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Tolbutamide does not alter insulin requirement in Type 1 (insulin-dependent) diabetes

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Summary. We examined whether tolbutamide has any acute or short-term effects on insulin action in Type 1 (insulin-dependent) diabetes. A euglycaemic glucose clamp was performed in seven Type 1 diabetic patients without clinical insulin resistance by infusing glucose at a constant rate of 0.01 mmol · kg^{-1} · min^{-1} for 3 h together with a simultaneous insulin infusion using an 'artificial pancreas'. The insulin infusion rate required to maintain blood glucose at 6.7 mmol/l at a set low glucose infusion rate provides an index of insulin action in vivo. The euglycaemic clamp was performed on 3 separate days in the same patient: (1) in the basal state; (2) during simultaneous intravenous tolbutamide infusion of 0.5 g/h, and (3) after treatment with 2.5 g tolbutamide/day for 6 days in addition to insulin. The insulin infusion rate needed to maintain the set blood glucose level did not differ significantly between the three experimental conditions (1.2 ± 0.2 versus 1.3 ± 0.3 versus 1.2 ± 0.3 U/h). Plasma glucagon, growth hormone, non-esterified fatty acid and glycerol levels did not differ between control or sulphonylurea treatment studies. The results suggest that tolbutamide does not exert any acute or short-term effects on insulin action in vivo in Type 1 diabetes. Our results do not provide support for the idea that this agent is a clinically useful adjunct to insulin in such patients.

Key words: Tolbutamide, insulin, euglycaemic glucose clamp, β cell, Type 1 diabetes.

The extra-pancreatic effects of sulphonylureas have been reviewed extensively [1, 2]. Potentiation of insulin action after sulphonylurea treatment has been described in dogs [3] and Type 2 (non-insulin-dependent) diabetes [4–6]. Conversely, other studies in-vivo and in-vitro failed to confirm the effect of sulphonylureas on insulin-mediated glucose uptake or insulin receptor binding [7–14].

Resistance to the hypoglycaemic effect of insulin in non-obese, Type 2 diabetic subjects and patients with impaired glucose tolerance has been documented with a variety of techniques [15–18]. More recently, impaired insulin action in Type 1 diabetes has been demonstrated, using the somatostatin modification of the quadruple infusion technique [15] or the euglycaemic insulin clamp technique [19]. Both hepatic and peripheral resistance to the action of insulin may contribute to hyperglycaemia in Type 1 diabetes [20], although it is well known that insulin receptor binding is either normal or somewhat above normal in this condition [10, 21]. Since sulphonylurea compounds can alter post-receptor insulin action [22], this study examined whether tolbutamide exerts any acute or short-term effects on insulin action in Type 1 diabetes.

Subjects and methods

Subjects

Seven male non-obese Type 1 diabetic patients, aged 20–46 years were studied (Table 1). All were admitted to the hospital to improve their diabetic control. They were all ketosis-prone and insulin-dependent since diagnosis. None had any other illness or nephropathy. Background retinopathy was present in four patients, and two had neuropathy. None was taking any drugs other than insulin. Four patients had no significant endogenous insulin secretion (fasting C-peptide levels < 0.08 nmol/l), whereas three had fasting C-peptide concentrations between 0.09 and 0.41 nmol/l (Table 2). Informed consent was obtained after fully explaining the purpose and nature of the study. These studies were approved by the local Ethical Committee.

Assessment of insulin sensitivity in vivo

An euglycaemic glucose clamp was performed by means of a glucose controlled insulin infusion system (Biostator, Life Science Instruments, Elkhart, Indiana, USA). Carbohydrate metabolism was well controlled by four injections of soluble insulin before the study. On the day of the experiment, the patients received their last injection of soluble insulin at 02.00 h. After an overnight fast, patients were connected to the Biostator at 07.00 h. After a 30 min control period, the computer was programmed to achieve a blood glucose level of 6.7 mmol/l (static plus dynamic control of insulin infusion). Fasting hyperglycaemia (ranging from 8–12 mmol/l) was rendered normal by the glucose-controlled insulin infusion and the pre-programmed blood glucose concentration of 6.7 mmol/l was achieved within 2 h. After an additional 30 min period in which the pre-programmed blood glucose level of 6.7 mmol/l was maintained, an intravenous glucose infusion of 0.01 mmol · kg body weight^{-1} · min^{-1} was given for 3 h. The plasma glucose concentration was determined every minute and the mean steady-state glucose concentration was calculated for every hour of the glucose insulin infusion.

