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EFFECT OF THIOPENTONE ON BLOOD SUGAR AND GLUCOSE TOLERANCE

BY

JOHN W. DUNDEE

From the Department of Anaesthesia, University of Liverpool

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Attention has recently been drawn by Hunter and Greenberg (1954) and Merivale and Hunter (1954) to the abnormal blood sugar response to glucose that occurs in patients who are receiving large doses of sedative and hypnotic drugs, particularly barbiturates. All types of glucose tolerance curves have been reported, and, as yet, no really satisfactory explanation for the abnormalities has been found.

Similar disturbances in glucose metabolism have been reported by Booker and his associates (1946, 1949) in dogs following thiopentone administration. In animals on normal diets liver glycogen was found to be progressively depleted during long anaesthesia, and the administration of glucose before the induction of anaesthesia produced hyperglycaemia and glycosuria. Even animals whose livers were depleted of carbohydrate by starvation, before the administration of thiopentone, were unable to convert glucose to glycogen, and remained hyperglycaemic. Intermediate metabolism of carbohydrates was also depressed by prolonged thiopentone anaesthesia, as shown by a rise in the blood lactic acid content. All these changes could be mitigated by the use of small doses of insulin, if given along with or immediately following the administration of the thiopentone. Other workers (Blackberg and Hrubetz, 1937; Hrubetz and Blackberg, 1938; Richards and Appel, 1941) have also reported finding a mild hyperglycaemia during thiopentone anaesthesia in animals.

No significant changes in blood sugar were noted during thiopentone anaesthesia in man by Carraway (1939) or by Sessoms, Watts, Chase, and Andrews (1955). Other workers (Cameron, 1937; Thomas, 1938; Marshall, 1939; Ruth, Tovell, Milligan, and Charleroy, 1939) found a transitory slight hyperglycaemia returning to normal within a few hours of return of consciousness. Sessoms *et al.* (1939) found that patients receiving thiopentone–nitrous oxide–oxygen behave in a similar manner to those receiving thiopentone alone. It has also been noted by Bass, Watts, and Chase (1953) that ether hyperglycaemia is inhibited by induction of anaesthesia with thiopentone.

Stern, Papper, Bueding, and Rovenstine (1945) have studied glucose tolerance in three subjects who were anaesthetized for 45 to 60 min. with thiopentone. They found that the intravenous administration of 1.5 g. of 50% glucose produced a greater rise in blood sugar than when the same amount was administered in the conscious state. Their findings suggest a similarity in behaviour of glucose tolerance in man and dogs during thiopentone anaesthesia. However, these observations are open to criticism in that all three subjects were admitted to hospital with acute alcoholism, since hyperglycaemic responses are also found in chronic alcoholics (Bowman, Wortis, Orenstein, and Goldfarb, 1939).

This paper describes observations made in man on blood sugar changes during thiopentone anaesthesia with and without operations. Changes in the glucose tolerance curve produced by thiopentone have also been studied in healthy subjects. A preliminary mention of some of this work has appeared elsewhere (Dundee, 1956).

METHODS

This study was carried out on eight healthy adult volunteer subjects (6 males, 2 females), aged 23–51 years. These were admitted to hospital for ligation of varicose veins. Observations were made as follows:

(a) Blood sugar determinations at 30 min. intervals, during prolonged administration of thiopentone.

(b) Blood sugar determinations at 10–20 min. intervals, during operation for ligation of veins. Anaesthesia was with thiopentone–nitrous oxide–oxygen, and morphine 10 mg. with atropine 0.6 mg. was given as pre-operative medication.

(c) Glucose-tolerance test, no anaesthesia; 50 g. glucose in 150 ml. water was given by mouth and blood samples drawn at approximately 30, 50, 70, 100, and 130 min. thereafter (six subjects).

(d) Glucose-tolerance test under thiopentone anaesthesia. Glucose given as above and anaesthesia induced 10 min. later and continued for a period of 100–270 min. This was done on the same six subjects as in (c).

All patients had fasted for 3–4 hr. before each procedure save (b), when the time from the last meal varied from 4 to 11 hr. The blood sample for the control blood sugar reading was withdrawn immediately before the administration of the thiopentone in (a) and (b) and before the glucose in (c) and (d). The order in which the above investigations were carried out varied in each case, but the interval between each administration of thiopentone was always longer than one week. The normal response to glucose (c) was estimated at different times, depending on circumstances—on two occasions on the day before operation; in three subjects during the second week after operation and once about six weeks after the patient had left hospital.

All anaesthetics were given personally and all administrations were smooth throughout with no marked respiratory depression or hypotension. As far as possible the same dose of thiopentone was given on each occasion, but in no instance was the amount of drug given more than appeared necessary to maintain the desired degree of narcosis. The doses of thiopentone which, following pre-operative medication and combined with 6 l. nitrous oxide and 2 l. oxygen/min., produced satisfactory operating conditions, if given alone were sufficient to produce light narcosis with the occasional return of the corneal reflex. There were no untoward sequelae following any of the anaesthetics and convalescence after operation was uneventful, in all cases.

