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Metabolic Studies in Diabetics on Tolbutamide. Comparison of a Single Dose with a Divided Dose Regimen

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Summary. This study compares blood glucose, plasma insulin and tolbutamide values throughout 48 h in 10 subjects on a single daily dose of tolbutamide and on a divided dose regimen (the two regimens are equally effective in their blood sugar lowering effect at all times throughout the 48 hours). — A plasma tolbutamide of 2—5 mg per cent was found to have some blood sugar lowering effect, and 24 h after a single oral dose effective levels were detectable in the plasma of some subjects. — Plasma insulin appears to respond to fluctuating glucose levels rather than to the tolbutamide levels and cannot fully account for the prolonged action of tolbutamide. — Tolbutamide given intravenously 3 h after a previous oral dose elicited a further rise in plasma insulin. The response was enhanced when the interval was increased to 18 h. A second peak in plasma insulin levels was often seen one hour after intravenous tolbutamide. — No insulin response was seen to repeated *oral* doses given at six to eight hour intervals. — An unexpected rise in plasma FFA was frequently observed ten minutes after intravenous tolbutamide. This may be attributed to the high circulating levels of tolbutamide which are measured as FFA by the method employed. — The mechanism of prolonged tolbutamide action remains unclear. These findings and their possible relationship to this action are discussed.

Etudes métaboliques chez des diabétiques traités par le tolbutamide. Comparaison entre les effets d'une seule dose et ceux de doses fractionnées

Résumé. Cette étude compare les valeurs de la glycémie, de l'insuline plasmatique et du tolbutamide pendant 48 h consécutives chez dix sujets, les uns recevant une seule dose de tolbutamide par jour, les autres recevant des doses fractionnées (les deux types d'administration sont également efficaces quant à leur effet d'abaisser la glycémie pendant toute la durée des 48 h). — On a constaté que 2 à 5 mg pour cent de tolbutamide dans le plasma provoquaient une certaine diminution de la glycémie, et 24 h après une seule dose administrée oralement, on a trouvé des taux efficaces dans le plasma de certains sujets. — L'insuline plasmatique semble réagir à la fluctuation des taux de glucose plutôt qu'aux taux de tolbutamide et ne peut pas expliquer entièrement l'effet prolongé du tolbutamide. — Le tolbutamide administré par voie intraveineuse trois heures après une dose précédemment prise par voie orale provoqua une augmentation supplémentaire de l'insuline plasmatique. Cet effet était accentué lorsque l'intervalle était porté à 18 h. On a souvent observé un second pic dans les taux d'insuline plasmatique une heure après une injection intraveineuse de tolbutamide. — Aucune réponse insulinique n'a été constatée après des doses *orales* répétées, administrées à des intervalles de 6 à 8 h. — On a souvent observé une augmentation inattendue des FFA du plasma dix minutes après une injection intraveineuse de tolbutamide. Ceci peut être attribué aux taux très élevés de tolbutamide circulant qui sont mesurés comme FFA par la méthode employée. — Le mécanisme de l'action prolongée du tolbutamide demeure obscur. Ces constations et leurs relations possibles avec cette action font l'objet de discussions.

Stoffwechseluntersuchungen bei mit Tolbutamid behandelten Diabetikern. Vergleich einer einmaligen Gabe mit der Verabreichung in verteilten Dosen