Using the euglycaemic glucose-clamp technique, the rate of exogenous insulin infusion was adjusted by the Biostator to maintain normoglycaemia with a set low glucose infusion rate. The insulin infusion rate needed to maintain the pre-programmed steady-state plasma glucose level provides a measure of insulin action in vivo. We have assumed that the insulin requirement reflects tissue sensitivity to insulin. We have considered the steady-state glucose concentration during the last hour of the study in order to calculate the insulin requirement. Blood samples were obtained simultaneously for the measurement of C-peptide, growth hormone, pancreatic glucagon, non-esterified fatty acid and glycerol concentrations.

Table 1. Clinical characteristics of the patients studied

Patients	Age (years)	Duration of diabetes (years)	Body weight (kg)	Relative body weight (%)	Insulin requirement	
					(U/day)	($U \cdot kg^{-1} \cdot day^{-1}$)
1	41	22	70.0	104	68	0.97
2	20	10	57.5	98	46	0.80
3	22	5	77.8	105	38	0.48
4	20	7	74.3	102	42	0.56
5	46	1	50.2	95	22	0.43
6	36	9	80.6	98	40	0.49
7	38	8	77.0	101	30	0.38
Mean ± SEM	31.9 ± 4.1	8.9 ± 2.5	69.6 ± 4.3	150 ± 1.3	40.8 ± 5.4	0.59 ± 0.08

Table 2. C-peptide values during an infusion of glucose (0.01 $mmol \cdot kg^{-1} \cdot min^{-1}$) controlled by the 'Biostator' in six Type 1 diabetic patients

	Patients	C-peptide (nmol/l) at time (min)								
		0	10	20	30	60	90	120	150	180
Control study	1	0.03	0.03	0.02	0.03	0.03	0.03	0.03	0.03	0.03
	2	0.03	0.03	0.03	0.03	0.04	0.03	0.03	0.03	0.03
	3	0.13	0.11	0.11	0.12	0.13	0.15	0.14	0.13	0.13
	4	0.02	0.01	0.02	0.02	0.03	0.03	0.03	0.03	0.03
	5	0.09	0.10	0.09	0.09	0.09	0.09	0.11	0.09	0.10
	6[a]	0.41	0.50	0.50	0.60	0.80	0.78	0.74	0.68	0.64
	Mean ± SEM	0.12 ± 0.06	0.13 ± 0.08	0.13 ± 0.08	0.15 ± 0.09	0.19 ± 0.12	0.19 ± 0.12	0.18 ± 0.11	0.17 ± 0.10	0.16 ± 0.10
Intravenous infusion of 0.5 g tolbutamide/h for 3 h	1	0.02	0.01	0.02	0.01	0.01	0.02	0.01	0.01	0.01
	2	0.01	0.00	0.01	0.00	0.01	0.01	0.01	0.01	0.00
	3	0.09	0.12	0.13	0.15	0.19	0.20	0.21	0.21	0.19
	4	0.01	0.01	0.02	0.02	0.02	0.02	0.02	0.02	0.02
	5	0.18	0.10	0.09	0.11	0.14	0.12	0.13	0.13	0.12
	6	0.11	0.20	0.23	0.27	0.34	0.35	0.36	0.38	0.35
	Mean ± SEM	0.07 ± 0.03	0.07 ± 0.03	0.08 ± 0.04	0.09 ± 0.04	0.12 ± 0.05	0.12 ± 0.06	0.12 ± 0.06	0.13 ± 0.06	0.12 ± 0.06
Oral treatment with 2.5 g tolbutamide/day in addition to insulin therapy for 6 days	1	0.02	0.01	0.01	0.01	0.02	0.01	0.02	0.02	0.01
	2	0.01	0.01	0.01	0.02	0.02	0.01	0.02	0.01	0.01
	3	0.08	0.08	0.10	0.09	0.09	0.08	0.09	0.10	0.09
	4	0.03 (3)	0.04	0.04	0.04	0.04	0.04	0.04 (4)	0.03	0.04
	5	0.11	0.12	0.14	0.14	0.14	0.14	0.11	0.14	0.12
	6	0.40	0.40	0.40	0.40	0.36	0.39	0.37	0.36	0.6
	Mean ± SEM	0.11 ± 0.06	0.11 ± 0.06	0.12 ± 0.06	0.12 ± 0.06	0.11 ± 0.05	0.11 ± 0.06	0.11 ± 0.05	0.11 ± 0.05	0.15 ± 0.09

Results expressed as mean ± SEM. [a] The C-peptide values of one patient were below the detection limit of the method used

In each patient, insulin sensitivity was studied according to the following protocol on three occasions on 3 separate days: (1) insulin sensitivity was evaluated in the fasting state; (2) after 3 days, the study was repeated with a tolbutamide infusion (0.5 g/h) simultaneously with the glucose infusion; (3) all patients were treated with 2.5 g tolbutamide/day for 6 days in addition to their insulin. The patients received the last dose of 1.0 g tolbutamide before they were connected to the Biostator.

