Reports and Letters

Hypoglycemic Action of Sulfonylureas in Patients with Diabetes Mellitus

Although it has been known since 1941 that a variety of sulfonamide derivatives are effective as hypoglycemic agents in animals, the recent reports by Franke and Fuchs (*1*) and Bertram, Bendfeldt, and Otto (*2*) have stimulated interest in the application of the sulfonamide compounds to the treatment of patients with diabetes mellitus. These investigators demonstrated that the oral administration of sulfanilyl-*n*-butylurea was effective in eliminating the need for exogenous insulin in many adult patients with diabetes mellitus. The subsequent demonstration that the sulfonylureas are noncompetitive inhibitors of the enzyme responsible for the destruction of insulin (insulinase) and that a decrease in insulinase activity is associated with the hypoglycemia that follows the ingestion of the sulfonylurea by rats (*3*), prompted an extension of the afore-mentioned clinical observations (*4*).

The present preliminary report deals with observations on the acute action of 1-butyl-3-*p*-tolylsulfonylurea (*5*) by mouth on the blood sugar of adult patients with diabetes mellitus of various degrees of severity. The tolylsulfonylurea was used in this study because it was found to be more potent than the sulfanilyl-*n*-butylurea in the production of hypoglycemia and insulinase inhibition in the rat (*3*).

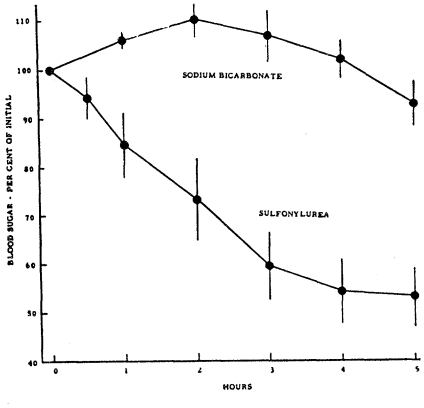

Fig. 1. Hypoglycemic action of tolylsulfonylurea by mouth in adult patients with diabetes mellitus. The blood sugar concentration at each interval was expressed as the percentage of the concentration prior to the ingestion of the solution. The sulfonylurea curve represents the mean ± S.E. of the percentages of the initial blood sugar of 34 patients who showed a decrease in the blood sugar.

The patients varied from 21 to 73 years in age. The age of onset of the metabolic disorder varied from 6 to 65 years and the duration from less than 1 year to 30 years. Those patients who were maintained with 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 were fasted overnight and were not given any insulin on the morning of the test. Forty-four patients were given 50 mg of the tolylsulfonylurea per kilogram of body weight, as a 2-percent solution in 0.5-percent sodium bicarbonate adjusted to *p*H 8. Twenty-four patients served as controls and were given 5 ml of 0.5-percent sodium bicarbonate per kilogram. Venous blood samples were taken before and at intervals after the ingestion of the solution, and the concentration of glucose was determined by Nelson's procedure (*6*). The blood sugar values for each interval were expressed as the percentage of the pretest value.

A statistically highly significant hypoglycemic response occurred in 34 of the patients with diabetes who were given the sulfonylurea. The mean (± S.E.) response of these 34 subjects is illustrated in Fig. 1. In contrast is the slight increase in blood sugar that occurred in the patients who were given sodium bicarbonate. Five patients showed no decrease in blood sugar after they had taken the sulfonylurea, while five subjects showed a negligible decrease.

The ten subjects who did not respond significantly to the ingestion of the tolylsulfonylurea developed the metabolic disorder before the age of 20 years (mean age of onset ± S.E. = 13.6 ± 1.7 years) and had the syndrome for 8 to 30 years (mean duration ± S.E. = 17.2 ± 2.1 years). Although the response appears to bear a direct relationship to the age at which the diabetic syndrome developed (Fig. 2), the duration of the syndrome also plays a role in determining the response. Thus, calculation of the multiple regression of the mean percentage decrease in the blood sugar during the 5 hours after the sulfonylurea (y) on the age of onset (x_1) and the duration (x_2) of the metabolic syndrome reveals that both variables are involved ($y = 57.8 - 0.64x_1 - 0.28x_2$). The influence of these and other factors on the hypoglycemic response to the sulfonylureas will be considered in greater detail in a subsequent report.

