THE ROLE OF ADRENALIN IN THE CHANGE OF BLOOD-SUGAR CONTENT PRODUCED BY ADMINISTRATION OF PHENAMINE

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Phenamine, a preparation synthesized in the USSR, is widely used in medical practice as a nervous system stimulant. It is analogous to benzedrine in its physiologic action.

Investigations [2, 3, 4, 9] have shown that phenamine given in optimal doses (0.01-0.03 g) increases excitability and, apparently, favors concentration of the inhibitory process in the central nervous system.

There are indications [1] that phenamine exerts a tonic effect both on the sympathetic and parasympathetic nervous systems.

Relatively few communications are devoted to the influence of phenamine on blood-sugar content. Those which do deal with this aspect of the preparation give conflicting results. Thus, for example, M. Ya. Sereisky [6] found no appreciable differences when he estimated blood-sugar levels in subjects before administration of phenamine and for some hours (at half-hour intervals) after administration of 0.02 g phenamine. V. V. Vasilyeva [2] noted sometimes increase and sometimes decrease in blood sugar following administration of phenamine. A. M. Timofeeva [8], N.Yu. Belenkov and E. N. Speranskaya [1] found the blood sugar to be increased by administration of the substance. I. S. Kanfor [5] studied the effect of phenamine on diurnal changes in blood-sugar levels in monkeys and also found some increase in the blood-sugar content. N. P. Smirnov [7] investigated the effect of phenamine on blood-sugar levels in dogs with alloxan-induced diabetes, and observed, in the majority of cases, some increase in blood-sugar content 1-2 hours after administration of the preparation.

In view of these conflicting findings, it was decided to undertake another investigation of the influence of phenamine on blood-sugar content. Investigations were carried out on healthy human subjects and on dogs.

METHODS

Fasting blood sugar (8-10 samples every 5 minutes) was estimated in the morning. In the case of human subjects, the blood was taken from the finger; in the case of dogs – from the femoral artery. The sugar was determined by the Hagedorn-Jensen method. It was found that the blood-sugar level was subject to considerable, but not strictly rhythmic, fluctuations. However, the arithmetic mean values for blood-sugar content calculated separately for the first 4-5 samples and for the subsequent 4-5 samples taken in one experiment proved to be very stable (the difference between the mean values did not, as a rule, exceed ± 5 mg %).

Experiments with administration of phenamine were carried out as follows. In the morning, fasting specimens (5-7) of blood were taken every 5 minutes for 30-35 minutes. After this, phenamine was given by mouth. Human subjects received 0.01 or 0.02 g; dogs weighing 18-22 kg received 0.01 g of the preparation. 30-45 minutes after administration of phenamine, blood samples were again taken at short intervals of time.

TABLE 1

The Effect of Phenamine on Blood-Sugar Levels in Healthy Human Subjects and Dogs

Dose of phenamine in g	No. of samples		Arithmetic mean values (mg %)			Maximal amplitudes of fluctuations (mg %)		
	Before administration phenamine	After administration phenamine	Before administration phenamine	After administration phenamine	Difference	Before administration phenamine	After administration phenamine	Difference
Observations on human subjects								
0.01	6	10	90	88	−2	10	9	−1
0.02	6	10	89	90	+1	9	20	+11
0.02	6	14	91	94	+3	6	11	+5
0.02	6	14	90	87	−3	10	20	+10
0.01	6	13	88	80	−8	11	24	+13
0.02	6	13	90	83	−7	5	12	+7
0.02	6	12	96	82	−14	8	16	+8
0.01	6	12	75	71	−4	5	7	+2
0.02	6	13	71	72	+1	9	9	0
0.01	6	15	79	83	+7	13	26	+13
Observations on dogs								
0.01	6	8	80	69	−11	14	6	−8
0.01	5	10	79	78	−1	11	27	+16
0.01	5	6	78	86	+8	12	27	+15
0.01	5	5	69	76	+7	12	30	+18
0.01	5	9	80	79	−1	14	27	+13
0.01	6	10	88	83	−5	13	13	0
0.01	6	6	80	64	−16	12	23	+11
0.01	5	9	85	76	−9	31	39	+8
0.01	6	10	93	113	+15	16	30	+14
0.01	7	7	88	79	−9	21	30	+9
0.01	5	7	90	106	+16	15	42	+27
0.01	6	10	71	79	+8	14	23	+9
0.01	5	7	69	69	0	19	11	−8

