Effect of Tolbutamide on Renal Glucose Reabsorption

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SUMMARY

In sixteen patients, thirteen examinations were carried out after intravenous administration of 1 gm. of tolbutamide, including measurements of inulin clearance and glucose T_{mG} before and after administration. Furthermore, four examinations were performed with administration of 1 gm. of tolbutamide daily over periods from fourteen days to 160 days. No alterations in inulin clearance were found. The changes in glucose T_{mG} presented fairly large individual variations and increases between 20 and 30 per cent were observed in a few patients. An average increase of 9.1 per cent was found after intravenous administration and of 4.8 per cent after oral administration. These variations are not significant. DIABETES *15*:90-92, February, 1966.

The clinical observation that after institution of tolbutamide therapy in diabetics, the urinary sugar excretion remained more or less unchanged in some cases, in spite of a suitable fall in blood sugar values, led us to suppose that tolbutamide might be capable of influencing the renal glucose reabsorption. Lee et al.[1] found a small insignificant fall in the maximal rate of tubular glucose reabsorption (T_{mG}) under the influence of carbutamide in dogs. Apparently, similar studies have not been carried out in man and not with tolbutamide.

The present investigation was undertaken to study the T_{mG} under the influence of tolbutamide, first observing the acute effect following intravenous administration and then the more prolonged effect after oral administration over periods from fourteen days to 160 days.

MATERIALS AND METHODS

The material comprises sixteen patients, six diabetics and ten patients with various diseases, but without known renal disorders and with normal renal function, all evaluated by serum creatinine determinations and urinalyses.

Table 1 presents some information about the patients.

The investigation was divided into two sections: (1) After four to eight control periods with determinations of T_{mG}, thirteen patients received intravenous injections of 1 gm. of tolbutamide (Rastinon® 5 per cent),* and measurements were then made over four to eight periods in which at least one hour was allowed to pass from the tolbutamide injection till the last T_{mG} period. (2) Three patients, all with recently discovered diabetes, not controlled by diet alone, were given a daily dosage of 1 gm. of tolbutamide by the oral route over periods from fourteen to 160 days, following control tests (and in some cases determinations after intravenous injections, as described under (1)), whereupon the patients were retested. These three patients responded adequately to the treatment, the blood sugar levels fell to normal values and the urinary sugar excretion disappeared. In one patient (No. 15), who had been on tolbutamide therapy for about one year, the T_{mG} was first determined during treatment, then tolbutamide was withdrawn for fourteen days, and the T_{mG} was again determined.

During the days prior to the examination the patients were confined to bed. The patients were on a full diet, with the exception of the diabetic subjects who were on a diet poor in carbohydrates.

Twelve hours before the investigation the patients were given 0.5 L. of water and from one to two hours before the test they got 1 L. of water. At the beginning of the test a Foley catheter with a 5 ml. balloon was introduced into the bladder. An indwelling needle was placed in each forearm, one for infusion and one for blood sampling. A single injection (priming dose) of 2 gm. of inulin was given, followed by constant inulin infusion of 40 mg. per min. in an 8 per cent solution by means of a motor pump. At the same time, drip infusion of a 20 per cent glucose solution was commenced, aimed at and maintaining a plasma glucose level of 500 to 800 mg. per 100 ml. The drip rate

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was checked photoelectrically by means of a tachometer. The arm from which the blood samples were drawn was constantly warmed by an electric heating pad.

In other respects we followed the usual procedure[2] in clearance determinations, involving emptying of the bladder followed by washing with 50 ml. of sterile water plus 50 ml. of air after each period of ten to fifteen minutes. The equilibration period was thirty to forty-five minutes. During the investigation, the urinary outputs were constantly at least 8 ml. per min. and in most cases 15 to 25 ml. per min.

Immediately after withdrawal, the blood samples were placed in a water bath at a temperature between 0 and 1° C.

The inulin-analyses were made by the method described by Bojesen.[3] On the basis of known glucose solutions, a curve was drawn of a standard optical density for the calculation of the optical density of the urine and plasma glucose and for correction of the total optical density.

The plasma glucose value was determined by the method of Hagedorn-Norman Jensen.[4] The urinary glucose value was determined by the Krarup[5] modification of this method.

The plasma concentration of inulin and glucose during the individual clearance periods was calculated as the mean value of the concentrations at the beginning and the end of the period, with a delay-time of four minutes.

The inulin clearance and the T_{mG} were calculated in the usual manner.[2] No correction for the surface area of the patient was made. The figures stated are mean values ± standard deviation. The statistical significance was calculated by Student's *t*-test for the 5 per cent significance level.

Apart from an almost intractable urethritis in a male patient, no complications occurred in connection with the examinations. Consequently, only two males are included in the material. The high concentrations of glucose were not troublesome for the diabetic subjects, and subsided in a few hours. No cases of ketoacidosis were encountered.

RESULTS

The results are presented in tables 2 and 3. No variations in the filtration, as measured by inulin clearance, were found after intravenous injection of 1 gm. of tolbutamide. The changes in T_{mG} varied between —3.5 per cent and +28 per cent. The average increase of 9.1 per cent is not significant.

