ETHER HYPERGLYCEMIA AS INFLUENCED BY PREMEDICATION AND PENTOTHAL INDUCTION * † ‡

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FEW studies have been made during clinical anesthesia concerning the possible methods by which the undesirable hyperglycemia produced by ether in man could be inhibited. That ether produces hyperglycemia in man is an accepted fact (1, 2, 3). Recent evidence seems to indicate that ether hyperglycemia is a result of stimulation of supraspinal autonomic centers and subsequent stimulation of the adrenal glands by way of the sympathetic nervous system, with outpouring of epinephrine and mobilization of liver glycogen (4, 5, 6, 7). After bilateral extirpation of the adrenal glands in animals, ether hyperglycemia does not occur. Ether hyperglycemia can also be inhibited in animals by high spinal anesthesia (above T4) which produces a block of the thoracolumbar sympathetic system (4). The stimulation of the sympathetic system which leads to ether hyperglycemia is an undesirable factor in clinical anesthesia that contributes to the blood pressure rise during induction of anesthesia, possibly to cardiac irritability and arrhythmias (3), and indirectly, by depletion of liver glycogen (8), to the metabolic acidosis produced during ether anesthesia.

One of us (D.T.W.) has demonstrated that in rabbits ether hyperglycemia is inhibited by pentobarbital premedication, the degree of inhibition increasing as the dose of pentobarbital is increased. He has also shown that morphine not only has no significant effect on ether hyperglycemia (9) but gives rise to hyperglycemia in animals by its own action, an effect also inhibited by previous medication with pentobarbital (10). The series of studies presented in this paper were done in an attempt to determine whether the above findings in animals could be applied in clinical anesthesia.

Does barbiturate premedication, in usual clinical doses, cause any significant inhibition of ether hyperglycemia and will barbiturate premedication plus a pentothal induction of ether anesthesia lead to a more

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significant decrease in ether hyperglycemia? Does morphine, in the usual clinical doses, give rise to significant hyperglycemia in man and, if so, is this inhibited by previously administered barbiturates?

METHOD

The patients used in this study ranged in age from 15 to 79 years, with an average age of 49 years. They were carefully chosen in an attempt to include only the patients on the daily operating schedule who varied least from the normal physiologically, nutritionally and organically. Twenty-seven of the 32 patients studied had no disease except that for which the surgical procedure was being performed. Several had moderate hypertension, without signs or symptoms of decompensation. No patients with diabetes, hepatic disease or deranged fluid or acid-base balance were included. If anemia had been present it had been corrected preoperatively by transfusions. Most of the patients were those scheduled first in the morning so that the timing of the premedications would be as accurate as possible. All patients had been in the fasting state for at least eight hours.

Blood glucose concentrations were followed during three types of preoperative and anesthetic management: (1) patients premedicated with morphine which was followed by nitrous oxide induction of ether anesthesia (10 cases); (2) patients premedicated with both a barbiturate and morphine which was followed by nitrous oxide induction of ether anesthesia (10 cases), and (3) patients premedicated with both a barbiturate and morphine which was followed by pentothal-nitrous oxide induction of ether anesthesia (12 cases). The barbiturate premedication was given by mouth at least two hours before induction of anesthesia (average 145 minutes). Seconal and pentobarbital were used in doses of 100 mg., with the exception of 3 patients who received 50 mg. Morphine was given subcutaneously at least one hour before induction of anesthesia (average 72 minutes), 22 patients received 11 mg. and 5 patients each received 16 and 8 mg. respectively. All patients were given atropine with the morphine in a ratio of 1:25. Blood specimens for sugar analysis were drawn immediately before the barbiturate premedication (control specimen), before morphine administration, immediately before induction of anesthesia and after surgical anesthesia was established. Before the final sample of blood was drawn (postinduction sample) anesthesia was carried to a depth sufficient to permit endotracheal intubation without adjuvant medication with curare, a depth considered to be lower plane II or upper plane III (all of the cases were carried to the same depth but 9 patients did not require intubation). In order to avoid complicating bouts of anoxia (1, 4), which were assiduously guarded against throughout induction, intubation was delayed until the final blood sample had been obtained. The average induction time was twenty-two minutes. In

Series III the average dose of pentothal used for induction was 240 mg. (9.8 cc. of 2.5 per cent solution). Narcosis with pentothal was carried to a point at which the eyelid reflex was obtunded before administration of nitrous oxide-ether was started. Nitrous oxide was never used in concentrations greater than 80 per cent. Blood dextrose was determined by the colorimetric method of Nelson (11) and color determinations were made on a Beckman model DU spectrophotometer. Standard errors and tests for significance were calculated by Fisher's "t" test for small samples in which P values of less than 0.05 are considered significant (12).