In each experiment, the results of blood analysis on samples collected before and after administration of phenamine formed the basis on which separate calculations were made of the arithmetic mean and the maximal differences which were designated conventionally as "maximal amplitude of fluctuation" (Table 1).

RESULTS

Analysis of data obtained revealed the following. The average blood-sugar content was not subject to appreciable changes under the action of phenamine. For example, of 10 investigations carried out on human subjects, any noticeable changes in the average blood-sugar content (exceeding 5 mg%) were obtained in only 4 cases; in three of these the blood sugar content decreased somewhat (by 7-14 mg%); and in one case it increased by 7 mg% following administration of phenamine.

Analogous results were also obtained in experiments on dogs. Of 13 experiments, four showed no noticeable changes in the average blood-sugar content. In 5 experiments, there was some rise in blood-sugar level (by 7-15 mg%), and in 4 experiments a fall of 7-16 mg% following administration of the preparation was observed.

In all cases the changes were within the limits of normal blood-sugar content.

The data presented also show that administration of phenamine, without appreciably altering the blood sugar content (mean values), leads to some increase in the fluctuations of its content compared with fluctuations

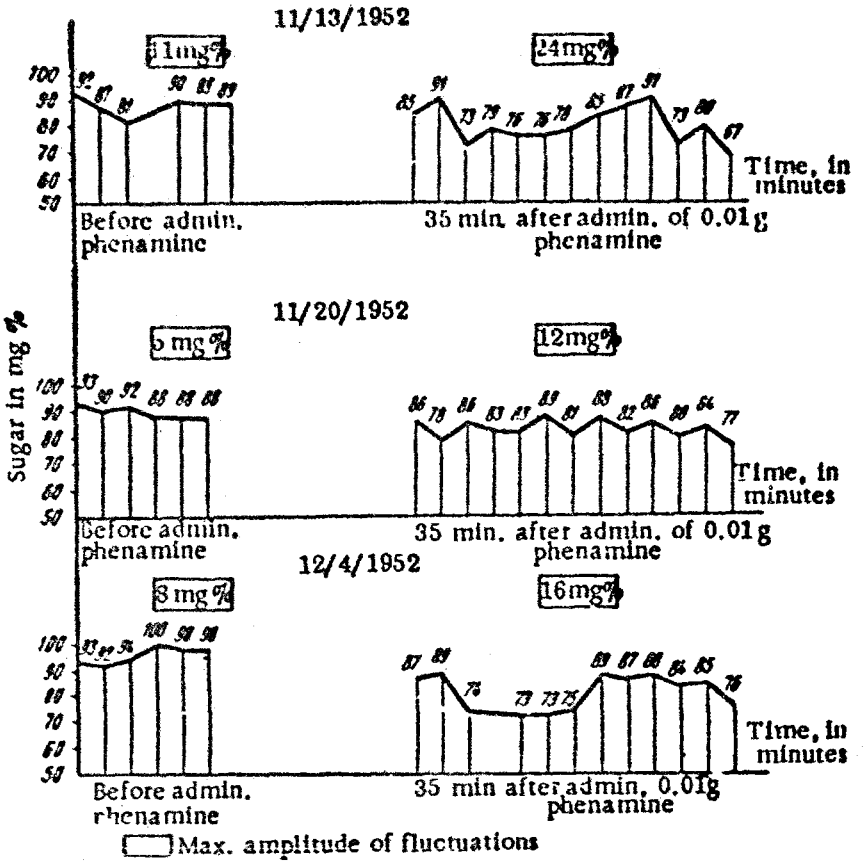

Fig. 1. Effect of phenamine on fluctuations in blood sugar over short intervals of time in subject Y.

