

Hypoglycemic Action of Indole-3-Acetic Acid by Mouth in Patients with Diabetes Mellitus.* (22678)

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The administration of indole-3-acetic acid by mouth to normal rats results in a statistically highly significant hypoglycemia and a concomitant reduction in the rate of insulin destruction.[†] Since a similar decrease in the blood sugar does not occur in the severely diabetic alloxanized rat, the response cannot be due to an inhibition of the secretion or action of glucagon or to an acute non-specific hepatotoxic action. Accordingly the hypoglycemic response must be dependent upon the presence of insulin. This insulin dependence may be due to either an increase in the secretion or to a decrease in the rate of destruction of endogenous insulin consequent to an inhibition of the enzyme system, insulinase, which is relatively specific in catalyzing the hydrolysis of insulin. In accord is the fact that indole-3-acetic acid is an inhibitor of insulinase *in vitro* and *in vivo*.[†]

The present report deals with observations in man on the acute action of indole-3-acetic acid by mouth on the blood sugar concentration.

Method. Twelve adult patients with diabetes mellitus and 6 subjects without any evidences of a disturbance in carbohydrate metabolism were studied. In all instances, the patients with diabetes mellitus developed clinical evidences of the disorder after the age of 40 years (mean age of onset $\pm$ SE = 49.2 ± 2.0 years). The duration of the syndrome was from 2 to 16 years (mean duration $\pm$ SE = 7.7 ± 1.3 years). Those patients who were maintained on long-acting insulins were transferred to regular insulin for 3 to 5 days before the study in order to obviate the effect of insulin depots. All subjects served as their own controls in that the effect of

drinking 5 ml of 0.5% sodium bicarbonate, (pH 7.8)/kg body weight on the blood sugar concentration was studied on one occasion and the effect of a similar volume of bicarbonate containing 100 mg indole-3-acetic acid/kg body weight was determined on another occasion. The subjects were fasted overnight before each test and those with diabetes were not given any insulin on the morning of the test. Venous blood samples were taken before and at hourly intervals for 5 hours after the patients drank the solution and the concentration of glucose was determined by Nelson's method(1).

Results. A small, but statistically significant decrease in the blood sugar concentration occurred in the apparently healthy subjects after the ingestion of the indole-3-acetic acid dissolved in sodium bicarbonate (Fig. 1). Whereas the blood sugar concentration (mean $\pm$ SE) showed a slight increase from 82.7 ± 5.8 to 93.5 ± 5.8 mg % by the end of the 5 hours after the ingestion of the sodium bicarbonate, the blood sugar decreased from 81.7 ± 4.0 to 68.6 ± 2.7 mg % during the same interval after the indole-3-acetic acid solution. By the third hour the difference between the 2 responses was statistically highly significant ($P < 0.001$).

The patients with diabetes mellitus likewise developed a hypoglycemic response to the indole-3-acetic acid (Fig. 2). Whereas these patients developed a maximum decrease in the blood sugar concentration from 257.3 ± 10.2 to 210.5 ± 13.3 mg % in 5 hours after the ingestion of the sodium bicarbonate solution, the blood sugar decreased from 232.9 ± 16.0 to 143.4 ± 11.8 mg % during the same interval after indole-3-acetic acid. The difference between the responses to the two solutions was statistically significant by the second hour ($P > 0.01$) and thereafter. A repeated measures analysis of variance(2) likewise revealed a significant difference ($P > 0.01$) between the curves of the blood sugar

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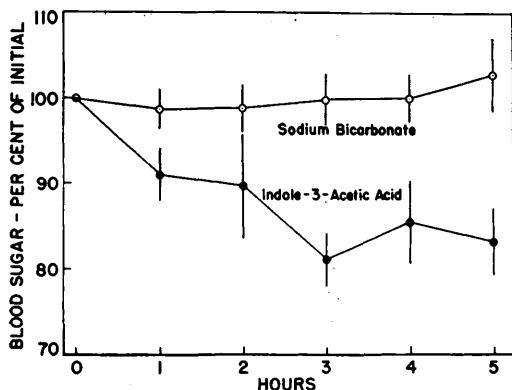


FIG. 1. Effect of indole-3-acetic acid on blood sugar concentration of non-diabetic subjects. Blood sugar concentration at each interval is expressed as the % (mean $\pm$ S.E.) of concentration prior to ingestion of the solution. Initial blood sugar concentration before the sodium bicarbonate solution was 82.7 ± 5.8 mg %, and 81.7 ± 4.0 mg % before the indole-3-acetic acid solution.

responses to the two solutions.

Discussion. The relatively gradual decrease in the blood sugar concentration after the ingestion of indoleacetic acid by the non-diabetic subjects differs from the rapid maximal hypoglycemia which results within one hour after 1-butyl-3-p-tolylsulfonylurea by mouth(3). Various considerations have led to the hypothesis that the immediate hypoglycemic response of non-diabetic subjects to the tollysulfonylurea is due to the discharge of insulin from the Islets of Langerhans into the circulation while the persistence of the hypoglycemia is due to the inhibition of insulinase and a consequent decrease in the rate of destruction of endogenous insulin(3). The response of the non-diabetic subjects to the indoleacetic acid, however, suggests that an acute stimulation of the Islets of Langerhans does not occur after the ingestion of this compound. Both the diabetic and non-diabetic groups show a gradual decrease in the blood sugar concentration which is similar to that observed in responsive patients with diabetes after the administration of tollysulfonylurea (4) and may be attributed to an inhibition of insulinase and a decrease in the rate of insulin destruction. The data are in accord with the hypothesis that the insulin insufficiency of many patients with diabetes mellitus is due to an increase in the rate of destruction

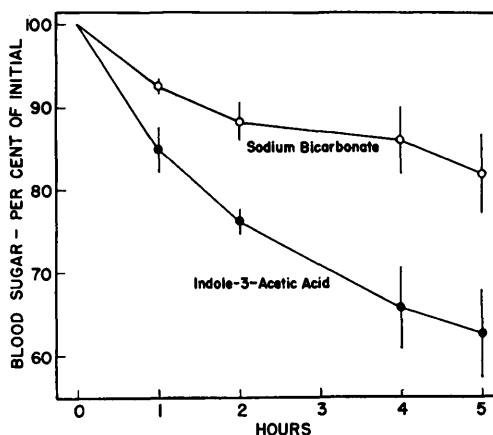


FIG. 2. Effect of indole-3-acetic acid on blood sugar concentration of patients with diabetes mellitus. Blood sugar concentration at each interval is expressed as % (mean $\pm$ S.E.) of concentration prior to ingestion of the solution. Initial blood sugar concentration before the sodium bicarbonate solution was 257.3 ± 10.2 mg %, and 232.9 ± 16.0 mg % before the indole-3-acetic acid solution.

of insulin by the tissues rather than to a marked decrease in the rate of production of insulin by a severely damaged pancreas(5).

Although the data reported herein suggest that indoleacetic acid can be effective by mouth in decreasing the blood sugar of patients who developed diabetes after 40 years of age, the relatively small number of patients studied and the lack of information concerning the long-term toxic effects of indoleacetic acid and other plant growth hormones precludes their application to the therapy of diabetes mellitus at the present time. The studies, however, do suggest an hitherto unsuspected relationship between plant and animal hormones.

Conclusions. Indoleacetic acid by mouth produces a decrease in the blood sugar of adult patients with diabetes mellitus.

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