. — General anaesthesia up to 3 hours' duration caused no changes in plasma concentrations of sodium, potassium, or calcium. This is to be expected since we had previously found that these electrolytes did not change during anaesthesia and general surgery.²¹ Plasma magnesium concentration decreased significantly (from 1.76 to 1.67 mg/100 ml) at mid-anaesthesia while inorganic phosphate decreased significantly (from 3.6 to 2.8 mg/100 ml) throughout anaesthesia.

The recently developed technique of estimating calcium activity by an ion-

specific electrode permits quantitation of ionized calcium in serum in a relatively direct, practical manner. Moore⁸ found that the mean values for calcium fractions in normal plasma were as follows: nondiffusible (protein-bound), 39.5 per cent; complexed (diffusible, but not ionized), 13.6 per cent; and ionized, 46.9 per cent. Results in our laboratory have been similar to these values. The proportion of total plasma calcium bound to protein is a direct function of the protein concentration and appears to follow the law of mass action. Ionized calcium concentration in heparinized plasma is generally lower than in untreated serum owing to the formation of a calcium-heparin complex. Parathyroid hormone is probably the major hormone which controls plasma concentration of calcium (negative feedback),^{12,28} though calcitonin may play a small role.²⁸ In the present study, during general anaesthesia with thiopentone-meperidine of 1½ hours' duration, there were no significant alterations in total and ionized calcium, total protein, and immunoreactive parathyroid hormone. It would appear that the mean change in pH from 7.43 to 7.34 was insufficient to affect these parameters.

SUMMARY

Energy metabolism and electrolyte values were studied in 28 volunteers during general anaesthesia without operation for periods up to 3 hours. Anaesthesia was induced and maintained with a combination of thiopentone sodium, meperidine, and succinylcholine given by intravenous injection. Ventilation was controlled and normal arterial oxygen and carbon dioxide tensions were maintained. Plasma sodium and potassium concentrations did not change but those of magnesium and inorganic phosphate decreased during anaesthesia. Plasma concentrations of total and ionized calcium, parathyroid hormone, and total protein concentration were unchanged. Blood glucose and plasma insulin concentrations increased from exogenous dextrose but those of fatty acids, ketone bodies, luteinizing hormone, and growth hormone showed no change. General anaesthesia with these nonvolatile agents produced no evidence of a stress response as reflected in energy metabolism.

RÉSUMÉ

Nous avons étudié le métabolisme énergétique et les valeurs électrolytiques chez 28 volontaires soumis à une anesthésie générale sans opération durant des périodes allant jusqu'à 3 heures. L'induction et le maintien de l'anesthésie ont été fait par l'injection endoveineuse de thiopentone sodique, de mépéridine et de succinylcholine. La ventilation a été contrôlée et les tensions artérielles d'oxygène et de CO₂ ont été maintenues près de la normale. Les taux plasmatiques de potassium et de sodium n'ont pas changé mais ceux du magnésium et des phosphates inorganiques ont diminué durant l'anesthésie. Les taux de calcium total et ionisé, l'hormone parathyroïdienne et le taux des protéines totales plasmatiques n'ont pas changé. La glycémie et l'insuline plasmatique ont augmenté à cause de l'apport extérieur de dextrose, mais les acides gras, les corps cétoniques, les hormones de croissance et du corps jaune n'ont pas changé. L'anesthésie générale avec ces agents non volatils

n'a pas laissé voir de réponse à l'agression comme l'aurait révélé le métabolisme énergétique.

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