Effect of Intravenous Tolbutamide in Juvenile Diabetes Mellitus

Ross de Belle, B.Sc., Mimi M. Belmonte, M.D., F.R.C.P.(C.), and Eleanor Colle, M.D., Montreal

SUMMARY

Intravenous tolbutamide was administered to three groups of children with diabetes mellitus: (A) those with newly diagnosed disease, (B) those diabetic for less than two and one-half years, and (C) those diabetic for more than three years. Children in Groups A and B were found to respond to tolbutamide with a drop in blood glucose which differed from the response of normal children in that it was slow in onset and persisted throughout a three-hour period of observation. Children in Group C were unresponsive to tolbutamide. Children in Groups A and B showed an interference with the expected starvation-induced rise in nonesterified fatty acids over the period of observation, while children in Group C showed gradually increasing levels. The effect of tolbutamide on nonesterified fatty acids was less striking and showed more individual variation than did the effect on blood glucose. A few children with early diabetes mellitus developed hypoglycemia which appeared resistant to the usual counter-regulatory mechanisms. The fall in blood glucose was not accompanied by increased levels of insulin in peripheral blood. DIABETES *16*:215-18, April, 1967.

Tolbutamide will induce a drop in blood glucose in children with diabetes mellitus of recent onset. The magnitude of the response diminishes during the early period of the disease and after three years is no longer elicited.[1] During the period of responsiveness, the drop in blood glucose that follows tolbutamide administration differs from that seen in healthy children and adults in that the decline is slow and the nadir reached only after several hours. The slow decline of blood glucose is also seen in patients with "maturity-onset" diabetes, in whom the administration of tolbutamide produces, in addition, a decrease in the level of nonesterified fatty acids. Following tolbutamide administration to normal individuals there is also a fall in nonesterified fatty acids, the nadir occurring within fifteen to thirty minutes after administration of the drug. There is generally a rebound, presumably as a part of the response to hypoglycemia, and levels at two to three hours are often greater than the fasting level.[2,3] Prolongation of starvation in normal individuals, without administration of tolbutamide, results in a continued rise in the nonesterified fatty acid level.[4]

Tolbutamide will produce increases in the level of peripheral vein insulin in normal individuals,[5] although these levels are less than those produced by glucose administration. Studies using insulin-responsive pentoses and 2-deoxyglucose, as well as observations on hypophysectomized and adrenalectomized animals have provided strong evidence that the initial fall in blood glucose in response to sulfonylurea administration is not accompanied by an accelerated utilization of glucose by extrahepatic peripheral tissues or by increased insulin-like activity.[6]

The present study was undertaken, first, to reinvestigate the period of responsiveness in the early stages of diabetes mellitus and, second, to examine the behavior on nonesterified fatty acids and peripheral insulin levels in relationship to blood glucose changes.

MATERIALS AND METHODS

The children studied were either attending a camp for diabetic children or were patients admitted to hospital for initial control of diabetes mellitus. Children studied at the onset of disease were given tolbutamide before treatment was instituted. Children controlled with insulin received no long-acting insulin for forty-eight hours and no crystalline insulin for eight hours prior to testing. All tests were done after a twelve-hour fast. Baseline glucose and nonesterified fatty acids were analyzed at ten, five and one minute before intravenous injection of tolbutamide (20 mg. per kilogram body weight to a maximum dose of 1.0 gm.). Blood glucose was measured by the glucose oxidase method,[7] nonesterified fatty acids by the method of Dole,[4] and insulin by the method of Berson and Yalow.[8] All determinations were done in duplicate.

From the Montreal Children's Hospital and the Department of Pediatrics, McGill University, Montreal, Quebec.

RESULTS

Effect on blood glucose

Results are presented in table 1 and figure 1. All children tested at the onset of disease (Group A) had a drop in blood glucose which was slow in onset and persisted throughout the test period. No return of blood glucose levels to fasting values was observed despite low values at two and three hours in some children (cases 1 and 4). Children in Group B (duration of diabetes less than two and one-half years) likewise showed a drop in blood glucose similar in magnitude and timing to that seen in the children in Group A. Differences between Group A and Group B were not considered significant except at the thirty-minute point (p at thirty minutes $< .05$; at sixty minutes $< .200$; 120 minutes $< .10$). Only one child in this group (case 16) failed to show a fall in blood glucose levels. The children comprising Group C (duration of diabetes greater than three years) failed to show a significant drop in blood glucose over the period of observation in most cases. One child with diabetes mellitus of ten years' duration did, however, manifest a drop in blood glucose of 20 per cent below fasting level (a drop of 60 mg. per 100 ml.).

Effect of nonesterified fatty acids

Results are presented in table 1 and figure 2. All of the children in Group A had a slight depression of nonesterified fatty acids at the thirty-minute sampling.