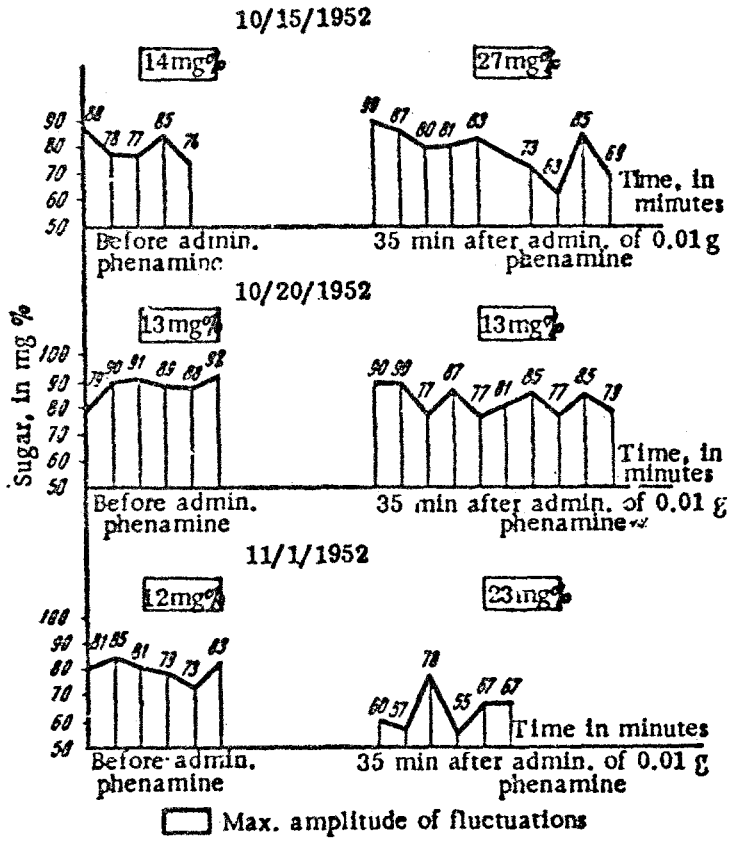

Fig. 2. The effect of phenamine on fluctuations of blood-sugar content over short intervals of time in a dog.

in the same individual on the same day before administration of phenamine. Of 10 human experiments, marked increase of "maximal amplitude of fluctuations" – by 7-10 mg% – was noted in six.

Experiments on dogs gave still clearer results.

An increase in the "maximal amplitude of fluctuations" was obtained in 10 of 13 cases and reached 13, 14, 16, 18 and even 27 mg%. In one experiment, noticeable changes were absent, while in two the extent of fluctuations was somewhat decreased (by 7 and 8 mg%).

Thus, in 16 of 23 experiments, the extent of fluctuations of blood-sugar content was increased after administration of phenamine; some decrease was noted in only 2 cases; and no appreciable changes were observed in 5 cases.

TABLE 2

The Effect of 0.01 g Phenamine on Blood-Sugar Levels in Dogs Following Denervation of the Liver and Adrenals

Experimental conditions	No. of experiment	No. of samples		Arithmetic mean values in mg%			Maximal amplitudes of fluctuations in mg%		
		before admin. of phenamine	after admin. of phenamine	before admin. of phenamine	after admin. of phenamine	Difference	before admin. of phenamine	after admin. of phenamine	Difference
Denervation of liver	1	6	11	93	102	+ 9	24	33	+ 9
	2	8	9	79	93	+14	20	32	+12
Denervation of liver, removal of one and denervation of other adrenals	1	9	10	71	73	+ 2	28	23	− 5
	2	9	10	77	76	− 1	11	13	+ 2
	3	7	9	83	85	+ 2	17	17	0
	4	8	8	83	73	−10	17	22	+ 5
Removal of one and denervation of other adrenals	1	7	10	77	74	− 3	16	19	+ 3
	2	8	10	73	71	− 2	13	14	+ 1
	3	8	10	76	73	− 3	13	18	+ 5
	4	7	6	72	72	0	20	28	+ 8

