

Comparison of Intravenous Glucose Tolerance and Intravenous Tolbutamide Response in Ischemic Cardiovascular Disease

Lars Hagenfeldt, M.D., and Fredrik Wahlberg, M.D., Stockholm

SUMMARY

The present investigation has shown a significant but weak correlation between the IVGT and the IVTR in patients with ischemic cardiovascular disease. For diagnostic purposes an adjustment of the criteria for IVTR given by Unger and Madison is suggested. *DIABETES* 16:15-17, January, 1967.

In the late 1950's Unger and Madison¹ introduced the intravenous tolbutamide response, IVTR, as a new parameter in the diagnosis of diabetes mellitus. According to their investigation, the test was very specific for diabetes and only three venous blood samples during a thirty-minute interval were required for diagnostic purposes.

The diagnosis of diabetic states today largely depends on glucose tolerance tests. Unger and Madison employed an oral glucose tolerance test, OGTT, to classify their subjects as normal or diabetic. The aim of the present study was to investigate how the results of an intravenous glucose tolerance test, IVGTT, and the IVTR corresponded in the same individual.

MATERIAL AND METHODS

A. Twelve patients, six men and six women, with a mean age of 60 yrs., ages ranging from 36 to 76 yrs., and with overt diabetes mellitus defined as repeated observations of fasting blood glucose 110 mg. per 100 ml. or more and glucosuria. None had received treatment with hypoglycemic agents.

B. Ten presumably healthy subjects, five men and five women, with a mean age of 31 yrs., ages ranging from 24 to 46 yrs.

In the subjects under A and B only IVTR's were measured.

C. Sixty patients with ischemic cardiovascular disease as manifested by myocardial infarction, angina pectoris, and intermittent claudication. There were forty-nine men and eleven women, with a mean age of 60 yrs., ages ranging 40 to 78 yrs.

All participants were ambulatory and in good physical and nutritional condition on their ordinary diets at the time of the tests. With the exception of the twelve diabetics under A, none had evidence of diabetes or other disease known to affect carbohydrate metabolism prior to the tests.

The tests were performed in the morning with the participants fasted for 12 to 16 hrs. All blood samples were capillary and taken from the earlobes, and blood glucose was determined enzymatically according to Marks.²

Fasting blood glucose level was determined from duplicate or triplicate samples.

The intravenous glucose tolerance test. Twenty-five grams of glucose in aqueous solution were injected intravenously during 2 to 4 min. Zero time was set at the end of the injection, and blood samples for glucose determination were taken at 10 and 20 min., and from then on every fifth minute until 60 min., the samples at 20 and 60 min. being duplicate. The blood glucose values between approximately 20 and 60 min. form an apparently straight line when plotted against time in a semilogarithmic system. From this line blood glucose half-life was determined graphically and a k -value for the disappearance of blood glucose in per cent per minute calculated according to the formula³

$$k = \frac{0.693 \cdot 100}{t \frac{1}{2}};$$

k -values 0.90 and lower were classified as diabetic, 0.91 to 1.10 as borderline, and 1.11 and higher as normal.^{4,5}

The intravenous tolbutamide response. One gram of

Presented in part before the Swedish Society of Internal Medicine, November 1963.

From the Departments of Clinical Chemistry and Internal Medicine at the Seraphimer Hospital, Stockholm, Sweden.

sodium tolbutamide in a 5 per cent aqueous solution was injected intravenously in 2 to 4 min. Zero time was set at the end of the injection, and duplicate blood samples for glucose determination were taken every tenth minute until 60 min. The reduction of blood glucose was expressed as per cent of the fasting value. Based on Unger's and Madison's results, criteria for normal IVTR were set as a minimum reduction of fasting blood glucose level with either 20 per cent after 20 min. or 25 per cent after 30 min.

Statistical analysis was performed with the Wilcoxon rank test and the Spearman rank correlation test. Only differences at the 5 per cent probability level or lower were considered significant.

