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Anesthesia induced by barbituric acid derivatives with special reference to associated blood sugar changes.

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During an attempt to study the regulatory influence of the central nervous system on the carbohydrate metabolism, it was noted that cats under the effect of iso-amyl-ethyl barbituric acid (amytal) developed hyperglycemia.

It is recognized that narcosis, however induced, is associated with changes in the blood sugar. Whether this change is due to specific drug effect, or whether it is a part of physiological changes associated with narcosis is an open question. Page's[1] observation that anesthesia induced by iso-amyl-ethyl barbituric acid (amytal) is not associated with blood sugar changes in rabbits and dogs is, therefore, of interest, though Bang[2] found that diethylbarbituric acid (veronal) raises the blood sugar of the rabbit, and Ellis and Barlow[3] state that the blood sugar of pigeons and cats is lowered several hours after the intraperitoneal injection of the sodium salt of diethylbarbituric acid (medinal).

In numerous investigations during the past years, various derivatives of barbituric acid, especially iso-amyl-ethyl barbituric acid (amytal) have been used for anesthesia, and from the blood sugar changes far reaching conclusions have been drawn as to changes in carbohydrate metabolism.

The investigation to be reported consists of fifty-three experiments on thirty-two cats and on five dogs. The freshly prepared sodium salts of diethybarbituric acid (in doses of 120, 150, 180, and 300 mg. per kilogram of body weight), of iso-amyl-ethyl barbituric acid (doses 38, 50, 60, 65, 80 mg. per kg. b. w.), and of iso-allyl-propyl barbituric acid (50, 60, 80 mg. per kg. b. w.) were injected intraperitoneally and intravenously. Blood sugar

[1] Page, I. H., *Lab. and Clin. Med.*, 1923, ix, 194.

[2] Bang, I., *Biochem. Ztschr.*, 1913, lviii, 236.

[3] Ellis, N. N., and Barlow, O. W., *J. Pharmacol. and Exp. Therap.*, 1924, xxiv, 259.

determinations were made according to Benedict's[4] "1925" method. After the blood sugar of the fasting animals was determined, repeated blood samples were taken up to six to twenty-four hours respectively following the administration of the hypnotics. The hemoglobin content was determined according to Cohen and Smith.[5] Blood was obtained from the jugular or femoral veins. The veins were exposed through a small nick, made with a sharp knife under phenol oil, local anesthesia. The animals were handled gently, and that no excitement was produced, is shown by the fact that the average blood sugar of the cats after having been prepared for experiment was 95 mg., that of the dogs 96 mg.

It may be stated, without going into the details of the experiment, that the administration of the three derivatives of the barbituric acid tested was associated with changes in the blood sugar. The change was more marked in the cat. All the blood sugar curves, following the administration of the hypnotics, show a sudden rise, reaching a maximal height within one or two hours after the injection. The increase may be 100 to 250 per cent of the normal value in cats and 80 to 150 per cent in dogs. The sudden initial rise of the curve is followed by a gradual fall, lasting as long as six to twenty hours, in the majority of the experiments. In the small number of the experiments there was a plateau, or a further very slow rise over four to six hours after the initial peak. In two dogs after an initial rise, the blood sugar fell below the normal value.

It is well known that the sympathetic nervous system of the cat is sensitive and active. In order to rule out the possiblity that excitement due to handling of the animal might have precipitated a late rise in the blood sugar, four cats were injected intraperitoneally with iso-amyl-ethyl barbituric acid, while in their cages and then left there until they were under the effect of the drug (thirty to seventy minutes). The blood sugar changes in these animals corresponded to the figures obtained on other animals, in which precaution was not taken.

Three cats were tied on the board without anesthesia and after the normal specimens were obtained, they were kept there for ten to thirty minutes in order to produce marked excitement. They

[4] Benedict, S. R., *J. Biol. Chem.*, 1925, lxiv, 207.

[5] Cohen, B., and Smith, A. H., *J. Biol. Chem.*, 1919, xxxix, 489.

were then returned to the semi-dark cage room. One and one-half hours later, the blood sugars were found normal. These experiments indicate that if excitement produces rise in the blood sugar, the latter falls abruptly to the normal value soon after the animals are in a quiet state. The result indicated that the duration of the changes in the blood sugar due to stimulation of the sympathetic nervous system through excitement depends on the duration of the stimulus and that, therefore, late changes in the blood sugar can not be attributed to an early short excitement.

It was thought that the initial rise in the blood sugar might be due to the stage of excitement of the lower sympathetic brain centers during the early stage of anesthesia. In order to shorten this period as far as possible, the hypnotics were injected intravenously. The blood sugar curves of these animals did not, however, differ from those obtained after intraperitoneal administration.

To compare the effect of sympathetic stimulation due to excitement of the blood sugar with that after the administration of the hypnotic, the blood sugar curves of four cats, kept on the board without anesthesia on the first day of the experiment, were compared with that determined on the second day after the intraperitoneal administration of iso-amyl-ethyl barbituric acid. Experiments of the reversed order were performed on three cats. The maximal rise of the blood sugar was always reached sooner in the experiments with hypnotics. The intensity of the rise was more marked on the first day of the experiment, suggesting that the animals cannot respond on the second day with such marked hyperglycemia, because their glycogen stores are partly exhausted.

The investigation suggests that the blood sugar changes, under experimental conditions described are due, at least partly, to the action of the barbituric acid derivatives. The pharmacodynamic action of this group of drugs on centers in, and perhaps around, the thalamus would suggest that the disturbance of these centers may be responsible for blood sugar changes. One observes, not infrequently, that pathological changes of these centers in man are associated with temporary disturbance of the carbohydrate metabolism.

One cannot say whether these changes are due to stimulation or depression of the centers. It is of interest that ergotoxin phosphate, when injected intravenously into cats, produces sym-

pathetic depression within 2 to 6 minutes, nevertheless, the animals showed blood sugar changes similar to that observed after the administration of the barbituric acid derivatives.

Changes in the hemoglobin content of the blood were not sufficiently uniform to justify conclusions as to changes in the blood concentration during the period of anesthesia.

Animals injected with the same dose of the identical solution of the hypnotics showed marked variation in the depth, in the uniformity of the narcosis, and in the severity of the disturbance in the heat regulation.

From these, and previously performed, and hitherto unpublished experiments on cats and dogs, there seems to be no justification for concluding that certain derivatives of barbituric acid are superior to others, as to safety and uniformity of sleep. This conception is substantiated by the numerous contradictions in the literature on the subject. The stage of excitement was perhaps longer and more marked in dogs after diethyl barbituric acid, than after the other derivatives tested.

When dilute solutions of the hypnotics were injected from a burette intravenously for a period of three hours, as large amounts as 166 mg. of amytal and 360 mg. of veronal per kilogram of body weight of cat were not fatal. Even by rapid intravenous administration the toxicity of the three derivatives is not more, but perhaps less, than after intraperitoneal or subcutaneous administration. Animals occasionally ceased to breathe rather abruptly during the stage of excitement. These findings illustrate the difficulties to be encountered in the determinations of the toxicities of the barbituric acid derivatives by intravenous administration.

After this investigation was completed, Hines, Boyd, and Leese,[6] in studying the response of dogs to intravenous glucose administration, report that certain phases of the carbohydrate metabolism are disturbed under the iso-amyl-ethyl barbituric acid anesthesia.

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[6] Hines, H. M., and Boyd, J. D., and Leese, C. E., PROC. SOC. EXP. BIOL. AND MED., 1925, xxiii, 228.