INTRAVENOUS GLUCOSE TOLERANCE IN LATE PREGNANCY*

MORRIS NOTELOVITZ,† M.B., B.CH., M.R.C.O.G., *Principal Gynaecologist and Obstetrician, Senior Lecturer and Deputy Head of the Department, University of Natal and King Edward VIII Hospital, Durban*

Before methods of blood-sugar analysis were available, glucose-tolerance tests were based on detecting the amount of reducing substances excreted in the urine on a given diet.[1]

Soon after the introduction of reliable blood-sugar analysis, Jacobson[2] studied the response of blood sugar to the administration of a standard dose of glucose, and thereby introduced the oral glucose-tolerance test.

Although this method has become firmly entrenched in the armamentarium of diagnostic procedures, a number of disadvantages to this test soon became apparent—thus, as early as 1922, Beeler *et al.*[3] showed that after the oral ingestion of glucose, 22 - 68% of the test load remains in the stomach for an hour, while 60% of the glucose in the oral test is said to be incorporated in the liver.[4] The value of this test is further obscured when abnormalities of absorption are present. Further, the reproducibility of the oral glucose-tolerance test is said to be poor,[5,6] while the discomfort of having to drink the nauseating glucose solution is an obvious added disadvantage.

The varying factors of gastric emptying and intestinal absorption are exaggerated by pregnancy and may account for the observed impaired glucose tolerance in 'normal' controls.[7,8] Thus, Benjamin and Casper,[9] in evaluating glucose tolerance in 200 women during the third trimester, found that 56% of patients with abnormal oral tests showed normal tolerance when tested intravenously, the two tests being done within 7 days of each other. Similar conclusions have been published by other authors.[7,8,10-12]

Since the validity of the oral glucose-tolerance test is subject to question, it was decided to compare the efficiency and accuracy of the oral test with an originally devised intravenous tolerance test, in the pregnant Natal Indian.

TYPES OF INTRAVENOUS TEST

In 1923 Jorgenson and Plum[13] tried to establish a practical intravenous glucose-tolerance test for use in clinical practice, but their method proved to be unacceptable and it was not until 1942, when Hamilton and Stein[14] published their observation, that a reliable method was established. They noted that after an intravenous injection of glucose, the rate of decline of the blood sugar was proportional to the blood-sugar level at the time. When plotted on semi-logarithmic paper a straight line was found, the slope of which was calculated and then expressed by one value, namely the percentage decrease per minute of the blood sugar.

Further refinements in technique and mathematical expression have resulted in the so-called 'rapid intravenous glucose-tolerance test'.

Rapid Intravenous Glucose-Tolerance Test[15]

Twenty-five G of glucose are given intravenously over 3 - 4 minutes, and samples of blood are obtained every 10 minutes for 1 hour. The response to glucose tolerance is then expressed by the 'K' value—i.e. the percentage fall of blood glucose per minute.

Lundbaeck[16] found that the 'K' value correlated well with the 3-hour level following oral glucose, and added that the intravenous test had the advantage of being less time-consuming; it avoided the gastro-intestinal tract and needed only one numerical index for expressing the result.

'Slow' Intravenous Glucose-Tolerance Test

One-half gram of glucose per kilogram of ideal body-weight is infused at a constant rate over a period of 30 minutes as a 20% solution in distilled water. Blood sugar is estimated in the fasting state, at the end of the infusion, and after 30 and 90 minutes. The test is abnormal if the blood sugar fails to return to normal levels within 90 minutes after the end of the infusion. Love *et al.*[11] have modified the interpretation of this test by expressing the difference between the fasting and 2-hour blood-sugar levels as a percentage of the fasting blood sugar.