RESULTS

The intravenous tolbutamide response in overt diabetics and in healthy subjects was studied in the twelve diabetics and the ten healthy subjects under A and B. The results were in accordance with those of Unger and Madison, and at 20 and 30 min. there was no overlapping in per cent reduction of fasting blood glucose between the diabetics and the healthy subjects. The mean values were 4.9 per cent and 7.7 per cent for the diabetics, and 26.5 per cent and 38.9 per cent for the healthy subjects.

The relation between the IVGT and the IVTR in the same individual was studied in the sixty subjects under C, of whom twenty-four had diabetic, fifteen borderline, and twenty-one normal IVGT. The mean blood glucose curves in these three groups after tol-

butamide administration are shown in figure 1. After 20, 30, and 40 min. the group with diabetic glucose tolerance differed significantly from that with normal glucose tolerance ($p < 0.001$). Otherwise no significant differences occurred. There was considerable overlapping between the three groups at all time intervals.

The relation between the glucose half-life determined by the IVGTT and the IVTR measured as per cent reduction of fasting blood glucose after 20, 30, and 40 min. is further illustrated in figure 2. Statistical analysis yielded significant negative correlations at all the three time intervals ($p < 0.001$, R being -0.46 , -0.53 , and -0.53 , respectively). Glucose half-life was preferred to k -value for graphic reasons.

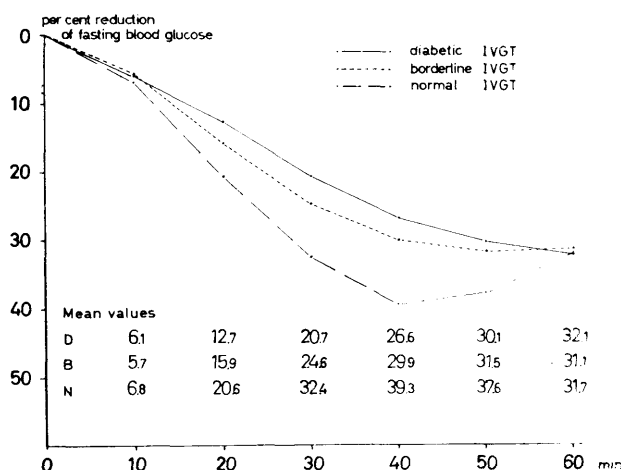


FIG. 1. The mean intravenous tolbutamide response in per cent reduction of fasting blood glucose in patients with diabetic, borderline and normal intravenous glucose tolerance.

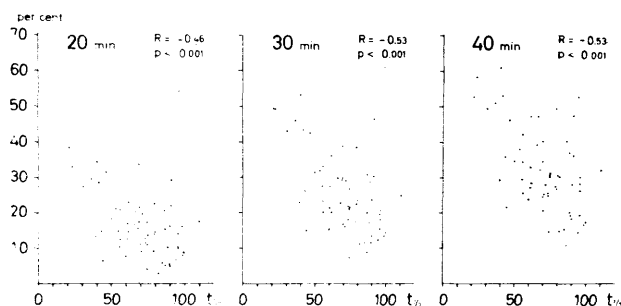


FIG. 2. Relation of the per cent reduction of fasting blood glucose twenty, thirty and forty minutes after tolbutamide injection and the glucose tolerance expressed as glucose half-life in minutes.

Classification according to IVGT and IVTR was made in the sixty subjects under C, and the results are shown in table 1. Of the twenty-one patients with normal IVGT, six had diabetic IVTR, and of the twenty-four patients with diabetic IVGT, eight had normal IVTR. Of the fifteen patients with borderline IVGT, seven had normal and eight diabetic IVTR.

DISCUSSION

The introductory investigation of a small group of overt diabetics and healthy subjects confirmed the results of Unger and Madison, which was not entirely

TABLE 1

Classification of patients according to intravenous tolbutamide and intravenous glucose tolerance

Intravenous tolbutamide response	Intravenous glucose tolerance		
	Normal	Borderline	Diabetic
Normal	15	7	8
Diabetic	6	8	16

the case as regards the main material of patients.

