The Effect of Dibenamine in the Insulin-Induced Hypoglycaemic Syndrome

By

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The hypoglycaemic syndrome, a state endangering life and eliciting Cannon's alarm reaction, is connected with an elevation of the blood adrenaline level. Chemical evidence has recently been presented to show that the urinary output of catecholamine increases following the administration of insulin. If there is no increase in catecholamine output, the hypoglycaemic syndrome appears in an unusual form, and sweating, palpitation and other symptoms of excitation are absent [1].

It has been known for long that the so-called alimentary hyperglycaemia can be prevented by blocking the sympathetic nervous system with ergotamine and the parasympathetic with atropine, while it is not possible to achieve this with large doses of insulin. [2, 3]. This has made us to investigate the action of the potent sympathicolytic drug Dibenamine on the insulin effect, studying (i) the influence of Dibenamine on the early phase of the insulin effect, and (ii) the changes in the responsiveness of the organism in insulin shock, following the administration of Dibenamine.

Methods

Twelve male rabbits weighing about 3 kg each and 5 dogs (4 males and 1 female) weighing from 15 to 20 kg each were used. The rabbits were given intravenously or subcutaneously a dose of insulin rapidly inducing a hypoglycaemic episode. The dogs had previously been treated with insulin over a period of one year so that they had developed tolerance to very large doses [4]. In some of them even 600 U of insulin was needed for eliciting hypoglycaemic symptoms.

The response to Dibenamine was studied by administering the drug either alone or together with insulin or in the state of hypoglycaemic shock. The dose for rabbits was 50 mg per animal, for dogs 10 mg per kg of body weight, by very slow intravenous drip infusion. The experiments were carried out after 14 hours of fasting and lasted from 4 to 8 hours. The interval between experiments on the same animal was never less than 10 days. Blood samples were taken before the experiment, then at 30 minute intervals. Blood sugar was estimated by Hagedorn and Jensen's method.

Results

In the dogs (6 observations) Dibenamine did not significantly affect the blood sugar level, the changes were in the range of ±15 mg per 100 ml. In 4 of the rabbit experiments similar results were obtained, but in 2 cases Dibenamine significantly increased the blood sugar level. In these (Fig. 1) the fasting blood sugar level was higher than usual, 133 and 205 mg per 100 ml, respectively, presumably due to excitation. (It has to be noted that introducing an injection cannula into a calm rabbit's ear vein does not increase the blood sugar level by more than 20 mg per 100 ml.) In one dog and one rabbit the administration of Dibenamine was followed by tremor but this ceased in one or two minutes and the animals were then free of symptoms.

The combined action of insulin and Dibenamine is shown in Table I. In 2 cases Dibenamine did not alter the pattern of the seizure. In 1 case blood sugar dropped significantly, but it was only after it had risen to normal that hypoglycaemic symptoms developed. These ceased promptly in response to intravenous glucose (Fig. 2).

Table I

Effect of Insulin + Dibenamine in Rabbits

Number of cases	Drug employed	Hypoglycaemic symptoms	Symptomfree
6	Insulin, 64 U Dibenamine, 50 mg	3	3
6	Insulin, 64 U	6	—

In Table II are presented the results for dogs. In one of the 2 dogs which had not developed hypoglycaemic symptoms the administration of Di-