Blood sugar estimations were carried out by the method described by Folin and Wu (1930), using venous blood from the forearm. For repeated withdrawals of blood and injections of thiopentone the Mitchell self-sealing needle (Mitchell, 1952) proved very useful.

RESULTS

Table I gives the average blood sugar readings and doses of thiopentone given in investigation (a) when no operation was carried out or other drugs given. At no time was the increase in blood sugar level significantly different from the control reading.

The average effects on blood sugar of thiopentone–nitrous oxide–oxygen after pre-operative morphine and atropine in subjects undergoing non-abdominal surgery are shown in Table II. These show a significant increase in glucose content of the blood samples drawn between 5 and 50 min.

TABLE I

AVERAGE BLOOD SUGAR READINGS IN 8 VOLUNTEERS WHO RECEIVED THIOPENTONE IN DOSES STATED BELOW BUT WHO WERE NOT SUBJECTED TO ANY OPERATION

Time in Minutes	No. of Observations	Average Dose of Thiopentone		Average Blood Sugar (mg./100 ml.)	Average Deviation from Control
		mg.	mg./kg.		
Control	8			84	
20–40	8	769 (450–1,750)	10·7	85	+0·8±4·0
50–70	8	850 (700–1,750)	16·1	84	0
80–100	6	1,228 (825–2,000)	19·5	83	+1·7±1·8
110–130	6	1,560 (900–2,800)	23·8	80	−1·7±1·4
140–160	5	1,700 (1,000–2,800)	26·7	82	0
200–220	4	2,212 (1,200–3,400)	30·1	80	−2·5±1·6
230–250	4	2,306 (1,325–3,400)	35·2	81	−1·2±1·2
260+	3	1,967 (1,400–2,900)	30·4	80	0

TABLE II

AVERAGE BLOOD-SUGAR READINGS AND DOSES OF THIOPENTONE IN 8 PATIENTS WHO WERE OPERATED ON FOR VARICOSE VEINS UNDER THIOPENTONE-NITROUS OXIDE-OXYGEN ANAESTHESIA

Time in Minutes	No. of Observations	Average Dose of Thiopentone		Average Blood Sugar (mg./100 ml.)	Average Deviation from Control
		mg.	mg./kg.		
Control	8			77	
5–15	8	950 (500–1,400)	13·6	92	+25·3±4·0
20–35	8	1,170 (850–1,700)	16·4	85	+8·3±3·6
50–70	7	1,143 (1,000–1,700)	16·2	88	+10·6±4·7
80–100 (awake)	8	1,350 (1,000–1,700)	19·5	75	−1·8±0·8

after induction of anaesthesia. The rise in blood sugar is not very great and its magnitude is decreased if one allows for a possible error of ±5 mg./100 ml. in the technique of estimation. However, despite this, the rise in blood sugar immediately after the induction of anaesthesia was significantly greater ($P<0.01$) than occurred in the same subjects after thiopentone alone.

Fig. 1 shows the average results in the six patients in whom all four investigations were carried out. The blood sugar readings with and without operation are essentially the same as in Tables I and II and require no further comment. This figure shows that thiopentone produces a marked effect on the blood sugar response to the oral administration of 50 g. glucose. The hyperglycaemic response produced by thiopentone was consistent in all cases, and an analysis of the average increases in blood sugar (Table III) shows the effect of thiopentone to be statistically significant. Urine samples collected in three subjects reduced Benedict's solution after the administration of thiopentone, whereas this only occurred in one of the three subjects when they did not receive any anaesthetic.

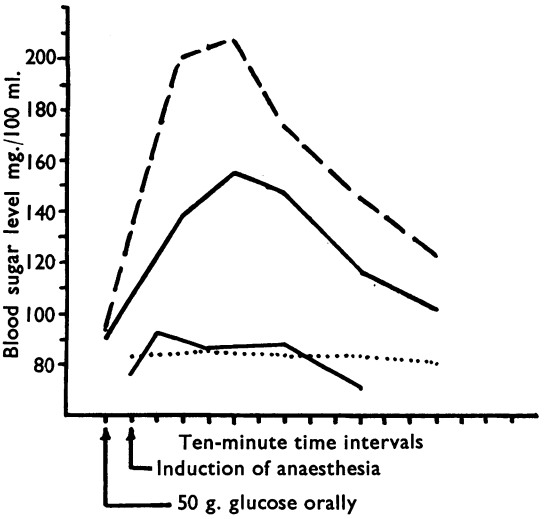

FIG. 1.—Average blood sugar readings on six subjects. ——— (upper curve) glucose tolerance test, no anaesthesia; – – – glucose tolerance test, thiopentone anaesthesia; ..... thiopentone anaesthesia alone; ——— (lower curve) thiopentone–nitrous oxide–oxygen anaesthesia: atropine and morphine as pre-operative medication. Operation for varicose veins.