The data reported herein are in complete agreement with those reported by Franke and Fuchs (*1*) and Bertram, Bendfeldt, and Otto (*2*). Further, the data support the hypothesis that the insulin insufficiency of the majority (approximately 75 percent) of patients with diabetes mellitus is due to an increase in the rate of destruction of insulin by the tissues rather than to a marked decrease in the rate of production of insulin by a severely damaged pancreas (*7*). Thus, the tolylsulfonylurea, acting as an insulinase inhibitor, may produce a decrease in the destruction of endogenous insulin with a consequent increase in the availability of insulin and a resultant hypoglycemia. The lack of response of patients in whom the metabolic disorder began in childhood or adolescence and in whom it persisted for many years may be due to exhaustion of the pancreas such as occurs in animals that are chronically exposed to increased demands for insulin by the peripheral tissues.

The usefulness of the sulfonylureas in the treatment of the patient with diabetes mellitus must await extensive clin-

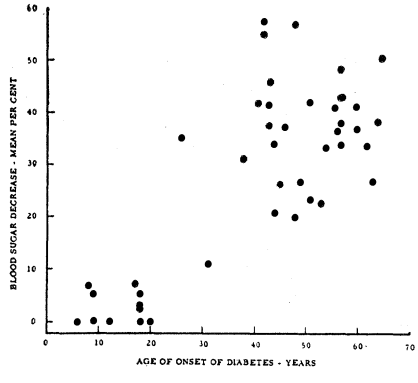

Fig. 2. Relation of age of onset of diabetes mellitus to hypoglycemic response to tolylsulfonylurea by mouth. The decrease in the blood sugar for each subject represents the mean percentage decrease computed from the five hourly samples that were taken after the ingestion of the tolylsulfonylurea.

ical trial. Such trial, however, should be performed with caution since the sulfonylureas are noncompetitive rather than competitive inhibitors of insulinase.

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References and Notes

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4. This investigation was aided by a grant from the Foundations' Fund for Research in Psychiatry.
5. We are indebted to C. J. O'Donovan of the Upjohn Company for generous supplies of 1-butyl-3-*p*-tolylsulfonylurea (Orinase).
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Orinase, a New Oral Hypoglycemic Compound

The necessity for the parenteral administration of insulin has stimulated the search for a drug that would be effective by oral administration for the treatment of diabetes mellitus. Recent reports by Franke and Fuchs (*1*), Achelis and Hardebeck (*2*) and Bertram, Bendfeldt, and Otto (*3*) have indicated that 1-butyl-3-sulfanilylurea causes reduction of blood sugar after oral administration. A related synthetic compound, different in that a methyl group is substituted for the *p*-amino group, has also been shown to cause a hypoglycemic response after oral administration to rats, dogs, rabbits, and human beings (*4*). This compound, 1-butyl-3-*p*-tolylsulfonylurea, is called Orinase (*5*) and is the subject of the present report.

Intact male rats weighing approximately 150 g were used for blood sugar and glycogen studies. These were obtained from the Upjohn colony (Sprague-Dawley ancestry). The animals were fasted 24 hours prior to oral administration of the drug and were also without food during the experimental period. Rat blood sugars were determined at intervals during a 15-hour period by the micro method of Shaffer and Williams (*6*), using tail blood. Groups of control and treated rats (five to ten each) were sacrificed after each determination. Since preliminary experiments indicated that 270 mg/kg was the optimal dosage of Orinase for a 150-g rat, the treated animals were given this amount of drug suspended in 0.5 ml of a 1-percent sodium carboxymethyl cellulose solution. Control rats were given the vehicle alone. Liver and muscle glycogen levels were determined by the anthrone method as described by Seifter and Dayton (*7*) on tissues removed 7 hours following the administration of the drug. Results obtained from animals given crystalline insulin in 0.2 ml of saline, injected subcutaneously, are shown for comparison.