Zusammenfassung. Die vorliegende Arbeit vergleicht das Verhalten von Blutzucker, Seruminsulin und Tolbutamidspiegeln im Plasma bei 10 Personen während 48 Std nach Verabreichung von Tolbutamid in einer Einzelgabe oder in verteilten Dosen. (Beide Arten der Verabreichung hatten während 48 Std den gleichen blutzuckersenkenden Effekt.) Schon 2 bis 5 mg% Tolbutamid im Plasma führten zu einer Blutzuckersenkung und bei einigen Probanden waren 24 Std nach einmaliger Tolbutamidgabe noch wirksame Konzentrationen im Plasma nachweisbar. — Das Seruminsulin scheint eher auf die Schwankungen des Blutzuckers als auf die Tolbutamidkonzentration anzusprechen und kann nicht in vollem Umfang für die verlängerte Wirkungsdauer des Tolbutamids verantwortlich gemacht werden. — Intravenöse Tolbutamidzufuhr 3 Std nach einer oralen Gabe führte zu einem weiteren Anstieg des Seruminsulins. Durch Verlängerung des Abstandes auf 18 Std wurde dieser Effekt verstärkt. Eine Stunde nach i. v. Tolbutamidgabe wurde häufig ein erneutes Ansteigen der Seruminsulinspiegel festgestellt. — Wiederholte *orale* Gaben in 6—8 stündlichen Abständen bewirkten keine Änderung der Seruminsulin-Konzentrationen. — Ein unerwarteter Anstieg der freien Fettsäuren im Plasma war ständig 10 min nach i.v. Tolbutamidgabe festgestellt worden. Dieser Anstieg ist durch die hohen Tolbutamid-Spiegel bedingt, die bei der Bestimmungsmethode der FFS miterfaßt werden. Die Wirkungsweise der verzögerten Tolbutamidreaktion bleibt noch ungeklärt. Die Ergebnisse und ihre Beziehungen zu dem verzögerten Tolbutamid-Effekt werden diskutiert.

Key-words: Tolbutamide, free fatty acids (FFA), insulin (IRI), glucose, single dose, divided dose, maturity onset diabetics, oral, intravenous.

Tolbutamide taken orally has a half-life of 3—8 h [3]. Its major action is to stimulate the release of insulin [21, 22, 29, 26], which itself has a half-life of about 20—30 min [5, 12]. Reports of prolonged hypoglycaemia after single small doses of tolbutamide [24, 2, 37, 19, 28, 9, 13, 7]. suggest either an effect apart from the stimulation of insulin release or a delay in tolbutamide catabolism and excretion.

In a previous report [35] we showed that in 89 per cent of tolbutamide-responsive maturity-onset diabe-

tics there was no difference in control whether the daily dose of tolbutamide was given all at one time or in divided doses throughout the day. We have obtained 48 h profiles of plasma glucose, insulin (IRI), free fatty acid (FFA) and tolbutamide levels in some of these subjects on both single and divided dose schedules, in the hope that this might help to explain the complexities of tolbutamide action.

Subjects

There were 10 subjects aged 48—65 years, 6 females and 4 males. Two were obese (15 per cent above average weight, Documenta Geigy Tables), 5 were overweight but not obese. Duration of diabetes ranged from four months to fourteen years.

Every subject had been assessed as an outpatient on each dose-schedule for three months. During the course of each regimen the subjects were admitted to hospital for two 48 hour periods. All subjects were on a "diabetic diet" providing 1600 calories, 85 g protein, 58 g fat, 190 g carbohydrate.

Tolbutamide was administered in divided doses at 7 a.m., 12 midday and 5.30 p.m. on the one regimen, and the single dose was given at 11 a.m. each day

Table 1. *The actual plasma values for glucose, insulin and tolbutamide are shown for the various times during the single dose (S) and divided dose (D) regimens*

48 h Plasma Values

Glucose mg/100 ml

	8A.M.		12M.D.		6P.M.		12MN.		8A.M.		12M.D.		6P.M.		12MN.	
	S	D	S	D	S	D	S	D	S	D	S	D	S	D	S	D
D.S.	115	177	186	245	108	247	131	197	110	197	90	202	84	—	104	222
H.G.	139	134	150	134	211	143	150	157	211	139	125	159	115	139	—	119
E.O.	222	143	148	191	150	208	177	195	193	177	124	106	197	119	208	146
G.N.	139	124	148	179	111	124	120	161	102	115	86	88	141	115	141	124
J.A.	99	131	95	117	101	—	70	154	106	141	197	159	92	—	120	150
A.L.	127	154	115	197	106	195	195	134	138	155	177	182	166	173	209	146
F.S.	65	86	70	97	79	88	—	—	72	88	90	119	79	102	95	86
G.A.	134	139	159	117	117	134	138	157	161	143	166	166	77	—	131	125
E.W.	—	145	—	209	138	134	186	—	188	141	217	270	95	150	124	—
A.P.	336	163	306	222	188	136	230	208	193	132	193	186	133	132	217	208
mean	153	139.6	155	175	131	156.5	155	170.4	147	142.8	147	163.7	118	132.9	150	147.3

