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Research Article

COMPARISON OF RESPONSE TO INTRAVENOUSLY ADMINISTERED SODIUM TOLBUTAMIDE IN MILD DIABETIC AND NONDIABETIC SUBJECTS [1, 2]

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The hypoglycemic response of moderately severe diabetic patients to an orally administered test dose of tolbutamide has been shown by Mirsky, Diengott, and Dolger (1) to differ strikingly from that of nondiabetic subjects. Indirect evidence of a correlation between tolbutamide responsiveness and pancreatic insulin content (1), coupled with experimental support for the view that the drug stimulates endogenous secretion of insulin (2–6), suggest that this difference may be of more than empirical interest. The purpose of the following study was to compare response to intravenously administered tolbutamide in nondiabetic and mild diabetic subjects, including those with a normal and near-normal fasting blood glucose level.

MATERIALS AND METHODS

One hundred nondiabetic controls were selected from the medical, surgical, and otolaryngological wards of the Dallas Veterans Hospital (85 subjects), and from among medical students (15 subjects). The nondiabetic status of all control subjects was established by means of history, physical examination, and a negative oral glucose tolerance test, interpreted according to the criteria of the American Diabetes Association (7). Seventy-nine mild, stable, diabetic patients, *none* of whom required insulin therapy, were selected from the Parkland Memorial Hospital Metabolic Clinic, from the wards of the Dallas Veterans Hospital, and from among subjects discovered by the Diabetes Detection Unit of the Dallas City Health Department. Diabetic subjects were subdivided according to their fasting blood glucose level on the morning of the test. Thirty-four patients had fasting hyperglycemia of diagnostic proportions (115 to 180 mg. per cent) and 45 had normal or slightly elevated fasting blood glucose levels (below 115 mg. per cent). Twenty-five of the latter had levels below 100 mg. per cent. The diabetic status of the latter group was established by means of three hour oral glucose tolerance tests. Because of the nonspecificity of this test, as usually interpreted, in the borderline zone (8, 9), the following stringent diagnostic criteria for diabetes were employed: peak blood glucose level, 200 mg. per cent or higher; two hour level, 170 mg. per cent or higher; and three hour level, 135 mg. per cent or higher.

All subjects were requested to adhere to a diet containing 300 Gm. of carbohydrate daily for at least three days before the test. After an overnight fast, and the withdrawal of a fasting blood specimen, 1 Gm. of sodium tolbutamide,[3] diluted in 11 ml. of distilled water, was injected intravenously at a constant rate over a two minute period. Blood specimens were drawn 20, 30, 40, 60, and, in some instances, 90 and 120 minutes after the midpoint of the injection period. Blood glucose concentration was determined in duplicate by the Somogyi-Nelson technique (10). In our laboratory the standard deviation of the replicate determinations included in this study was 1.10.

RESULTS

The typical blood sugar response, exhibited by nondiabetic subjects to intravenously administered sodium tolbutamide, simulated the pattern usually obtained after intravenous injection of insulin. Glucose concentration declined rapidly to a nadir in 20 to 50 minutes after injection, following which a rebound towards normal usually occurred (Figure 1). At 20 minutes after the injection, the blood glucose level of nondiabetic subjects had declined to an average of 60 per cent of the pretest value (S. D., ± 14.2), and the range was from 85 to 9 per cent. Thirty minutes after injection, the mean fall was to 51 per cent of the pretest level (S. D., ± 14.8), with a range of from 82 to 6 per cent. At 40 minutes, at which time rebounding values became increasingly prevalent, the mean percentage was 55.6 (S. D., ± 11.9), with a range of from 91 to 22 per cent. At 60 minutes the mean was 72 per cent (S. D., ± 12.1), and the range from 104 to 42 per cent (Figure 1, 2).

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[2] Presented in part at the annual meeting of the American Federation of Clinical Research, May, 1957.

[3] Sodium tolbutamide was generously supplied by Dr. C. J. O'Donovan, Upjohn Company, Kalamazoo, Michigan.

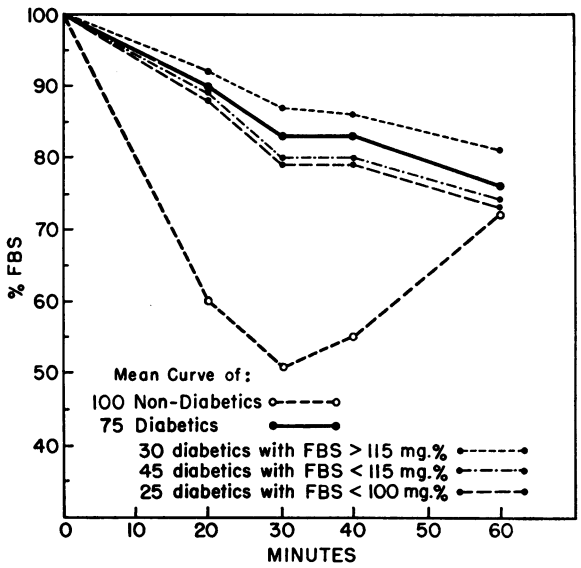

FIG. 1. MEAN TOLBUTAMIDE RESPONSE CURVES OF ALL BUT FIVE OF THE SUBJECTS STUDIED ILLUSTRATING THE BLOOD GLUCOSE RESPONSES TYPICAL OF NONDIABETICS AND OF MILD DIABETICS OF VARYING DEGREES OF SEVERITY

The curve of 45 diabetics with fasting blood specimen < 115 mg. per cent includes the 25 with fasting blood specimen < 100 mg. per cent whose mean curve is also shown separately. Five of the 79 diabetics in this study are not represented in this figure, but their omission does not perceptibly affect the results.