The studies were always performed in the same sequence. Each patient served as his own control. The daily treatment schedule, i.e. diet, insulin and physical activity remained unchanged during the entire study. The diet of 1800–2200 calories was divided into three meals and three snacks, each containing 50% carbohydrate, 30% fat and 20% protein of energy consumption. The body weight did not change during the study.

Analytical methods

The plasma glucose concentration was measured enzymatically (Biostator). C-peptide levels were measured after the removal of proinsulin and alcoholic extraction [23]. Growth hormone concentration was determined by radioimmunoassay [24]. Pancreatic glucagon was measured with specific antiserum R_4 which did not cross-react with porcine gut glucagon-like immunoreactivity in the physiological range [25]. Non-esterified fatty acids (NEFA) were estimated according to Duncombe [26] and glycerol concentrations according to Eggstein and Kreutz [27].

Results are presented as mean ± SEM, and the paired t-test was used for statistical analysis.

Results

Treatment with tolbutamide in addition to insulin for 6 days failed to improve glycaemic control in these Type 1 diabetic patients. The total daily insulin dose remained unchanged (41 U or 0.60 U/kg body weight), and the mean blood glucose values (mean of nine measurements in the course of 24 h) taken 1 day before

Table 3. Steady-state plasma glucose concentrations during an infusion of glucose (0.01 mmol · kg^{-1} · min^{-1}) controlled by the 'Biostator' in the control and tolbutamide treatment studies in seven Type 1 diabetic patients

	Steady-state plasma glucose concentration (mmol/l) at:		
	0–60 min	61–120 min	121–180 min
Control study	6.46 ± 0.44	6.65 ± 0.48	6.66 ± 0.42
Intravenous infusion of 0.5 g tolbutamide/h for 3 h	6.72 ± 0.47	6.63 ± 0.41	6.62 ± 0.39
Oral treatment with 2.5 g tolbutamide/day in addition to insulin therapy for 6 days	6.75 ± 0.38	6.75 ± 0.42	6.65 ± 0.44

Results expressed as mean ± SEM

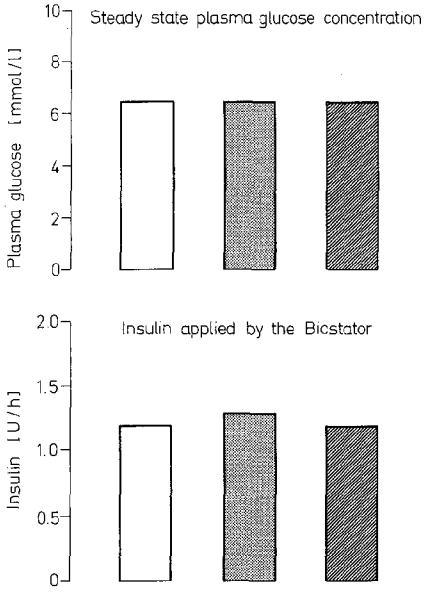

Fig. 1. Steady-state plasma glucose concentration (120–180 min) and insulin requirement during a continuous infusion of glucose (0.01 mmol · kg^{-1} body weight · min^{-1}) controlled by the 'Biostator' in seven Type 1 diabetic patients. □ = control study without tolbutamide; ▩ = combined infusion of glucose and tolbutamide (0.5 g/h); ▨ = study after treatment with 2.5 g tolbutamide/day in addition to insulin for 6 days

(7.7 mmol/l; range 5.3–10.2 mmol/l) and 6 days after sulphonylurea treatment (7.7 mmol/l; range 6.3–10.6 mmol/l) were comparable.