TABLE 1

Patient number	Age (years)	Duration of diabetes	Fasting glucose (mg. per 100 ml.)	Glucose Per cent change from fasting 30′	60′	120′	180′	Fasting NEFA (mEq./L.)	NEFA Per cent change from fasting 30′	60′	120′	180′
1.	4	Onset	83	—15	—24	—50	—59	1.770	— 6	19	30	48
2.	8	Onset	197	—16	—22	—54		1.170	—13	2	13	
3.	16	Onset	162	— 8	—12	—44						
4.	9	Onset	101	—23	—28	—44						
5.	6	Onset	288	— 7	—13	—26		2.050	—15	— 0	— 9	
6.	10	Onset	330	—11	—18	—27	—26	2.500	—36	—51	—31	—18
7.	14	Onset	300	— 2	— 3	— 8	— 9	2.013	—40	—38	—29	—18
8.	11	Onset	224	— 3	—10	—27		1.749	— 6	11	6	
		Mean	210.6	—10.6	—17.4	—35.0		1.874	—19.3	— 9.5	— 3.3	
		S.E.M.		2.5	2.8	5.8			6.1	11.5	9.6	
9.	7	6/12	87	—10	—31	—54	—61	1.720	—24	—17	—18	— 7
10.	16	8/12	108	— 9	—16	—33	—44	1.055				
11.	8	5/12	116	— 4	— 5	—31	—44	.910	— 1	—13	—17	0
12.	13	11/12	110	—13	—18	—37	—50	1.055	—12	6	12	72
13.	11	4/12	134	— 7	—18	—30	—42	1.105	— 4	—11	4	50
14.	13	4/12	265	— 3	— 4	— 9	—13	1.533	40	12	50	50
15.	9	9/12	205	0	— 9	—10	—21	.925	— 3	—19	8	—13
16.	12	1	200	14	22	25	15	1.570	—33	—26	—18	2
17.	14	2-3/12	249	— 6	— 8	—13	—19	1.645	— 1	1	13	16
18.	16	2-6/12	222	0	— 4	—13	—24	1.600	— 8	—22	—14	13
19.	14	2	170	0	— 4	— 9	—24	1.284	—13	—10	24	8
20.	13	1-6/12	342	— 3	—14	—19	—31	1.210	4	13	0	— 2
		Mean	184	— 3.4	— 9.2	—19.4	—30.2	1.323	— 6.2	—10.2	4.9	17.2
		S.E.M.		2.0	3.6	5.7	5.8		5.5	3.1	6.3	8.3
21.	16	14	152	3	9	12	5	1.525	— 2	10	17	36
22.	13	9	210	0	1	— 6	— 9	1.445	10	8	7	0
23.	12	9	320	0	2	1	— 2	2.000	0	2	16	25
24.	13.5	8	305	— 3	0	— 5	— 8	1.460	10	16	23	47
25.	10	7	334	0	7	— 5	— 3	2.440	0	16	50	52
26.	14	6	360	2	— 3	— 4	—11	2.445	2	8	4	30
27.	12	7	157	5	23	30	36	1.275	—20	—10	— 3	13
28.	12	5	279	1	1	— 4	— 7	1.570	— 4	18	44	27
29.	11	6	308	0	— 4	—10	—11	2.405	—12	— 2	31	14
30.	16	11	314	2	2	2	— 2	1.065	4	1	42	70
31.	11	10	300	— 4	— 5	—13	—20	2.000	— 1	— 3	3	47
32.	12	3	142	2	33	39	48	1.015	— 3	23	43	64
33.	7	3-5/12	215	0	— 1	1	— 4	1.600	4	13	29	37
34.	10	3-10/12	195	14	14	11	11	1.120	3	5	6	11
		Mean	256.5	1.1	5.6	3.5	1.6	1.726	6	7	2.2	33
		S.E.M.		1.1	2.9	4.0	5.0		2.1	1.6	2.6	6.0

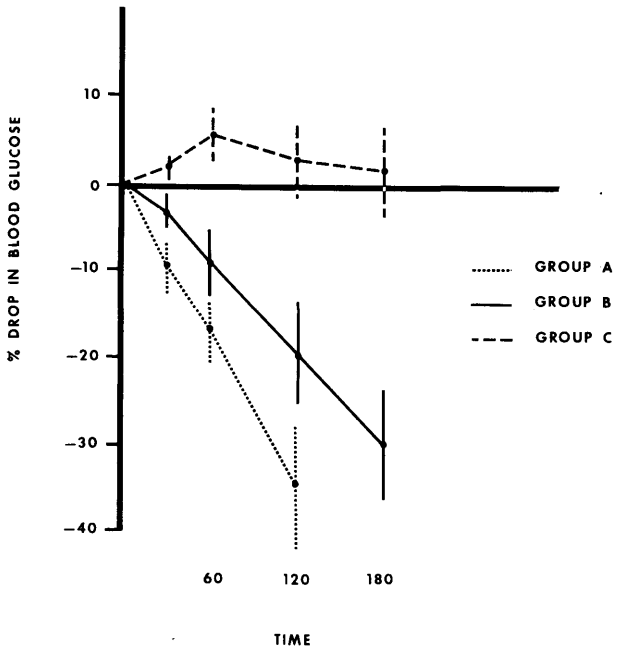

FIG. 1. Changes in the blood glucose levels (mean and S.E.M.) following the intravenous administration of tolbutamide to three groups of children with diabetes mellitus. Group A was tested at the onset of symptoms, Group B was tested within two and one-half years of onset of symptoms, and Group C had been diabetic for more than three years.