S. -Single Dose
D. -Divided Dose

Insulin Units/ml

D.S.	59	27	150	55	—	101	78	46	57	31	43	75	—	188	—	78
H.G.	26	141	46	250	125	250	—	146	58	153	40	250	78	250	66	250
E.O.	29	39	135	70	135	130	71	48	28	44	92	48	198	125	—	79
G.N.	38	23	46	117	58	87	48	46	49	34	55	69	77	53	68	27
J.A.	167	19	175	18	150	—	215	35	120	—	167	—	175	—	175	69
A.L.	37	16	38	35	118	58	103	16	50	26	150	42	150	48	150	20
F.S.	14	11	39	13	27	24	—	14	14	16	47	14	21	15	23	—
G.A.	32	—	53	—	29	22	23	9	28	23	49	63	46	22	25	22
E.W.	40	42	59	137	87	79	47	—	79	44	122	95	75	57	53	—
A.P.	170	39	129	205	129	125	105	102	60	88	117	138	83	169	100	160
mean	61.2	39.7	87.0	100.0	95.3	99.6	86.2	51.3	54.0	51.0	100.3	88.2	95.3	99.6	86.2	51.3

Tolbutamide mg/100 ml

	8A.M.		12M.D.		6P.M.		12MN.		8A.M.		12M.D.		6P.M.		12MN.	
	S	D	S	D	S	D	S	D	S	D	S	D	S	D	S	D
D.S.	6.3	5.4	—	9.8	—	8.2	—	4.9	2.6	1.1	10.6	4.6	16.7	6.1	5.7	8.6
H.G.	3.0	5.8	1.95	8.5	1.0	11.6	—	4.8	0	6.4	0	4.2	4.3	11.6	9.0	9.3
E.O.	4.9	14.2	4.5	8.7	12.0	11.7	7.6	12.7	3.5	12.6	12.5	7.8	10.3	6.2	—	8.5
G.N.	0.55	0	4.2	3.6	8.5	3.8	13.1	3.8	5.7	0	13.8	4.95	16.1	6.6	11.75	2.3
J.A.	2.0	0	5.7	4.4	12.1	—	2.2	3.95	2.8	—	3.9	0.7	5.6	—	8.6	3.9
A.L.	6.4	4.6	17.8	10.3	16.95	11.8	9.5	10.4	3.85	4.5	11.8	9.0	11.35	15.9	5.7	8.4
F.S.	2.5	—	6.4	—	13.8	5.3	—	—	4.4	2.2	3.0	11.3	15.4	12.1	3.3	4.0
G.A.	5.7	2.9	0	1.2	4.6	10.2	5.5	2.3	4.5	2.8	8.6	1.5	15.5	9.7	10.0	2.3
E.W.	3.3	2.4	3.1	6.1	20.2	9.8	5.6	11.2	3.6	3.7	3.8	4.5	18.7	11.0	7.95	7.95
A.P.	8.25	0	7.0	7.9	16.05	9.2	8.7	6.0	5.35	2.8	8.0	5.3	15.5	14.5	9.45	8.9
Mean	3.90	2.50	6.34	6.70	11.67	9.07	7.46	6.67	3.64	4.01	7.60	5.38	12.94	10.41	7.94	6.42

on the other. The total daily amount was 1.5 grams and remained the same for both treatment schedules. On the third day after admission standard 1 g intravenous tolbutamide tolerance tests were performed [33].