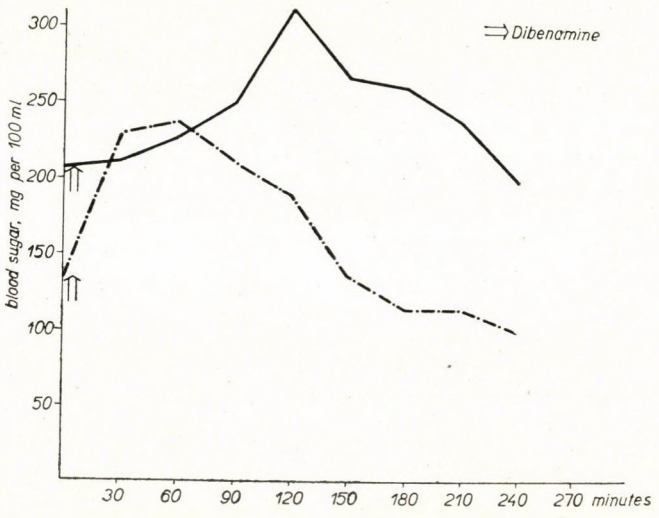

Fig. 1. Effect of Dibenamine on Blood Sugar Level

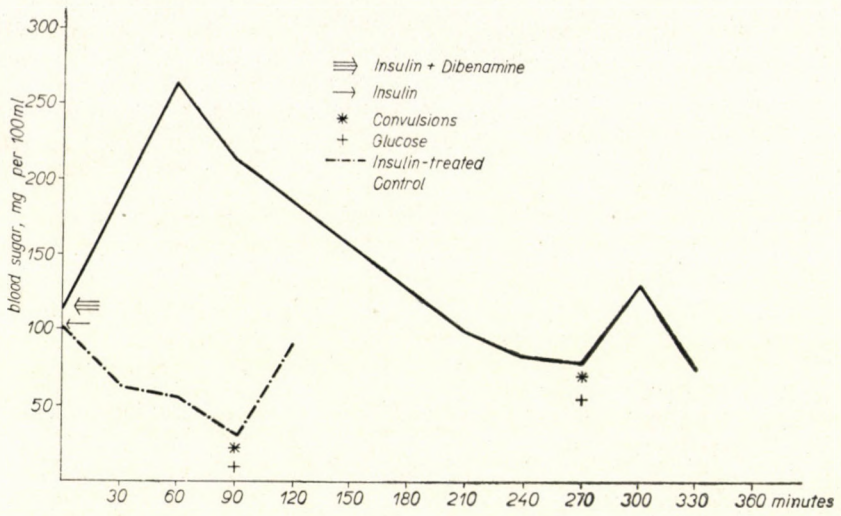

FIG. 2. Combined Actions of Insulin and Dibenamine

benamine provoked a reaction that promptly subsided on intravenous administration of glucose, but subsequently symptoms developed anew at the normoglycaemic level; these, too, immediately ceased in response to glucose (Fig. 3). In the other dog Dibenamine repeatedly failed to induce a reaction. In 3 dogs responding to insulin with shock, Dibenamine prevented the reaction.

TABLE II

Effect of Insulin + Dibenamine in Dogs

Number of cases	Drug employed	Hypoglycaemic symptoms	Symptomfree
5	Insulin, 200 U Dibenamine, 10 mg/kg	3	2
5	Insulin, 200 U	3	2

The effect of Dibenamine during insulin shock in rabbits is shown in Table III. In 4 cases the hypoglycaemic symptoms reappeared at about the same blood sugar level at which they had first taken place. In two cases the symptoms developed at a normal blood sugar level. In one case glucose was administered 10 minutes after onset of the convulsions, but

TABLE III

Effect of Dibenamine during Insulin Shock in Rabbits

Number of cases	Drug employed	Nature of the episode recurring after the administration of Dibenamine	
		unchanged	increased
6	Insulin, 64 U Dibenamine, 50 mg	4	2