In striking contrast to the response of nondiabetics, diabetic subjects exhibited a more gradual decline which sloped towards a nadir somewhere beyond the one hour specimen (Figure 1). Twenty minutes after injection, the blood glucose level of the diabetic group had fallen to a mean of only 90 per cent of the pretest level (S. D., ± 7.4), with a range of from 108 to 61 per cent. At 30 minutes, the mean percentage of pretest values was 83 per cent (S. D., ± 8.7) with a range of from 105 to 49 per cent. At 40 minutes after injection, the mean was 83 per cent (S. D., ± 9.8), with a range of from 107 to 53 per cent. At 60 minutes, the mean was 77 per cent (S. D., ± 10.9), with a range of from 129 to 49 per cent (Figure 1).

A separate analysis was made of the 45 diabetics with a fasting blood glucose level of less than 115 mg. per cent, and of 25 diabetics with a fasting level below 100 mg. per cent (Figure 1). The hypoglycemic response of the milder diabetics is somewhat more rapid than those whose fasting blood glucose levels exceed 115 mg. per cent. Nevertheless, the mean tolbutamide response curve of each of these groups is shown to parallel closely the mean response curve of the more severe diabetics, and to differ strikingly from the mean response curve of the nondiabetic group.

In Figure 3, the individual response curves of 12 nondiabetic controls are compared with those of 12 diabetic subjects whose fasting blood glucose levels were in a similarly normal range. The precipitous decline in the blood glucose level of the nondiabetics, followed typically by a rebound toward the pretest level, is in marked contrast to the more gradual and often irregular slope exhibited by the mild diabetics.

In Figure 2, the individual blood glucose levels of all diabetic and nondiabetic subjects, expressed as per cent of the pretest value, are recorded at 20, 30, 40, 60, and in a few instances, at 90 and 120 minutes after the tolbutamide injection. Separation of the two groups is maximal at 20 and 30 minutes, at which time the blood glucose level of nondiabetics approaches its nadir. Overlap between groups becomes increasingly prevalent thereafter, as the blood glucose level of the nondiabetics returns towards its pretest value, while that of the diabetics continues to decline. At 20 minutes after the injection of tolbutamide, the blood glucose level of 96 per cent of nondiabetics has declined to below 84 per cent of the pretest value, and in 94 per cent, has fallen to below 80 per cent of pretest level. In contrast, the blood glucose level of 94 per cent of the diabetic group remained at 84 per cent of the pretest level or higher, and in 95 per cent, remained at 80 per cent or more.

At 30 minutes after the tolbutamide injection, the blood glucose level of 99 per cent of the nondiabetics fell below 77 per cent of the pretest value (Figure 2). However, in 10 per cent of diabetic patients, declines to 73 per cent of the pretest level or less are noted.

DISCUSSION

The foregoing data indicate that the rate of hypoglycemic response of nondiabetic subjects to intravenously administered sodium tolbutamide differs from that of mild stable diabetics. While precise interpretation of this difference must await final elucidation of the mechanism of sulfonylurea-