As with the 'rapid' test, the estimation of glycosuria is discarded. It should be noted, however, that intravenous glucose-tolerance tests based on blood samples collected at one hour or longer after the injection of glucose are insensitive.[16] This is because blood-glucose concentrations fall rapidly, to reach a minimum value at approximately one hour, after which the blood-sugar level reflects stabilization processes such as the hepatic release of glucose.[17,18]

The 'Modified' Slow Intravenous Glucose-Tolerance Test

Before deciding upon the technique to be employed in the present study, it was decided that: (*a*) the test should be simple to perform and of short duration; (*b*) few blood samples should be required; (*c*) the result should be easy to determine and preferably be expressed as a single value; (*d*) the loading dose should vary with the weight and therefore the potential of response in each patient; and (*e*) as with all glucose-tolerance tests, a high degree of specificity, sensitivity and reproducibility was essential.

Since the 'rapid' intravenous test failed to meet some of the above criteria, a pilot survey of the 'slow' intravenous technique was instituted, but it failed to yield reproducible results. As a consequence, the following technique was evolved and forms the basis of the present report.

MATERIAL AND METHOD

The 'control' patients were all Natal Indian females in the third trimester of pregnancy who had been hospitalized antenatally for conditions other than diabetes. They were all of comparable age and parity and had no evidence suggestive of prediabetes.

To compare the efficiency and accuracy of the intravenous tests, 100-G oral glucose-tolerance tests were performed on the same patients, usually within a week of one another.

A further group of 100 pregnant proved diabetics were similarly tested, to ascertain the reliability of the intra-

*Date received: 24 October 1968.
†Now Head of the Department of Obstetrics and Gynaecology, Addington Hospital, Durban.

venous tolerance test in patients with disturbed carbohydrate balance.

After an unrestricted ward diet, the patients were instructed to fast overnight. Fasting venous blood samples were obtained for basal readings, after which an infusion of 10% dextrose water was set up, the amount of glucose given being calculated on the basis of 0·5 G of glucose/kg. body-weight. The calculated volume of glucose was administered at a constant rate over a period of 1 hour (Table I). A further venous blood sample (from a different venous channel, usually on the opposite arm) was obtained 1 hour after the completion of the infusion. The duration of the test was thus 2 hours.

TABLE I. MODIFIED SLOW INTRAVENOUS GTT DOSE AND RATE OF INFUSION CHART

Patient's weight (*lb.*)	*Volume of 10% dextrose-water to be infused over 1 hour* (*ml.*)	*Approximate rate of infusion* (*Baxter Regular*) (*drops/min.*)
70	175	25
80	200	30
90	225	35
100	250	40
110	275	45
120	300	50
130	325	55
140	350	60
150	375	65
160	400	70
170	425	75
180	450	80
190	475	85
200	500	90

After similar preparation, oral glucose-tolerance tests were performed by giving the patients 100 G of glucose to drink. Venous blood and urine samples were taken in the fasting state and 2 hours after ingestion of the glucose, and the sugar content was analysed. The oral glucose-tolerance tests were performed 4 days after the intravenous method.

Blood-Sugar Analysis

'True' blood-sugar levels were determined by the central laboratory at the King Edward VIII Hospital by processing on the Technicon Autoanalyzer.

RESULTS

Modified 'Slow' Intravenous Glucose-Tolerance Tests—'Normal' Curve

The intravenous glucose-tolerance curve was calculated using the formula of the mean plus 2 standard deviations, and was found to range from a fasting level of 84·78 - 114·02 mg./100 ml. to a 2-hour postglucose value of 97·02 - 146·00 mg./100 ml.

Standard 100-G Glucose-Tolerance Test Compared with the Intravenous Glucose-Tolerance Test

Standard, 100-G glucose-tolerance tests were performed on the same group of patients and the results calculated by the same formula. Thus the fasting values ranged from 81·71 to 104·11 mg./100 ml. and the postprandial values from 103·6 to 152·80 mg./100 ml. Although the mean 2-hour value following the intravenous test was lower, statistical analysis ('t' test) revealed that there was no significant difference between the two methods of testing for glucose tolerance ($p = > 0{\cdot}05$, Table II).