TABLE III

AVERAGE INCREASE IN BLOOD SUGAR AFTER 50 G. GLUCOSE BY MOUTH IN 6 SUBJECTS WITH AND WITHOUT THIOPENTONE ANAESTHESIA

Time after Administration of Glucose (Minutes)	Average Deviation of Blood Sugar Level (1 mg./100 ml.) from Control Value			
	No Anaesthesia (A)	Thiopentone (B)	Difference (A–B)	"t" Value
30	+48± 7·5 (18–100)	+110±10·8 (80–140)	62±13·4	4·7
50	+65± 9·7 (30–100)	+125± 9·2 (90–140)	60±15·0	4·0
70	+57±10·6 (40–80)	+78± 9·3 (40–110)	21±14·5	1·5
100	+27± 5·3 (10–50)	+52± 4·1 (35–80)	25± 6·8	3·7
130	+7± 1·9 (0–20)	+35±7·6 (0–60)	28± 8·0	3·5

DISCUSSION

The number of subjects used in this study is small; but, as they were willing to submit to repeated administrations of thiopentone, it is hoped that the results will be more valuable than would have been obtained from single observations on a larger number of subjects. One cannot be certain from the few results in Table I that thiopentone alone has no effect on blood sugar, but a comparison of Tables I and II shows that the combination of thiopentone with either morphine, atropine, nitrous oxide or operative stress produces a temporary mild hyperglycaemia.

The work of Sessoms *et al.* (1955) shows that, in the absence of hypoxia, nitrous oxide was not the cause of the hyperglycaemia. Factors other than the anaesthetic agents can cause a rise in blood sugar and these have recently been exhaustively reviewed by Foster and Francis (1955). Morphine, despite its depressant effect on the central nervous system, may raise blood sugar and can act as a "stressor" (Selye, 1950). Atropine has been shown by several workers to block insulin secretion produced by vagal stimulation (Portis, 1950; Portis and Zitman, 1943). However, Bass *et al.* (1953) and Goodman and Gilman (1955) consider the effects of therapeutic doses of morphine and atropine to be negligible. The alarm reaction, described by Selye (1950) as part of the body's response to stress, following the initial trauma of surgery may have caused a transient rise in blood sugar, produced by liberation of adrenaline. If marked apprehension had been present before induction of anaesthesia the control blood sugar reading in Table II should have been raised, whereas it was lower than before any of the other investigations.

A more likely explanation for the rise in blood sugar during operation is the combined respiratory depressant effects of thiopentone and morphine, which Eckenhoff and his colleagues (Eckenhoff *et al.*, 1954, 1955; Helrich *et al.*, 1956) have shown to be much more marked than that produced by thiopentone alone. Hypercarbia and hypoxia can both raise the blood sugar level; in fact, these are the reasons given by Goodman and Gilman (1955) for the hyperglycaemia that follows large doses of morphine.

Save for the report of Sessoms *et al.* (1955) sufficient data on dosage of thiopentone and nature of operations, etc., are not given to allow the results of this investigation to be compared with those of other workers. Sessoms found an insignificant drop in the blood sugar levels of patients undergoing dilatation of the cervix and curettage of the uterus under thiopentone alone or under thiopentone–nitrous oxide–oxygen anaesthesia. The operations are comparable in that neither involves the peritoneal cavity or autonomic nervous system. Although the doses of drugs used as pre-operative medication are not given in Sessoms' paper, they are unlikely to have differed greatly from those given before operation in this study. However, the average doses of thiopentone given by Sessoms and his colleagues were 675 (575–800) mg. when the drug was given alone and 463.8 (300–750) mg. when it was combined with nitrous oxide–oxygen.

The latter figure is approximately half that used for the first 5 to 15 min. in the operated patients in this study (Table II), and the consequently greater degree of respiratory depression is the most probable explanation for the different results obtained.

The altered glucose tolerance in patients receiving thiopentone (Fig. 1 ; Table III) is in full agreement with the findings of Booker (1946) in dogs and Stern *et al.* (1945) in man. It has been shown (Booker, 1946 ; Booker, French, and Molano, 1949) that intermediate metabolism of carbohydrates is also interfered with by thiopentone, and these workers consider the depression of the glycogenolytic-glycogenic activity of the liver by thiopentone to be indirect evidence of the role of this organ in its metabolism. The hepatic detoxication of thiopentone is now proved beyond all reasonable doubt (Shideman, Kelly, and Adams, 1947 ; Shideman, Kelly, Lee, Lovell, and Adams, 1949 ; Walker and Wynn Parry, 1949 ; Dundee, 1952 ; Meyers and Peoples, 1954), and it seems more likely that this is a manifestation of the hepatic toxicity of large doses of thiopentone, since the author (1955) has shown that similar doses interfere with other functions of the liver.

Summary

1. Thiopentone anaesthesia alone produces no appreciable effect on the blood-sugar levels in man.

2. Slight hyperglycaemia was observed when thiopentone–nitrous oxide–oxygen anaesthesia, following morphine and atropine as pre-operative medication, was used as anaesthesia for operations on varicose veins.

3. The rise in blood sugar during operation differed significantly from that produced by the anaesthetic alone, and may be secondary to respiratory depression from the morphine–thiopentone combination.

4. Thiopentone markedly depresses the ability of the body to deal with an extra load of glucose.

5. The depression in glucose tolerance is thought to be a manifestation of the hepatotoxic effect of large doses of thiopentone.

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