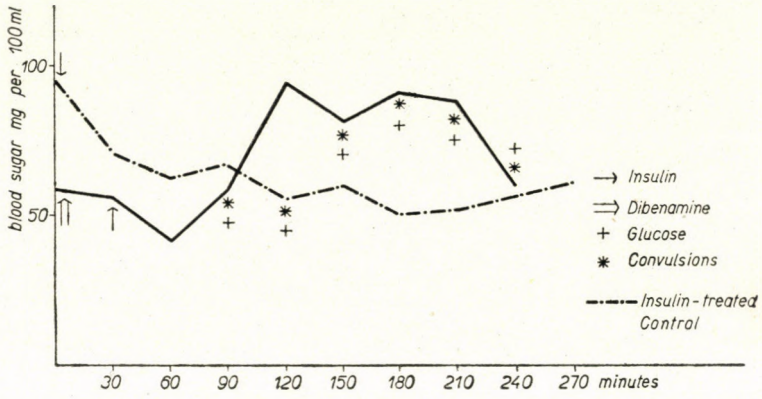

FIG. 3. Combined Actions of Insulin and Dibenamine

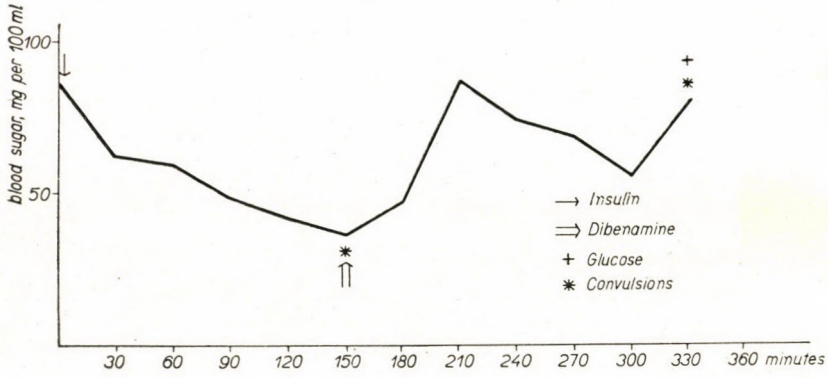

FIG. 4. Effect of Dibenamine during Insulin Shock

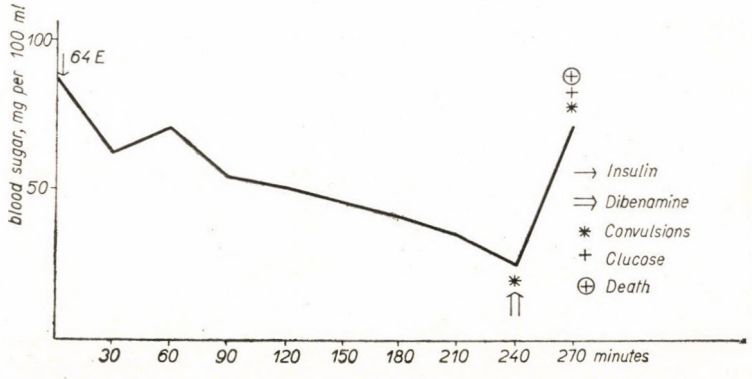

FIG. 5. Effect of Dibenamine during Insulin Shock

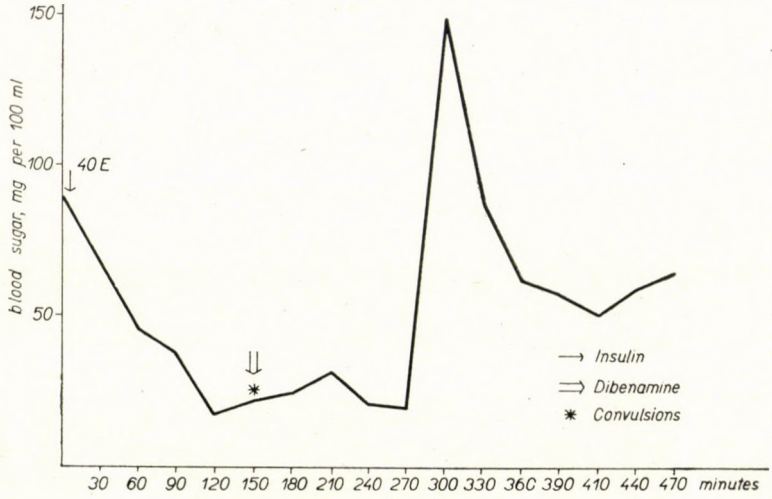

FIG. 6. Effect of Dibenamine during Insulin Shock

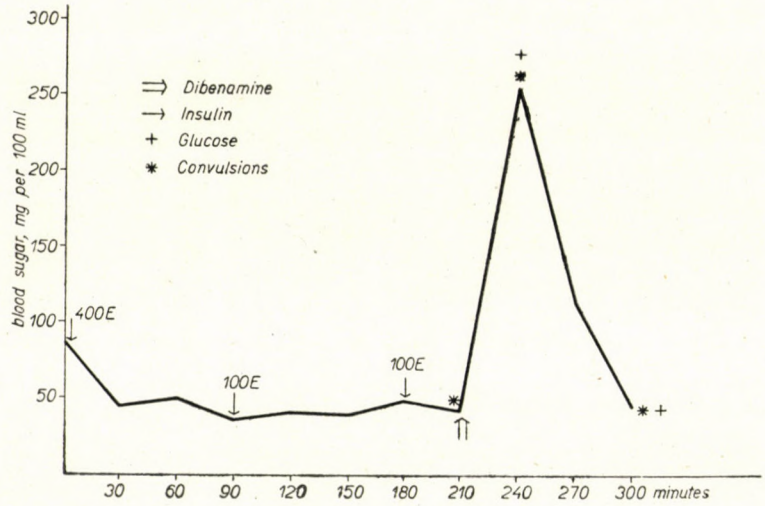

FIG. 7. Effect of Dibenamine during Insulin Shock

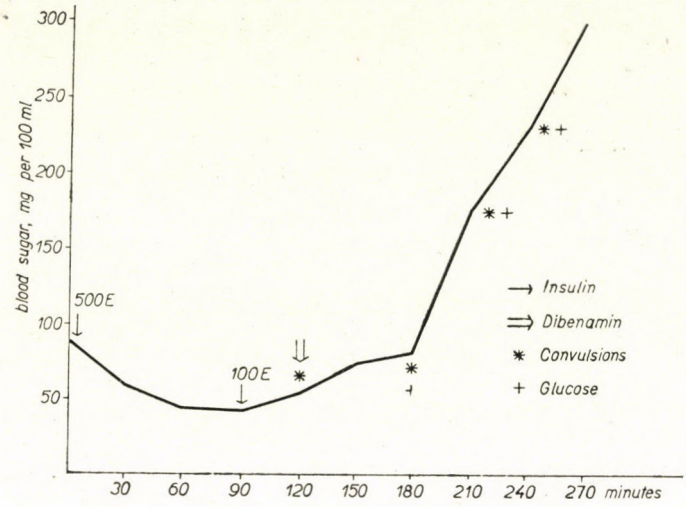

FIG. 8. Effect of Dibenamine during Insulin Shock

this animal could not be saved (Figs. 4 and 5). In one case there was intensive counter-regulation, but the symptoms did not reappear (Fig. 6).

The effect of Dibenamine during insulin shock in dogs is shown in Table IV. The two cases in which recurrent episodes were observed at normoglycaemia are illustrated in Fig. 7 and Fig. 8. In both of these 600 U of insulin were needed to elicit the symptoms, after 300 U had been given in vain.

TABLE IV

Number of cases	Drug employed	Nature of the episode recurring after the administration of Dibenamine	
		ceased	reappeared at higher level
4	Insulin, 600 U Dibenamine, 10 mg/Kg	2	2

DISCUSSION

According to the results obtained Dibenamine may raise the blood sugar level. (i) In two rabbit experiments the blood sugar level was significantly increased following the administration of Dibenamine; (ii) in a rabbit experiment the combined administration of insulin and Dibenamine was followed by a rise of the blood sugar level; and (iii) during insulin shock the blood sugar level showed a significant rise in response to Dibenamine, in both rabbits and dogs.

In all of these cases there must have been a state of adrenergic preponderance. In support of this is the high fasting blood sugar level found in the cases mentioned under (i). As regards the observations listed under (ii) and (iii), it has to be remembered that the blood adrenaline level increases following administ-

ration of insulin. In the adrenergic state occurring in our experiments the Dibenamine effect was paradoxical and the blood sugar level was increased. Such a paradoxical effect is rather exceptional. Large doses of Dibenamine, 10 to 20 mg/kg usually reverse the effect of considerable amounts of adrenaline so that a fall in blood pressure results [5]. However, in the early phase of their effect sympathicolytic drugs often elicit a release of adrenaline.