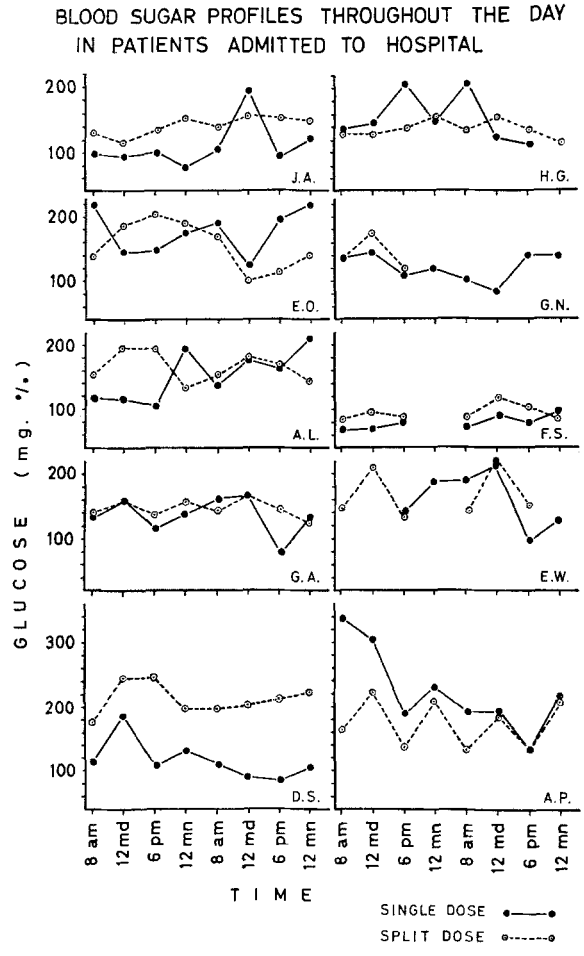

Fig. 1. Continuous lines indicate blood glucose levels with patients on the "single tolbutamide dose" scheme and interrupted lines indicate the same on divided doses

Measurements

Venous blood for insulin and tolbutamide was taken at 8 a.m., 12 midday, 6 p.m. and 12 midnight, and allowed to stand for about one hour, after which the serum was separated and stored at −20°C until estimations were performed up to some months later. Venous blood for glucose was taken into fluoride/oxalate tubes and immediately refrigerated until the end of the test when all samples were estimated.

Insulin was measured by the HALES-RANDLE method [16], as modified by the Radiochemical Centre, Data Sheet 5661. Glucose was measured by the Autoanalyzer HOFFMAN method [18]. Tolbutamide was measured by a modified Spingler method [30], and free fatty acid by the procedure of TROUT et al [32].

Results

1. Forty-eight hour profiles (Table 1 shows all values for the two dose-schedules)

Blood Glucose. Fig. 1 shows the blood sugar levels in the subjects on the two regimens. Fig. 2 shows their mean values. No significant difference in glucose values emerges for any of the test times. One subject, D.S., was better controlled on the single-dose schedule. With divided doses slightly higher mean glucose values were seen at 12 midday and 6 p.m. The mean midnight and fasting glucose values were similar on both regimens despite differences of $6^1/_2$ h in time since last dose of tolbutamide.

Plasma Tolbutamide. The blood levels of tolbutamide run approximately parallel to each other in the two regimens (Table 1 and Fig. 2). Maximum values were generally found at 6 p.m. on both regimens. A level as low as 3—5 mg per 100 ml produced a blood