TABLE II. STATISTICAL ANALYSIS OF FASTING AND 2-HOUR POST-GLUCOSE LEVELS: COMPARISON OF ORAL *vs.* INTRAVENOUS METHOD

	Intravenous mg./100 ml.	*Oral mg./100 ml.*
Fasting		
Mean	84·78	81·71
SD	14·62	11·62
Variation	213·90	125·55
't' test for significance	$p = > 0{\cdot}05$	
2-hour value		
Mean	97·02	103·60
SD	24·49	24·60
Variation	599·98	605·10
't' test for significance	$p = > 0{\cdot}05$	

Individual Interpretation

To assess the specificity of the modified intravenous glucose-tolerance test (i.e. the ability to identify correctly a person with normal glucose tolerance), 100 normal pregnant non-diabetic controls were tested with both the oral and the intravenous methods. When the results differed, the GTT was repeated and the original values were classified as being falsely positive and negative if they failed to correlate with the confirmatory test. Similar results were recorded in 89 of these patients, and, of the remaining 11, the intravenous test yielded false positives in 3 and the oral test yielded false positives in 8 patients. Therefore, the specificity of the intravenous test was 97% compared with 92% for the oral test. The sensitivity of a glucose-tolerance test measures the ability of the method to correctly identify abnormal glucose tolerance. Of the 100 diabetics tested, records were complete in only 88 subjects. Of these, the intravenous test provided a false-negative result in 4 cases, whereas the oral tests were correct in all patients. Thus the sensitivity of the intravenous test was 95·5% and that of the oral test 100%.

The above results are based on single blood-sugar assays, as duplicate determinations were not performed. Variations in the results due to technical errors are therefore not excluded and this may be responsible for some of the false positives and/or negatives.

Reproducibility

To assess individual variation in response to the modified intravenous glucose-tolerance tests, duplicate tests were performed in 40 patients, of whom 11 were known diabetics and the remainder normal pregnant controls in the third trimester. The repeat tests were performed 4 days following the initial test.

Reproducibility was judged according to two criteria:

(*i*) The intra-individual difference in glucose tolerance in duplicate tests, measured in the fasting state, and 1 hour following completion of the intravenous infusion.

TABLE III. DIFFERENCE IN GLUCOSE TOLERANCE FOLLOWING DUPLICATE INTRAVENOUS TESTING: FASTING VALUES COMPARED WITH 2-HOUR BLOOD-SUGAR LEVELS

	Fasting	*2-hour*
Range of difference	0-72 mg./100 ml.	0-73 mg./100 ml.
Mean difference	13·7 mg./100 ml.	19·8 mg./100 ml.
% above mean	35%	30%

(*ii*) The significance of this variation in the interpretation of the duplicate glucose-tolerance curves.

From a summary of these results (Table III) it can be seen that there is very little difference in variation between the mean blood-sugar level in the fasting state and that obtained 2 hours later—13·7 mg./100 ml. compared with 19·8 mg./100 ml., respectively. Once again, duplicate testing of the blood samples was not performed, and this might account for the disparity in some of the tests.

Although the range of differences was wide (0 - 72 mg. and 0 - 73 mg./100 ml. in the fasting and 2-hour levels, respectively), individual interpretation of the results would have resulted in only 1 patient—who was a known diabetic—being wrongly classified (Table IV). Thus, on the basis of the classification of the patients, the modified intravenous glucose-tolerance test was reproducible in 97·5% of cases (39/40).

