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Depressed Tolbutamide-Induced Insulin Response in Subjects Treated with Propranolol*

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Summary. The effect of propranolol on 1 g i.v. tolbutamide-induced insulin response was studied in 11 subjects. The drug depressed this response, the effect being more noticeable in the patients receiving 200 mg/day *per os* for three days. The corresponding blood glucose curves, however, were unaffected by propranolol. The finding suggest that the beta-receptors play a part in sulphonylurea-induced insulin secretion in man.

Réduction de la libération de l'insuline produite par la tolbutamide chez des patients traités par propranolol

Résumé. Les Auteurs ont examiné chez l'homme (11 patients) l'effet du propranolol sur la libération de l'insuline produite par la tolbutamide (1 g par voie endoveineuse). Les résultats montrent que le propranolol réduit l'augmentation de l'insulinémie due à la tolbutamide. Ce phénomène est plus évident chez les patients traités par des doses de 200 mg per os, par jour, pendant trois jours de suite. D'autre part, les courbes glycémiques correspondantes ne sont pas modifiées significativement par cette administration de propranolol. Ces observations suggèrent que chez l'homme les bêta-récepteurs jouent un rôle dans les mécanismes de libération de l'insuline produite par les sulphonylurées.

Herabsetzung der durch Tolbutamid verursachten Insulinsekretion bei mit Propranolol behandelten Patienten

Zusammenfassung. Die Verfasser untersuchten bei 11 Patienten die Wirkung von Propranolol auf die durch 1 g intravenös verabreichtes Tolbutamid verursachte Insulinsekretion. Die Ergebnisse zeigen, daß Propranolol die Zunahme der durch Tolbutamid verursachten Insulinämie vermindert und dies ganz besonders bei jenen Patienten, welche mit Dosen von 200 mg per os pro Tag an 3 aufeinanderfolgenden Tagen behandelt wurden. Die entsprechenden Glycämiekurven wurden jedoch durch Propranololverabreichung nicht bedeutend verändert. Diese Befunde deuten darauf hin, daß beim Menschen die Beta-Receptoren bei der durch Sulphonylurea verursachten Insulinsekretion eine Rolle spielen.

Key-words: Tolbutamide, plasma insulin, propranolol.

In man, stimulation of beta-adrenergic and alpha-adrenergic receptors increases blood insulin levels and inhibits secretion respectively [10, 11]. Beta-receptors seem also to be involved in glucose- [3] but not in glucagon-induced [10] insulin release mechanisms. The present paper investigates the effect of propranolol, a beta-receptor blocking substance on the insulin response to tolbutamide.

Materials and Methods

Following an overnight fast, 5 normal and 2 slightly obese women and 4 normal men, aged from 23 to 48 yr (some with small non-toxic goitres) on a diet containing at least 200 g carbohydrate per day were subjected at 9 a.m. to 2 tests at three-day-intervals. In the first test, 1 g tolbutamide (Rastinon diagnostic test, Hoechst) was given i.v. in one minute; in the second, tolbutamide was preceded by propranolol (Inderal, I.C.I.) according to two modalities:

1. 5 subjects received 200 mg/day orally for three days in 4 administrations; the last tablet was given 1 h before tolbutamide.

2. 6 patients received 10 mg propranolol in 100 ml saline solution i.v. in 10 min before the tolbutamide (in the first test, these subjects received the 100 ml saline solution only).

For blood sugar (method of Somogyi & Nelson [9]) and plasma insulin (radio-immunological method: CEA CEN Sorin kit) determination specimens were withdrawn immediately before and 2′, 5′, 15′, 30′, 45′ and 60′ after the commencement of the tolbutamide injection; with i.v. propranolol, the 5′ withdrawal was not done. Plasma insulin determinations for the two tests were made simultaneously for the same subject.

Results

Basal insulin values were not influenced by propranolol (Tables 1, 2).