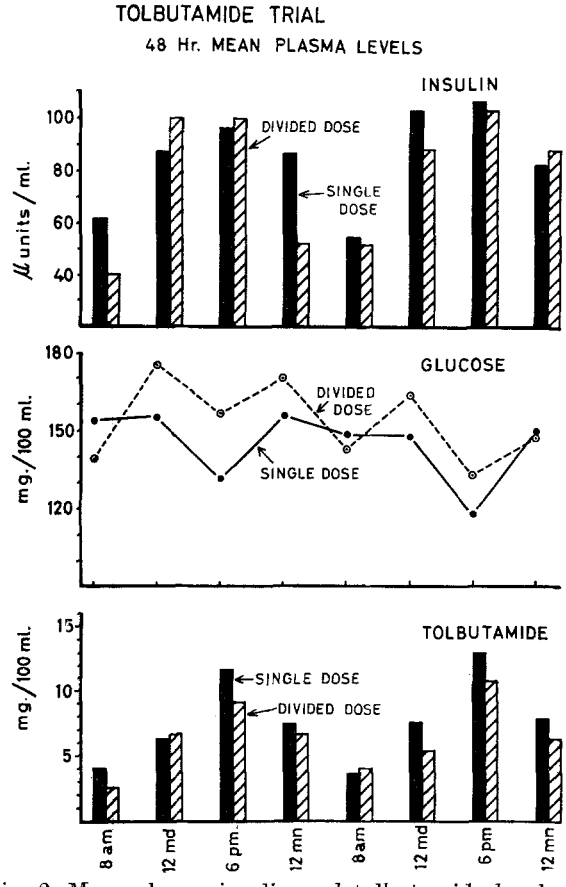

Fig. 2. Mean plasma insulin and tolbutamide levels are shown in relation to the mean glucose levels for the two regimens throughout the course of 48 h. (18 h and 3 h indicate time since previous oral doses of tolbutamide)

sugar-lowering effect. This can be seen in subjects with high fasting blood glucose levels on admission and no detectable plasma tolbutamide, in whom the later fasting glucose values became normal with plasma tolbutamide levels of 3—5 mg per cent.

Table 2. *The actual values for glucose, insulin, tolbutamide and FFA during standard intravenous tolbutamide tests performed 3 and 18 h after a previous oral dose are shown*

Intravenous Tolbutamide Test

Glucose mg/100 ml

	fast		10 min		20 min		30 min		45 min		60 min		90 min		120 min	
	18 h	3 h	18 h	3 h	18 h	3 h	18 h	3 h	18 h	3 h	18 h	3 h	18 h	3 h	18 h	3h
D.S.	—	184	—	182	—	146	—	145	—	143	—	131	—	148	—	150
H.G.	143	134	129	129	146	129	141	132	141	129	154	134	134	124	136	120
E.O.	175	152	172	150	172	132	163	146	157	131	155	131	146	122	138	108
G.N.	164	88	168	75	155	72	177	72	—	72	163	77	146	75	138	81
J.A.	113	119	102	—	84	113	86	117	95	106	88	—	86	99	86	101
A.L.	148	150	145	146	148	145	141	136	134	132	134	138	127	129	125	127
F.S.	83	141	70	124	70	90	61	70	56	65	48	70	57	74	65	79
G.A.	153	170	147	161	140	159	143	150	128	146	132	141	120	131	103	152
E.W.	190	148	181	136	181	127	164	122	161	113	159	102	148	99	148	99
A.P.	158	92	151	106	136	97	153	101	—	99	144	92	129	90	117	84
mean	147	138	141	134	137	121	137	119	125	114	131	113	121	109	117	110

Insulin Units/ml

D.S.	—	42	—	67	—	54	—	49	—	110	—	59	—	29	—	47
H.G.	89	114	90	81	98	—	108	66	80	59	63	72	50	78	31	78
E.O.	124	99	134	108	128	92	100	81	103	175	106	250	114	156	51	100
G.N.	—	27	—	49	—	37	—	40	—	29	—	28	—	30	—	25
J.A.	54	49	72	178	57	93	73	81	82	49	64	59	43	30	45	26
A.L.	95	20	67	36	79	26	65	40	147	19	92	25	72	53	63	14
F.S.	50	67	67	198	69	64	64	37	53	45	38	35	50	67	44	25
G.A.	44	44	137	60	86	61	57	55	36	46	50	53	29	75	70	51
E.W.	55	60	82	107	112	57	62	47	62	35	72	54	52	98	88	83
A.P.	73	56	250	38	177	60	109	40	—	112	117	112	89	49	97	45
mean	73	58	112	92	101	60	80	54	80	64	75	75	62	67	61	49