On prolonged administration of tolbutamide the

TABLE 1

Data of patients

Number	Sex	Age (yrs.)	Diagnoses	Blood pressure mm. Hg.	Serum creatinine (mg./100 ml.)	Ht. (cm.)	Wt. (kg.)
1	F	65	diabetes mellitus	180/110	1.0	161	70
2	M	67	diabetes mellitus	150/90	1.1	167	84
3	F	51	hyperthyroidism	130/80	0.8	167	80
4	F	47	muscular rheumatism	120/80	0.9	163	58
5	F	23	transposition of the intestine	110/65	1.1	161	50
6	F	22	ulcer of stomach	90/60	1.0	170	60
7	F	47	colitis	110/60	0.9	157	44
8	M	19	gastroduodenitis	120/75	0.9	180	65
9	F	55	lipothymia	110/70	0.7	163	67
10	F	70	diabetes mellitus	200/100	1.4	162	68
11	F	68	muscular rheumatism	160/90	0.9	161	71
12	F	39	dyspepsia	120/80	0.8	165	53
13	F	24	malabsorption	100/70	0.8	170	51
14	F	65	diabetes mellitus	115/65	1.0	155	47
15	F	66	diabetes mellitus	170/100	1.1	161	90
16	F	63	diabetes mellitus	175/105	1.0	160	98

TABLE 2

Inulin clearance and maximal glucose reabsorption in fourteen patients who received 1 gm. of tolbutamide intravenously

	Before administration of tolbutamide		After administration of tolbutamide		Variation	
No.	Inulin clearance (ml./min.)*	T_{mG} (mg./min.)*	Inulin clearance (ml./min.)*	T_{mG} (mg./min.)*	I per cent	T_{mG} per cent
1	80±4*	201±13	79±4	197±19	— 1.3	— 2
2	104±4	210±13	98±4	222±19	— 5.8	— 5.7
3	106±10	269±50	109±6	326±31	+ 2.8	+21
4	109±8	205±11	107±8	210±10	— 2	+ 2.4
5	71±6	175±25	66±3	169±34	— 7	— 3
6	100±6	197±35	95±5	198±26	— 5	+ 0.5
7	71±5	199±39	78±2	255±10	+10	+28
8	97±2	251±6	102±6	299±21	+ 5	+14
9	93±13	203±18	98±4	190±9	+ 5	— 3.5
10	50±3	138±31	50±3	144±17	0	+ 4
11	79±3	160±15	81±2	205±19	+ 2.5	+28
12	120±5	256±41	124±4	307±35	+ 3.3	+20
13	115±3	277±20	111±7	240±44	— 3.5	+ 6
Average					+ 0.3	+ 9.1

*Mean value ± standard deviation.

TABLE 3

Inulin clearance and T_{mG} in three patients (Nos. 10, 14, and 16) who were treated over a prolonged period with 1 gm. of tolbutamide daily. As regards No. 15, cf. text.

	Before administration of tolbutamide		After administration of tolbutamide		Variation		
Number	Inulin clearance (ml./min.)*	T_{mG} (mg./min.)*	Inulin clearance (ml./min.)*	T_{mG} (mg./min.)*	I per cent	T_{mG} per cent	Number of days
10	50±3	138±31	53±4	143±13	+ 6	+ 4	28
14	51±7	113±25	54±5	149±26	+ 6	+32	160
16	97±3	236±20	97±3	224±15	0	− 5	14
15	103±9	327±30	124±4	286±14	+20	−12	—
				Average	+ 8.0	+ 4.8	

*Mean value ± standard deviation.

inulin clearance rate showed increases between 0 and 20 per cent, average 8 per cent, which is not significant. The T_{mG}-changes varied between —12 per cent and +32 per cent, average +5.7 per cent. None of these variations is significant ($P > 0.05$).

DISCUSSION

The studies on the changes in T_{mG} following intravenous injection of tolbutamide (Group 1) revealed considerable individual variations and, consequently, we made a relatively large number of determinations. The average result of this group showed no significant changes in T_{mG}, although an increase in the maximal glucose reabsorption was observed during the tolbutamide periods in a few patients.

In the four patients, in whom a possible prolonged effect of tolbutamide was studied (Group 2), no significant changes in T_{mG} were found.

Lee et al.[1] studied T_{mG} in two groups of dogs. One group received carbutamide for seventy-five days, the other group was untreated. They found that in the carbutamide-treated dogs T_{mG} averaged 249 ± 11 ml./min./m.^{2} and in untreated dogs it was 265 ± 5 ml./min./m.^{2} The creatinine clearance was unchanged. No control experiments were made, and the differences were not significant.

In man, Gutsche and Riegel[6] found equal decreases in blood sugar concentration and urinary sugar excretion after carbutamide treatment and concluded that the renal threshold is unaffected.

When studying the daily urinary sugar excretion in conjunction with the corresponding blood sugar concentration, Stowers et al.[7] found no ground for assuming that tolbutamide or carbutamide changed the renal glucose threshold significantly.

Hümmer et al.[8] found improved tubular function as measured by the phenol red excretion in carbutamide-treated and tolbutamide-treated diabetic subjects, but they did not show that any change in the glucose reabsorption could be demonstrated. However, neither Gutsche and Riegel,[6] nor Stowers et al.,[7] nor Hümmer et al.[8] determined the glucose-T_{mG}.

Thus, no evidence is presented in the literature in support of an effect on the renal glucose reabsorption by oral treatment of diabetes.

On the basis of our investigations we conclude that usually no consistent changes in the maximal renal glucose reabsorption occur from brief or prolonged administration of tolbutamide, although a slight increase has been found in a few cases. However, this latter finding will hardly be of any clinical importance.

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