During the euglycaemic glucose clamp, the glucose concentration was held close to the pre-programmed level. The mean steady-state plasma glucose concentration of the entire study period (3 h) was identical in all the three experimental conditions (Table 3). We used the steady-state glucose concentration during the last hour of the study to calculate the insulin requirement. The stability of the plasma glucose concentration during the last hour of the euglycaemic glucose clamp (120–180 min) is indicated by the coefficient of variation which averaged 3.5 ± 0.5%, 4.4 ± 0.8% and 3.1 ± 1.4% on the three occasions, respectively.

The rate of insulin infusion needed to maintain euglycaemia with the set low glucose infusion was not significantly altered by acute or short-term tolbutamide treatment (Fig. 1). The mean rates of insulin infused by the Biostator during the glucose clamp were to 1.2 ± 0.2, 1.3 ± 0.3 and 1.2 ± 3 U/h, respectively. Endogenous insulin secretion was not significantly altered under the experimental conditions in the control and sulphonylurea treatment studies as indicated by C-peptide measurement (Table 2). There were no significant differences in the fasting glucagon levels at the beginning of the experiment on three separate days (Table 4). In addition, glucagon response patterns did not differ significantly between control and sulphonylurea treated patients. There were major individual variations among patients in growth hormone response as shown by the large standard deviations (Table 4). During the period of steady-state plasma glucose concentration, i.e. during the last hour of the glucose clamp, growth hormone concentration did not differ significantly between the control and the tolbutamide-treated patients (Table 4).

Mean plasma NEFA and glycerol concentrations were not significantly altered during either the glucose infusion alone or during acute or short-term tolbutamide treatment. In addition, the plasma NEFA and glycerol levels did not differ between the control and the sulphonylurea treatment studies (Table 4).

Discussion

Over the past 15 years, several studies have dealt with the question of whether sulphonylureas exert an extrapancreatic effect. Potentiation of insulin action on various tissues by sulphonylureas has been described [22, 28–33]. Several reports indicate that these drugs increase the number and/or affinity of insulin receptors [4, 34–36]. Conversely, other workers have been unable to demonstrate the effectiveness of sulphonylureas in vitro on insulin receptor binding in rat adipocytes [22], human fibroblasts, lymphocytes, mammary carcinoma cells, and rat hepatocytes [37, 38]. In addition, other authors have shown that various sulphonylureas have no acute or short-term effects on insulin action in vitro [8, 9, 11, 12, 37].

Our short-term study with tolbutamide in addition to insulin demonstrated neither improved glycemic control nor altered insulin requirement in Type 1 diabetes. Thus, we were unable to show that this agent is a clinically useful adjunct to insulin in this condition. In agreement with our findings, Grunberger et al. [10] and Ward et al. [13] failed to demonstrate any additive effect of sulphonylurea treatment to insulin on the control of blood glucose in Type 1 diabetic patients.

In accordance with these clinical observations, our findings demonstrate that tolbutamide does not exert any acute or short-term effects in augmenting the efficacy of insulin action in vivo in Type 1 diabetes. In the present study, we compared the insulin requirement for a pre-programmed low glucose infusion rate with a eu-

Table 4. Plasma glucagon, growth hormone, NEFA and glycerol responses during a fixed rate of glucose infusion controlled by the 'Biostator' in seven Type diabetic patients