Oral propranolol (200 mg/day) was always followed by a marked reduction in insulin response to tolbutamide in the first 15 min (Table 1, Fig. 1), with a mean curve depression that was significant at 5′ and 15′ ($P < 0.05$, paired t-test).

* Part of this study has been presented at the 3th Congress of Italian Association for the study of Diabetes (Modena, Aprile 1970), and accepted in abstract form (by title) at the 7th Congress of the International Diabetes Federation.

Table 1. *Blood glucose and plasma insulin response to tolbutamide before and after oral 200 mg/day propranolol for three days*

Case	Name age sex	before							after						
		B.	2′	5′	15′	30′	45′	60′	B.	2′	5′	15′	30′	45′	60′
		Blood Glucose mg/100 ml													
1	B.A.M.[a] 30 F	90	90	87	79	55	52	58	93	93	93	82	61	55	67
2	B.A. 44 F	85	79	82	72	61	49	52	93	87	87	79	61	52	61
3	N.G. 23 M	90	87	90	61	31	54	73	87	82	85	72	48	49	64
4	E.M. 35 F	87	90	87	79	58	55	61	85	83	83	79	55	54	63
5	C.S.G.[a] 42 F	93	90	90	85	61	58	73	93	90	87	82	67	67	70
	Mean ± S.E.M.	89 ± 1.37	87 ± 2.13	87 ± 1.46	75 ± 4.10	53 ± 5.66	53 ± 1.50	63 ± 4.17	90 ± 1.74	87 ± 2.07	87 ± 1.67	78 ± 1.82	52 ± 3.21	55 ± 3.07	65 ± 3.53
		Plasma Insulin μU/ml													
1[a]		57	302	188	176	110	73	76	44	128	121	141	87	53	80
2		36	98	140	120	54	52	32	30	35	102	62	60	42	28
3		38	177	164	124	59	58	41	36	78	148	102	46	42	43
4		34	102	164	114	62	56	64	38	90	70	80	50	46	45
5[a]		42	—	166	180	76	72	42	36	—	126	94	56	52	62
Mean ± S.E.M.		41 ± 4.11	169 ± 47.6	164 ± 7.60	142 ± 14.47	72 ± 10.13	62 ± 4.31	51 ± 8.17	37 ± 2.24	82 ± 19.15	113 ± 13.09	96 ± 13.18	59 ± 7.21	47 ± 2.36	51 ± 8.91

[a] Slightly obese

Table 2. *Blood glucose and plasma insulin response to tolbutamide before and after i.v. 10 mg propranolol*

Case	Name age sex	before						after					
		B.	2′	15′	30′	45′	60′	B.	2′	15′	30′	45′	60′
		Blood Glucose mg % 100 ml											
6	D.A. 25 F	90	90	82	73	58	67	73	79	73	55	61	70
7	R.L. 35 M	85	85	73	51	48	65	85	85	76	52	52	64
8	P.M. 41 F	73	70	55	22	38	49	96	93	85	61	54	73
9	C.G. 48 M	113	99	79	62	53	48	101	—	73	59	53	56
10	F.M. 31 F	79	79	68	48	51	59	73	76	62	45	45	53
11	S.A. 42 M	79	85	73	54	50	58	82	87	73	55	47	67
	Mean ± S.E.M.	86 ± 6.10	84 ± 4.01	71 ± 3.90	51 ± 7.00	49 ± 2.71	57 ± 3.22	85 ± 4.74	84 ± 3.00	73 ± 3.00	54 ± 2.31	52 ± 2.31	64 ± 3.22
		Plasma Insulin μU/ml											
6		28	33	66	50	48	46	35	76	63	48	27	36
7		24	52	98	61	48	44	28	64	110	59	40	52
8		24	86	108	48	34	40	30	82	94	52	36	38
9		40	128	90	58	42	30	32	78	70	42	36	26
10		59	94	102	80	71	72	74	80	94	84	68	74
11		42	90	70	51	41	40	40	72	74	56	42	42
	Mean ± S.E.M.	36 ± 5.58	80 ± 13.93	89 ± 7.09	58 ± 4.86	47 ± 5.19	45 ± 5.80	40 ± 7.06	75 ± 2.65	84 ± 7.35	57 ± 5.97	41 ± 5.72	45 ± 6.83

Following i.v. propranolol (Table 2), the mean tolbutamide-induced increase curve was lower than the control curve. This difference was not significant for the paired data, however, owing to variations in the point of time at which the insulin increase was inhibited in the individual subject.