TABLE IV. REPRODUCIBILITY OF MODIFIED INTRAVENOUS GLUCOSE-TOLERANCE TEST EXPRESSED IN TERMS OF PATIENT CLASSIFICATION

Patient	*Fasting value*	*2-hour value*	*Classification*	*Patient*	*Fasting value*	*2-hour value*	*Classification*
P.N.	70	69	+	R.N.*	187	187	+
	66	77			155	222	
M.N.*	125	170	+	D.M.*	142	188	+
	122	240	+		146	260	
C.S.	103	121	+	Z.K.*	108	141	+
	128	130			111	160	
F.B.M.*	90	174	+	P.G.	80	70	+
	102	160			60	72	
I.P.*	90	197	—	P.N.	89	107	+
	67	124			74	80	
S.M.	105	125	+	S.P.*	106	173	+
	97	133			108	176	
S.B.G.	75	183	+	G.C.	70	75	+
	85	196			61	83	
M.B.	75	69	+	J.A.K.	97	84	+
	66	72			111	104	
S.M.	167	202	+	R.M.	92	93	+
	95	170			93	84	
K.B.	75	86	+	T.M.	78	70	+
	70	125			70	56	
L.P.	109	109	+	M N.	67	70	+
	85	98			86	75	
B.N.	96	83	+	B.D.	50	118	+
	78	96			84	130	
B.S.	115	100	+	F.M.	85	85	+
	75	75			84	78	
T.N.	63	63	+	A.M.	78	80	+
	100	120			78	72	
A.R.	75	92	+	A.L.	70	84	+
	92	90			78	65	
P.D.	75	112	+	S.A.	85	92	+
	66	135			78	95	
H.B.S.	107	108	+	R.M.	73	90	+
	93	65			90	107	
A.M.	66	82	+	E.N.	81	85	+
	83	83			85	85	
C.B.	105	183	+	M.B.*	115	210	+
	90	193			103	166	
C.M.	69	80	+	C.G.	61	83	+
	60	72			72	66	

* Diabetic.
+ = correct; — = incorrect classification.

DISCUSSION

Advantages of the Modified Glucose-Tolerance Test

Modified intravenous and standard oral glucose-tolerance tests were conducted on the same patients under similar standardized conditions, as it was hoped to correlate the results of the intravenous technique with the generally accepted oral method.

The results of this study have indicated that there is no statistical difference between the mean values of the oral and intravenous techniques when performed within a period of one week on the same patients. However, the intravenous method has a number of advantages, in that it is now possible to assess the individual response to a predetermined stimulus, calculated so as to vary with the patient's weight, and infused over a fixed period of time at a constant rate. Furthermore, the unpredictable and variable absorption of glucose from the gastro-intestinal tract is excluded, while patients are not required to drink large amounts of nauseating glucose solutions.

It might be suggested that the direct infusion of large amounts of carbohydrate during pregnancy would result in overstimulation of the already taxed pancreas. If this were so, one would expect an abnormal response in a high proportion of the controls. This did not occur, as only 4 of the 100 non-diabetic pregnant controls responded with postprandial blood-sugar values of 150 mg./100 ml. or more, while the comparable number for the oral test was 5.

Kyle[19] has stated that the normal blood-sugar levels following the rapid intravenous test 'may result from such an excessive release of insulin, that the placental degradation system is overwhelmed'. It was for this reason that the dose (0·5 G/kg. body-weight) and duration of infusion were chosen, since the rate of absorption of glucose closely approximates this figure.

It is therefore reasonable to conclude that the healthy, non-diabetic, pregnant subject is able to metabolize 0·5 G of carbohydrate/kg. of body-weight when infused intravenously over a period of one hour, and that values of 150 mg./100 ml. or more are indicative of an abnormal response.

It is hoped that the value of this work will be considerably enhanced when used for the detection of prediabetics and diabetics, particularly when simultaneous serum immunoreactive insulin studies are incorporated. Thus, Soeldner[20] stated recently that the depressed serum immunoreactive response of prediabetics was more marked following intravenous than oral, or cortisone-primed, glucose-tolerance tests.

Sensitivity and Specificity

Wilkerson and O'Sullivan,[21] in a study based on the 100-G oral glucose-tolerance test, concluded that the values obtained 2 hours after glucose administration reflected abnormal glucose tolerance most favourably, as they had a 95·8% sensitivity and a 94·6% specificity. Similar results were recorded by others.[22] By comparison, therefore, the reliability of the modified intravenous glucose-tolerance test is comparable, since the degree of sensitivity recorded was 97% and that of specificity 95·5%.