A study of the graphs draws attention to the marked shortening of time between successive rises in blood-sugar level evoked by phenamine in a number of cases; in other words, the rhythm of fluctuations is markedly accelerated (Figs. 1 and 2).

These changes in blood-sugar level fluctuations evidently result from reflex effect on organs directly involved in the maintenance of blood sugar at a definite level.

In this connection, attention should be directed first of all towards the liver and particularly the adrenals, since it is well known that there is direct connection between excitation of the CNS and reflex adrenalinemia. With this in mind, we carried out two preliminary experiments on animals with partially denervated livers.

The operation consisted of removal of all tissues, including the nerves, constituting the hepato-gastric-duodenal ligament. Only the blood vessels and bile duct were left intact. The animals were allowed to recover from the surgical procedure, after which an experiment with administration of phenamine was performed on each animal. This led to increased fluctuation of the blood-sugar content in both animals ("maximal amplitudes of fluctuations" increased by 9 and 12 mg%). There was also some increase in the average blood-sugar content (Table 2).

Interruption of the main nerves leading to the liver thus did not abolish the characteristic phenamine effect expressed in increasing range of blood-sugar content fluctuations.

To elucidate the situation further, we subjected two dogs with denervated livers to a second operation aimed at preventing the possibility of reflex adrenalinemia. The operation consisted of removal of the right and denervation of the left adrenals. When the animals had recovered from surgery they were used for experiments with administration of phenamine. Four such experiments were staged on 2 dogs. In all 4 experiments, administration of phenamine failed to produce increased amplitude of fluctuation of blood-sugar levels. The mean blood-sugar content also remained substantially unchanged (Table 2).

Further investigations were carried out on a dog with intact innervation of the liver, but with the possibility of reflex adrenalinemia removed (removal of right and denervation of left adrenals). Four experiments with administration of phenamine were performed on this dog. In three of these, no increase in the amplitude of fluctuations of blood-sugar content was noted. The difference between the "maximal amplitudes of fluctuation" did not exceed 5 mg%, i. e., the possible experimental error. Only in one experiment did the "maximal amplitude of fluctuations" increase by 8 mg% (Table 2). The mean blood-sugar content in all 4 experiments remained virtually unchanged.

It can thus be considered that exclusion of reflex adrenalinemia prevents increased fluctuations in blood-sugar content which occur in healthy animals on administration of phenamine and that adrenalin participates in changes in blood-sugar levels evoked by administration of phenamine. Under these conditions, however, increased secretion of adrenalin by the suprarenals does not lead to stable hyperglycemia but is reflected only in the degree of blood-sugar level fluctuations.

SUMMARY

The effect of phenamine on the changes of blood-sugar level was studied in healthy people as well as in dogs. 5-7 blood tests were performed at 5-minute intervals. Then the dose of 0.01-0.02 g of phenamine was introduced. In 30-45 minutes blood tests were taken again at 5-minute intervals. Blood-sugar level was determined by Hagedorn's and Jensen's method in 6-10 specimens of blood, thus obtained. Analysis of data showed that phenamine introduction causes increased variations of blood-sugar level and acceleration of the rhythm of these variations. Partial denervation of liver in dogs (removal of all nerves passing through the gastro-hepatic-duodenal ligament) is not reflected in increased variations of glycemic level, which appears in healthy animals after phenamine introduction. If the possibility of reflex adrenalinemia is excluded (by removal of right and denervation of the left suprarenal gland), there is no increase in the variations of contents of sugar in the blood after introduction of phenamine in animals.

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