In hypoglycaemic shock no spontaneous elevation of blood sugar takes place when the condition is deteriorating. (This we have unequivocally ascertained in 12 rabbit experiments [6].) If Dibenamine was administered during the insulin shock, then after a transitory symptomless period a typical shock developed at a high blood sugar level. This type of shock is also easily and promptly controlled by the administration of glucose. This was observed in several rabbit experiments, but especially in the dogs. In the latter such episodes sometimes occurred at blood sugar levels higher than 200 mg per 100 ml (Fig. 7). Following the administration of glucose the symptoms often reappeared (Fig. 8). In one case the administration of glucose had been delayed and the animal died.

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We have previously observed both in patients and in animal experiments that insulin shock may develop at relatively high blood sugar levels [7, 8]. In these cases of counterregulatory insulin shock, as we have termed them, stressor effects represent a decisive eliciting factor [9]. If the administration of Dibenamine is followed by an elevation of the blood sugar level, it may be assumed that a true counteraction has been elicited by the sympathicolytic drug. The tendency to develop a so-called counterregulatory insulin shock following the combined administration of Dibenamine and insulin is another evidence indicating that during the counterregulatory increase of the blood sugar level insulin shock may develop at normoglycaemic and hyperglycaemic levels.

Summary

The effect of Dibenamine has been investigated, as administered in combination with insulin and during insulin shock. It has been found that the simultaneous administration of insulin and Dibenamine causes a tendency to develop a so-called counterregulatory insulin shock. This develops at normo- or hyperglycaemic levels and ceases promtly in response to the administration of glucose.

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