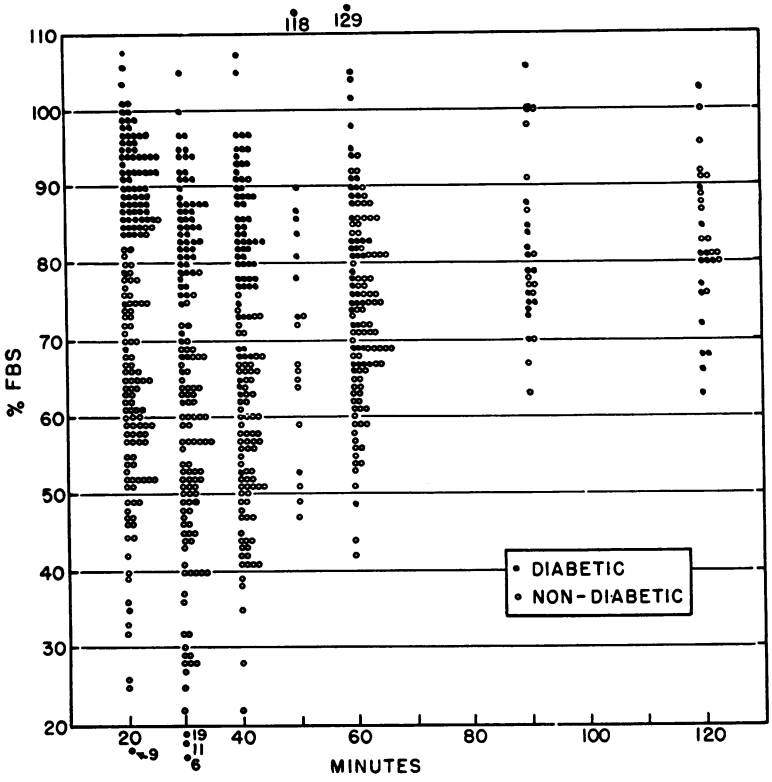

FIG. 2. THE TOLBUTAMIDE RESPONSE TESTS OF 100 NONDIABETIC AND 79 MILDLY DIABETIC SUBJECTS ARE RECORDED

Blood glucose levels are expressed as per cent of the fasting concentration. Separation of the two groups is maximal at 20 and 30 minutes.

induced hypoglycemia, speculation as to its significance is of interest.

Although this study in no sense contributes to clarification of the problem of its mechanism of action, the results are in harmony with the concept that tolbutamide enhances the release of insulin from the beta cells (2–6). The resemblance between the nondiabetic tolbutamide response curve and the normal insulin tolerance curve is compatible with a release of stored insulin from the beta cells (1). If this were the case, the more gradual hypoglycemic response to tolbutamide exhibited by diabetic subjects could be ascribed either to diminished insulin stores, or to decreased rate of insulin release in response to betacytotropic stimulation, although extrapancreatic interference with insulin degradation is also possible. The apparent inverse correlation between the rate of hypoglycemic response and the fasting blood glucose concentration noted in the diabetic group (Figure 1) may be a quantitative expression of the severity of the disease, or merely a nonspecific function of the pretest blood glucose level.

There is, however, experimental evidence that tolbutamide potentiates the action of exogenous insulin in totally depancreatized animals (11–13). The results of the present study can also be explained on the basis of potentiation by tolbutamide of independently secreted endogenous insulin.

Validation of either of these theories of sulfonylurea action would provide a rational basis for the observed differences in tolbutamide response. In this event, the intravenous tolbutamide response test would constitute an index of beta cell function, which might prove useful as a new parameter for the diagnosis of mild diabetes. Attention is called to the fact that the blood glucose concentration at 20 and 30 minutes, expressed as per cent of pretest level, correctly segregated diabetic patients from nondiabetics in approximately 95 per cent of cases; this includes the mildest dia-

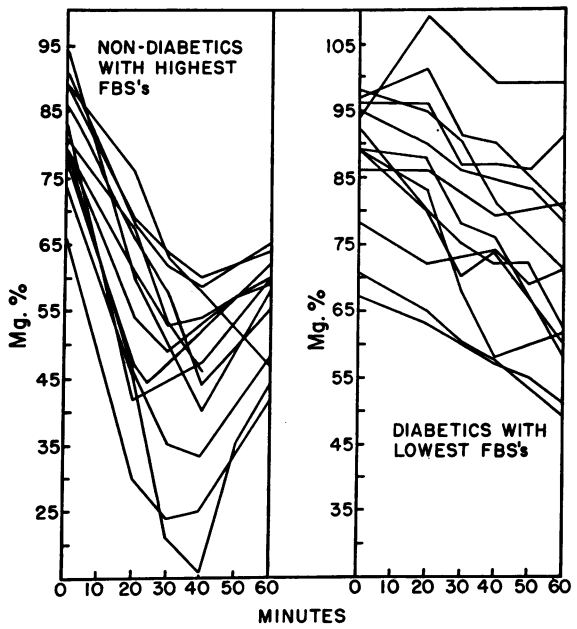

FIG. 3. COMPARISON OF THE TOLBUTAMIDE RESPONSE CURVES OF 13 NONDIABETICS AND 13 MILD DIABETICS WHOSE FASTING BLOOD GLUCOSE LEVELS WERE IN A SIMILAR RANGE

The rapidity and magnitude of the decline of blood glucose levels which characterize the nondiabetic group are in contrast to the more gradual and occasionally irregular responses of the diabetics.

betics, whose fasting blood glucose levels were in a normal or near-normal range. Since this record compares favorably with other routine clinical tests now employed in the diagnosis of mild diabetes (8, 9), further evaluation of the tolbutamide response test as a diagnostic procedure seems warranted.

SUMMARY

Intravenous sodium tolbutamide response tests were performed in 100 nondiabetic and 79 mild, stable diabetic subjects, and blood glucose concentration determined at 20 minute intervals for up to two hours thereafter. Whereas the blood glucose levels of nondiabetics fell rapidly, reaching a nadir between 20 and 40 minutes after injection, diabetics, including those with a normal or near-normal fasting blood glucose value, exhibited a more gradual decline. Possible explanations for this striking difference in tolbutamide response are discussed, and the practical implications of these findings considered.

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