		Time (min)									
		0	10	20	30	60	90	120	150	180
Control study	Plasma glucagon (pmol/l)	10.2 ± 2.3	10.7 ± 0.9	8.5 ± 1.8	8.3 ± 1.7	8.3 ± 1.9	7.8 ± 1.7	8.5 ± 1.7	6.7 ± 1.2	7.5 ± 1.3
	Growth hormone (nmol/l)	0.17 ± 0.11	0.13 ± 0.07	0.12 ± 0.07	0.08 ± 0.03	0.06 ± 0.01	0.10 ± 0.04	0.22 ± 0.19	0.26 ± 0.10	0.28 ± 0.10
	NEFA (mmol/l)	0.27 ± 0.10	0.25 ± 0.08	0.25 ± 0.08	0.28 ± 0.03	0.28 ± 0.09	0.31 ± 0.07	0.31 ± 0.08	0.32 ± 0.10	0.39 ± 0.11
	Glycerol (µmol/l)	49.5 ± 9.4	49.7 ± 8.9	58.8 ± 13.1	52.2 ± 9.1	48.3 ± 4.5	56.5 ± 10.1	54.8 ± 14.6	78.8 ± 12.5	61.8 ± 17.4
Intravenous infusion of 0.5 g tolbutamide/h for 3 h	Plasma glucagon (pmol/l)	10.3 ± 1.3	9.3 ± 1.4	10.9 ± 2.1	11.2 ± 1.9	10.5 ± 1.4	10.1 ± 1.9	10.6 ± 1.4	10.7 ± 1.8	11.5 ± 1.9
	Growth hormone (nmol/l)	0.21 ± 0.12	0.18 ± 0.07	0.35 ± 0.17	0.32 ± 0.17	0.36 ± 0.20	0.37 ± 0.15	0.37 ± 0.18	0.39 ± 0.14	0.35 ± 0.13
	NEFA (mmol/l)	0.31 ± 0.03	0.33 ± 0.04	0.33 ± 0.04	0.31 ± 0.05	0.33 ± 0.07	0.31 ± 0.06	0.35 ± 0.09	0.30 ± 0.06	0.32 ± 0.06
	Glycerol (µmol/l)	65.8 ± 15.8	67.1 ± 23.8	48.8 ± 4.4	62.0 ± 9.5	49.6 ± 8.1	54.6 ± 5.1	59.6 ± 12.7	56.6 ± 6.3	51.2 ± 8.9
Oral treatment with 2.5 g tolbutamide/day in addition to insulin therapy for 6 days	Plasma glucagon (pmol/l)	13.8 ± 1.1	10.5 ± 1.7	12.3 ± 1.5	11.2 ± 1.6	10.7 ± 1.6	11.8 ± 2.5	9.9 ± 1.0	9.0 ± 0.7	9.1 ± 1.9
	Growth hormone (nmol/l)	0.29 ± 0.06	0.16 ± 0.04	0.35 ± 0.23	0.39 ± 0.29	0.35 ± 0.28	0.35 ± 0.25	0.32 ± 0.11	0.38 ± 0.21	0.33 ± 0.18
	NEFA (mmol/l)	0.33 ± 0.14	0.39 ± 0.15	0.41 ± 0.16	0.30 ± 0.07	0.27 ± 0.08	0.22 ± 0.07	0.32 ± 0.09	0.36 ± 0.09	0.33 ± 0.08
	Glycerol (µmol/l)	61.8 ± 17.2	57.6 ± 13.6	58.1 ± 12.0	47.3 ± 6.1	43.0 ± 14.7	60.6 ± 15.5	73.4 ± 6.7	88.8 ± 21.4	87.0 ± 19.1

Results expressed as mean ± SEM

glycaemic glucose clamp before and during acute and short-term tolbutamide treatment. We assumed that the insulin infusion rate under the experimental conditions reflected insulin sensitivity. Thus, the insulin requirement needed to maintain a pre-programmed steady-state plasma glucose concentration was used as a rough index of the body's sensitivity to insulin.

Studies using a priming-constant 3-H^3-glucose tracer infusion have shown that hepatic glucose production is markedly, but not totally, suppressed during a superimposed low glucose infusion of 0.01 $mmol \cdot kg^{-1} \cdot min^{-1}$ in healthy subjects and patients with diminished insulin response [39]. Our previous studies [6, 40, 41] and other investigations [42–44] have shown that an insulin infusion in the range used in the present study resulted in a mild degree of physiological hyperinsulinaemia. Since the peripheral utilization of glucose is augmented during the low glucose load [39], we assume that insulin acts both on hepatic glucose production and peripheral glucose uptake under the current experimental conditions. The present experiments do not differentiate whether tolbutamide exerts any effect on insulin-mediated suppression of hepatic glucose production or tissue glucose uptake. However, our approach provides a means of comparing the efficacy of insulin action in vivo before and after tolbutamide treatment. Endogenous insulin secretion, and hormonal and metabolic insulin antagonist levels, such as pancreatic glucagon, growth hormone and NEFA, were not significantly altered by acute or short-term tolbutamide treatment under these experimental conditions.

The failure to demonstrate any acute or short-term extra-pancreatic effects of tolbutamide in Type 1 diabetic patients is in agreement with reports on forearm insulin-mediated glucose uptake in normal and diabetic man [7, 14]. Grunberger et al. [10] demonstrated similar results. Short-term treatment with sulphonylureas in addition to insulin in Type 1 diabetic patients did not alter insulin binding to circulating monocytes or erythrocytes.

We conclude that tolbutamide does not exert any acute or short-term effect on the efficacy of insulin action in vivo in Type 1 diabetes. Our results do not provide support that this agent is a clinically useful adjunct to insulin in Type 1 diabetes.

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