Reproducibility

The modified intravenous glucose-tolerance test also compares favourably with the standard oral test in reproducibility. Thus, West *et al.*[23] noted that the mean intra-individual difference between the 2-hour values of their subjects when tested by the oral route was 18 mg./100 ml.

This conforms to the general pattern of other workers[18,24,25] in this field and it can be concluded that variations in the 2-hour blood-glucose levels exceeding 20 mg./100 ml. can be expected in almost half of the instances when oral glucose-tolerance tests are repeated.[23] With variations of this magnitude it is difficult to interpret with any degree of confidence single glucose-tolerance tests that show abnormalities which are not extreme.[6] It

has therefore been suggested[23] that a fairly broad range of values be used in the interpretation of borderline results. The mean intra-individual difference of the modified intravenous glucose-tolerance test was 14·8 mg./100 ml. In our series, only 30% of the subjects had mean differences of 20 mg./100 ml. or more at the 2-hour level, while 35% had values above the mean difference in the fasting state.

Although West *et al.* found the correlation coefficient to be almost identical in patients with different grades of carbohydrate tolerance,[23] the variability is usually more pronounced at the upper levels of glucose tolerance. Individuals with high blood-sugar levels may, however, have low variability, and those with low levels have high variability.[6] The mean intra-individual difference of blood sugar in the 11 diabetics in the present series was 30·5 mg./100 ml. as compared with a difference of only 14·5 mg./100 ml. in the controls. Thus 54·4% of diabetics were found to have wide variability in glucose tolerance, whereas the same was true for only 24·1% of the subjects with normal to borderline tolerance.

The lowest degree of variability in the series of McDonald *et al.*[6] was in those men who had had greater physical activity, and it is therefore possible that the reproducibility of the modified intravenous test would have been greater in ambulatory Natal Indian controls.

Since no statistical difference in reproducibility was found when age, weight and race were compared,[6] these factors were not analysed in the present series. The mean age and parity of the diabetic and control groups were comparable.

It may therefore be concluded that the modified intravenous glucose-tolerance test has, if anything, a smaller degree of error in reproducibility than the standard oral glucose-tolerance test, particularly in those patients with normal or borderline carbohydrate metabolism.

Disadvantages of the Modified Glucose-Tolerance Test

The minor practical disadvantge of this test is that it is somewhat cumbersome—the patient has an intravenous drip and is therefore immobilized for an hour, and closer nursing supervision is required.

The main disadvantage is that it is unphysiological, since the important factors associated with the absorption of glucose from the bowel are excluded. For example, McIntyre *et al.*[26] and others[27,28] have shown that the serum insulin response to orally administered glucose is greater than stimulation by intravenous infusion. But the cortisone-augmented tests as advocated by Fajans and Conn[29] are also unphysiological, yet preliminary studies have indicated that they are of value in the detection of prediabetics.

It is hoped that the modified intravenous glucose-tolerance test will serve the same purpose, and that, together with serum insulin studies, the prediabetic pregnant patient will be unmasked earlier and so allow for preventive therapy.

SUMMARY

An originally devised intravenous glucose-tolerance test is described, based on the infusion of 0·5 G of glucose/kg. bodyweight, over the period of 1 hour. Blood-sugar levels of 150 mg./100 ml. or more at 1 hour after completion of the infusion are indicative of abnormal carbohydrate tolerance.

Oral glucose-tolerance tests performed in the same patients were found to correlate closely with the results of the intravenous method, in both normal controls and established diabetics.

The modified intravenous glucose-tolerance test was found to be as reliable as the oral glucose-tolerance test when compared in terms of sensitivity, specificity and reproducibility.

The value of this method is discussed with particular reference to its use as a test together with serum insulin studies for the detection of prediabetics.

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