Blood sugars in dogs and rabbits were determined (*8*) by the method of Folin and Wu (*9*). Both species were fasted 15 hours before the initial blood sample was taken, and after Orinase (or its sodium salt) was administered, they were continued without food during the entire experimental period. In dogs, blood sugars were run on starving controls at each blood-sampling period so that changes in blood sugar due to starvation alone could be considered in evaluating the hypoglycemia induced. Plasma levels of Orinase were followed by a new procedure based on the spectrophotometric measurement of the ultraviolet absorption of the drug after extraction from plasma (*10*).

Orinase produced substantial decreases in fasting blood sugar levels when compared with control rats at ½ hour; this decrease was maintained for at least 6 hours (Fig. 1). At 12 and 15 hours, the blood sugars were slightly higher than they were for the controls. It is of interest that at 7 hours the liver glycogen was increased in the Orinase-treated animals (Table 1), whereas the muscle glycogen was not changed from the control value. In contrast, insulin produced a substantial increase in muscle glycogen with no consistent change in liver glycogen. These results suggest a difference in mechanism of action between Orinase and injected insulin. Further, it is important to recall that Synthalin, essentially a liver poison, produces a depression of liver glycogen (*11*), indicating that Orinase acts via a different mechanism than Synthalin. From the data in Fig. 1 and Table 1, it is apparent that blood sugar levels decreased while liver glycogen increased. This suggests that in the rat one of the primary sites of drug action is the liver. This hypothesis is being tested by administering Orinase to hepatectomized and eviscerated rats under various experimental conditions.

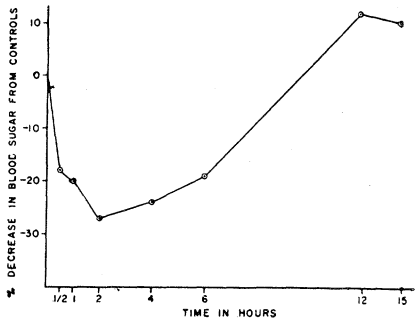

Fig. 1. Effects of a single oral dose of Orinase (270 mg/kg) on fasting blood sugar levels in the rat.

Table 1. Comparison of orally administered Orinase and subcutaneous insulin on liver and muscle glycogen of intact fasting rats.

Treatment	No. of animals	Glycogen (%)	
		Liver	Muscle
Controls	23	0.21	0.31
Orinase, 270 mg/kg	22	0.51	0.28
Controls	10	0.34	0.40
Insulin, 6.7 units/kg	10	0.48	0.65
Insulin, 13.4 units/kg	8	0.34	0.82

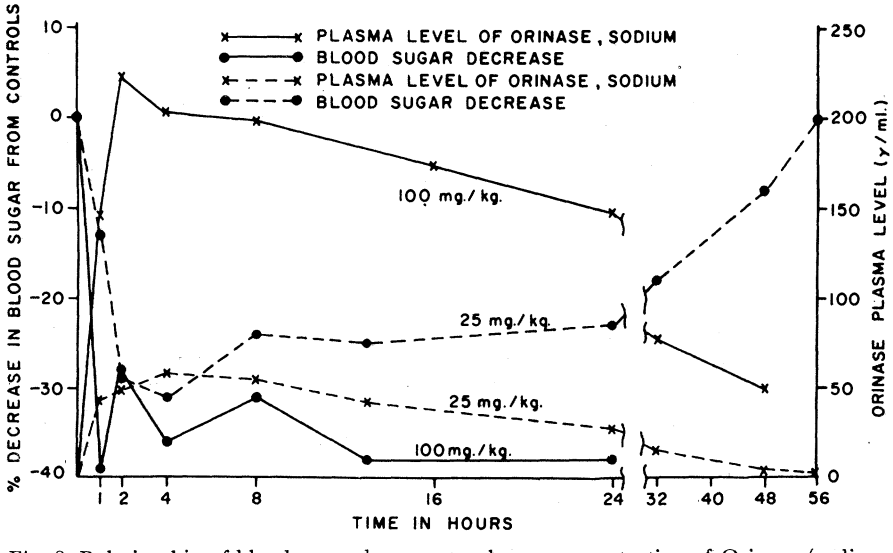

Fig. 2. Relationship of blood sugar decrease to plasma concentration of Orinase (sodium salt) after a single oral dose to fasting dogs. Each point represents an average of values determined from three dogs at each dose level; six dogs were used in all.