For the study of the relation between IVGT and IVTR, patients with ischemic cardiovascular disease but without overt diabetes were selected, as the range of k -values in groups of such patients is wide and contains many diabetic and borderline values.⁵ There is no evidence that the low IVGT often met with in these patients biochemically differs from that in patients without ischemic cardiovascular disease.

The results of the present paper showed a significant correlation between the intravenous glucose tolerance measured as a k -value and the intravenous tolbutamide response measured as per cent reduction of fasting blood glucose at the 20-, 30-, and 40-min. intervals. However, the correlation was rather weak.

Borderline IVGT is designated to a range of k -values where overt diabetes occurs but rarely, and the even distribution of normal and diabetic tolbutamide responses in this group is to be expected with a good correspondence between the results of the two tests. On the other hand, the rather extensive overlapping between diabetic and normal and vice versa when comparing the results of the two methods is remarkable and reflects the above-mentioned weak correlation. In spite of the use of a group with borderline IVGT, where the results of the two methods have not been considered discordant, full accordance was only obtained in 69 per cent of the patients. This discrepancy cannot be due to methodological errors, as no overlapping between diabetic and normal or vice versa occurred in the twenty-four patients of this material in whom at least two IVGTT's were performed, and only two patients overlapped between borderline and normal.

Intravenous loads of glucose and of sodium tolbutamide both normally elicit an increase in serum insulin-like activity, SILA, which in the former case acts upon hyperglycemia and in the latter case upon fasting and lower blood glucose levels. This difference and the fact that the results of the tests are not solely dependent on changes in SILA make it probable that the two tests measure different phases of carbohydrate metabolism, which may partly explain the discrepancies obtained in this study.

The results of Unger and Madison, where less over-

lapping occurred, may be due to their selection of nondiabetic subjects, who were young and healthy, and in whom glucose tolerance seldom is in the lower normal ranges. It is also possible that the results of the oral glucose tolerance test correspond better to the IVTR than do those of the IVGTT. If, according to our results, overlapping between the methods is to be reduced, the criteria for diabetic IVTR should be a reduction of fasting blood glucose of less than 10 per cent at 20 min. or less than 15 per cent at 30 min. and for normal IVTR a reduction of more than 25 per cent at 20 min. or more than 35 per cent at 30 min. Intermediate results should be regarded as borderline and indecisive. With these criteria only four patients showed overlapping between diabetic and normal or vice versa.

The results of available diagnostic tests for diabetes leave a certain number of subjects in an intermediate zone, and the implications of these results for the subjects are not well known. Diabetes mellitus is today defined by its low glucose tolerance. In lack of better knowledge its diagnosis should therefore primarily be founded on oral or intravenous glucose tolerance tests, and the intravenous tolbutamide response should only be looked upon as a simple means to predict glucose tolerance.

ACKNOWLEDGMENT

This study was supported by grants from Svenska Nationalföreningen mot Hjärt-och Lungsjukdomar.

REFERENCES

- ¹ Unger, R. H., and Madison, L. L.: A new diagnostic procedure for diabetes mellitus. Evaluation of an intravenous tolbutamide response test. *Diabetes* 7:455, 1958.
- ² Marks, V.: An improved glucose-oxidase method for determining blood C. S. F. and urine glucose levels. *Clin. Chim. Acta* 4:395, 1959.
- ³ Hamilton, B., and Stein, A. F.: The measurement of intravenous blood sugar curves. *J. Lab. Clin. Med.* 27:491, 1942.
- ⁴ Lundbaek, K.: Intravenous glucose tolerance as a tool in definition and diagnosis of diabetes mellitus. *Brit. Med. J.* 1:1507, 1962.
- ⁵ Wahlberg, F.: The intravenous glucose tolerance test in atherosclerotic disease with special reference to obesity, hypertension, diabetic heredity and cholesterol values. *Acta Med. Scand.* 171:1, 1962.