RESULTS

In table 1 are tabulated the blood dextrose levels resulting from three anesthetic regimens: Series I, premedication with morphine followed by nitrous oxide-ether anesthesia; Series II, premedication with

TABLE 1

BLOOD SUGAR ALTERATIONS WITH PREMEDICATION AND ETHER ANESTHESIA

	No. of Cases	Control	Blood Dextrose (mg. %-mean ±S.E.)					
			71 Min. After Barbiturate	72 Min. After Morphine	After 22 Min. Ether Anesthesia	Change from Control	P*	P**
Series I	10	76 ±4	——	77 ±4	106 ±8	30 ±8	<0.01	——
Series II	10	82 ±4	79 ±4	85 ±4	109 ±8	28 ±6	<0.01	>0.7
Series III	12	77 ±4	76 ±4	77 ±4	89 ±4	12 ±4	<0.02	<0.05
						Series II Compared to Series III		<0.02

* The P values in this column indicate the degree of significance between the blood dextrose rise for the indicated series and the control level of the same series.

** The P values in this column indicate the degree of significance between the change in blood dextrose for the indicated series when compared to the change in Series I (M. S.-nitrous oxide-ether).

All P values were determined by Fisher's "t" test for small samples. P values of < .05 are considered significant.

barbiturate and morphine followed by nitrous oxide-ether anesthesia; and Series III, premedication with barbiturate and morphine followed by pentothal-nitrous oxide-ether anesthesia. Blood dextrose levels following morphine only, or barbiturate plus morphine, as premedication showed no significant changes. In the patients who received only morphine premedication (Series I) the mean increase in blood dextrose after ether anesthesia was 30 mg. per 100 cc. In the patients who received both barbiturate and morphine premedication the mean increase in blood dextrose after ether anesthesia was 28 mg. per 100 cc. In Series I and II this is a significant rise from the control level as shown by P values of less than 0.01. The addition of bar-

biturate premedication before ether anesthesia did not significantly inhibit the blood dextrose rise as shown by a P value of greater than 0.7 when comparing the rise in Series I and II. In patients who received both barbiturate and morphine premedication followed by a pentothal-nitrous oxide induction of ether anesthesia (Series III) the mean increase in blood dextrose was 12 mg. per 100 cc. This is still a significant rise as shown by a P value of less than 0.02, but not as significant as the rise in Series I and II. Pentothal induction before ether anesthesia causes a significant reduction of the blood dextrose rise from ether as shown by a P value of less than 0.05 and 0.02 when Series III is compared to Series I or to Series II, respectively.

COMMENT

It is evident that we have failed to confirm for clinical doses in man what had previously been shown in animals when large doses were used: namely, that hyperglycemia follows administration of morphine and that barbiturate premedication prevents the hyperglycemia produced by either morphine or ether (9, 10). In this series of studies the possible protection against ether hyperglycemia afforded by barbiturate premedication may have been masked by a tendency to hyperglycemic action by morphine. Pentothal induction of ether anesthesia would seem to offer some degree of protection against the upsets in body physiology which result from ether hyperglycemia and the flooding of the blood stream with increased amounts of epinephrine. It has been postulated that ether hyperglycemia in the dog is directly related to a quantitative output of epinephrine (13); the level of blood dextrose rise may be an indirect method of crudely estimating epinephrine output during ether narcosis. In a series of studies now under way it will be interesting to determine whether barbiturate premedication, in varying doses, without morphine, will significantly inhibit ether hyperglycemia as it does in animals.

SUMMARY

This series of studies has shown that the usual clinical doses of morphine alone and of barbiturates plus morphine used as anesthetic premedication have in themselves no significant effect on blood dextrose levels in man. The addition of barbiturate premedication before nitrous oxide-ether anesthesia does not significantly inhibit the blood dextrose rise when compared with premedication with morphine only. Pentothal induction of ether anesthesia produces a statistically significant inhibition of ether hyperglycemia.

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