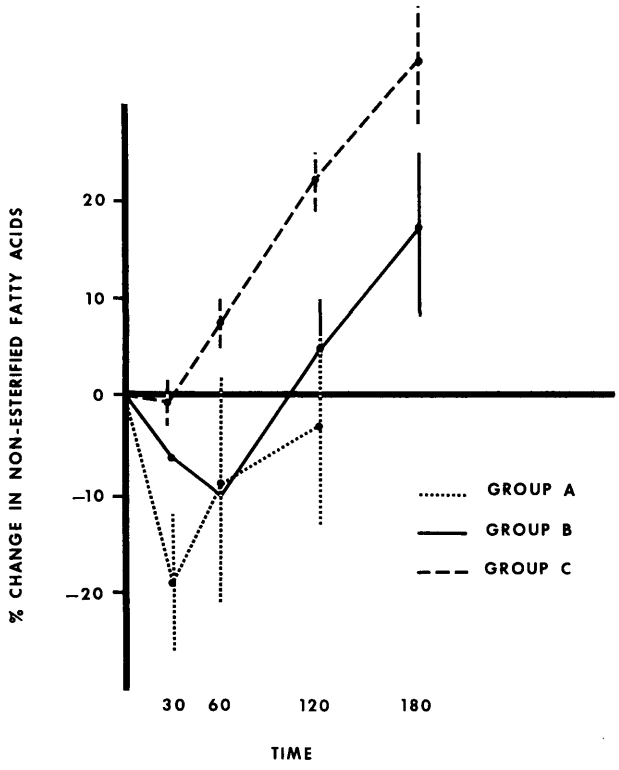

FIG. 2. Changes in the nonesterified fatty acid levels in plasma (mean and S.E.M.) following the intravenous administration of tolbutamide to three groups of children with juvenile diabetes mellitus. Group A was tested at the onset of symptoms, and Group B was tested within two and one-half years of onset of symptoms. Group C had been diabetic for more than three years.

In two, the depression was prolonged below the baseline throughout the testing (cases 6 and 7), and in one case (case 1), in whom low levels of glucose occurred, there was a marked rise. In the others, values remained around baseline. In Group B the responses were likewise mixed. In Group C there was a transient drop in one child at thirty minutes, but the majority exhibited continually increasing levels over the period of the test.

Effect on insulin levels

Peripheral levels of insulin could be assayed only in those children who had never received insulin. The results are presented in table 2. In general, the values were either low or undetectable and no significant rise was seen with the administration of tolbutamide.

TABLE 2

Patient number	Insulin μU./ml. Fasting	30′	60′	120′	180′
1	9	10	11	11	—
2	0	14	6	0	—
5	12	—	0	0	—
6	0	0	0	0	0
7	0	11	8	0	0
8	20	22	22	20	—

DISCUSSION

The fall in blood glucose of the children in Groups A and B is significantly different from that of those in Group C. It differs from the response seen in normal children and adults in that the drop is slow, prolonged, and reaches its lowest point three hours after administration of the drug. In addition, compensatory mechanisms to return blood sugar to the normal range were apparently ineffective in those children in whom hypoglycemia was produced (cases 1, 9 and 12). The response is similar to that seen in maturity-onset diabetics.[2]

The response of the nonesterified fatty acids is more variable. All of the observed decreases in nonesterified fatty acids were small but, whereas prolongation of the fasting state produced a steady increase in nonesterified fatty acids in the nonreacting Group C, interference with this rise is seen in Groups A and B. There is, therefore, evidence of some peripheral insulin action in Groups A and B. In general, however, the results

are less striking than those reported for maturity-onset diabetics in whom those individuals responding to tolbutamide with blood glucose depression also had prolonged depression of nonesterified fatty acids. The results in the juvenile diabetics here reported are consistent with the hypothesis that the blood glucose-lowering effect is caused mainly by inhibition of hepatic glucose output.

The levels of insulin in peripheral blood were low in those in whom it was measured. Since a large percentage of secreted insulin is, however, known to be trapped by the liver, it is still possible that tolbutamide-induced insulin release is responsible for the blood sugar depression in these children. Alternately, the changes in the levels of both glucose and fatty acids may be due to a direct action of tolbutamide. The persistence of hypoglycemia in three of these children is worthy of note. The evidence that tolbutamide, in addition to its effect in stimulating islet cells, influences the operation of the liver in handling insulin has been recently reviewed. A sensitization of hepatic cells to insulin effect[9] and the conversion of insulin from a bound to a free form[10] have been suggested as possibilities although confirmation of the latter has not been forthcoming.[11] Why this effect should be refractory to normal counter-regulatory mechanisms of the body remains unexplained.

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