Discussion

Propranolol does not affect basal plasma insulin values.

The 200 mg/day oral dose, normally employed therapeutically, is responsible for significant depression of insulin response to tolbutamide. Similar findings have been reported for tolbutamide in the rat [2] and for glybenclamide in the dog [12].

It has recently been shown [4] that, given equal plasma levels, propranolol is decidedly less active when administered intravenously as opposed to *per os*. The lesser effect observed with i.v. propranolol may be an outcome of the use of this route and/or of the doses employed. It cannot be excluded, however, that this

lesser effect may also be due to the lesser response of blood insulin levels to tolbutamide observed, quite by chance, in this group of patients.

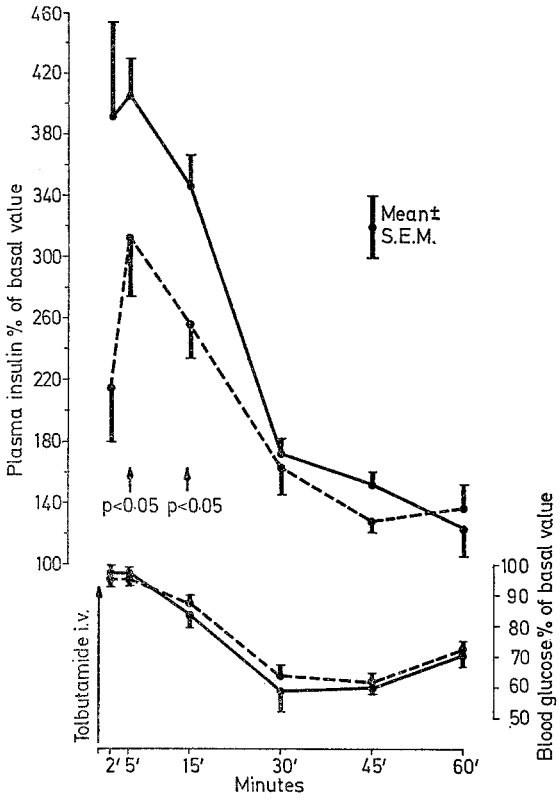

Fig. 1. Tolbutamide test in 5 subjects (3 normal, 2 slightly obese) before (———) and after (- - - - - - -) propranolol (200 mg/day for three days). P = paired t-test

The findings suggest that the beta-adrenergic receptors play a part in sulphonylurea-induced increases in insulin secretion.

Depression of such increases as a result of endogenous catecholamine secretion is not a valid explanation here, since depression occurred within 5' after tolbutamide, i.e. in a period where the absence of catecholamine activity could be deduced from the maintenance of unchanged blood sugar levels.

As suggested by Bressler *et al.* [2] for the rat, however, propranolol may perhaps inhibit the release of insulin by acting on the beta cells at different levels from those of the beta receptors. Nor must the possible interference of haemodynamic factors be overlooked.

As already shown in the rabbit [6] and the dog [12], the tolbutamide blood sugar curve was not significantly influenced by propranolol, although a smaller fall in values might have been expected as a consequence of decreased insulin secretion. This discrepancy may be partly explained by the fact that beta-receptor block potentiates, albeit inconsistently in different subjects, the hypoglycaemic effects of insulin [1, 7, 8].

Note should, however, be taken of the evidence, conflicting with the present data, namely the observation of reduced hypoglycaemic response to tolbutamide in man [5] following i.v. propranolol.

Our results are also of clinical interest, since the frequent association of diabetes and coronary disease means that patients may occasionally be subjected to simultaneous tolbutamide and propranolol treatment.

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