Free fatty acid

Equivalents/ml

	fast		10 min		20 min		30 min		45 min		60 min		90 min		120 min	
	18 h	3 h	18 h	3 h	18 h	3 h	18 h	3 h	18 h	3 h	18 h	3 h	18 h	3 h	18 h	3 h
D.S.	—	982	—	630	—	682	—	717	—	630	—	542	—	630	—	682
H.G.	1172	927	1083	734	996	734	699	787	857	787	962	804	1048	996	1154	1014
E.O.	1207	768	857	874	577	332	839	332	945	437	1048	559	1154	699	1154	752
G.N.	647	262	647	367	594	489	507	489	—	542	699	699	594	1312	647	1364
J.A.	1154	677	1626	819	1381	756	1154	756	768	771	927	819	962	866	1102	1055
A.L.	787	610	908	857	734	717	734	734	908	927	1083	945	1083	1014	1172	1014
F.S.	489	1055	1469	1039	822	771	559	614	454	567	419	551	610	708	1469	1275
G.A.	839	1039	647	1039	1312	1008	717	756	577	598	559	976	647	551	839	504
E.W.	1083	804	1067	752	874	647	996	908	927	908	577	577	839	891	—	1031
A.P.	630	507	996	908	857	454	1207	525	—	664	822	734	1067	610	857	927
mean	890	763	1033	802	905	659	824	662	777	683	825	721	889	828	1049	962

Tolbutamide mg/100 ml

D.S.	—	8.0	—	21.0	—	22.5	—	23.4	—	18.6	—	17.7	—	21.7	—	—
H.G.	—	2.9	—	35	—	—	—	24.0	—	18.6	—	17.8	—	17.5	—	19.7
E.O.	6.9	4.2	27.5	27.0	23.1	25	21.2	23.5	21.4	24.4	20.8	20.5	20.4	18.3	18.5	20.0
G.N.	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
J.A.	—	1.1	—	21.6	—	20.8	—	17.7	—	17.5	—	16.4	—	15.3	—	12.9
A.L.	3.4	8.3	35	26.4	23.2	29.3	20.8	25.3	18.4	23.2	18.3	22.8	—	21.5	—	21.2
F.S.	0.6	4.4	24.2	28.6	24.8	25.4	25.6	23.7	21.9	24.4	19.7	19.9	18.3	19.3	14.9	18.5
G.A.	1.6	3.2	25.9	28.9	21.8	24.0	20.8	24.3	19.0	25.7	16.2	19.7	15.6	23.2	17.5	18.3
E.W.	—	1.9	—	21.0	—	17.8	—	16.3	—	17.3	—	15.4	—	14.8	—	15.3
A.P.	1.3	9.2	23.0	35	19.4	27.9	19.0	26.4	—	23.3	18.8	23.7	13	20.8	12.6	19.9
mean	3	4.6	27.2	27.3	22.4	25.4	21.6	22.7	20.0	21.4	18.8	19.4	16.7	19.2	16.2	18.3

We found no direct relationship between the plasma tolbutamide level and its blood sugar lowering effect, except at 6 p.m., when the highest mean tolbutamide values corresponded with the lowest blood glucose levels. Tolbutamide levels were not enhanced by the repeated oral doses of tolbutamide given on the divided dose regimen. Even up to 24 h after a single oral dose, tolbutamide was detectable in the plasma of some subjects.

Plasma Insulin. There was no significant difference in the plasma IRI on the two regimens.

There was a rise in IRI levels after the first daily dose of tolbutamide, and maximum plasma IRI and tolbutamide levels corresponded with the lowest glucose levels. At other times the IRI values bore no relationship to the plasma tolbutamide levels. They appeared to be more dependent on the fluctuations of plasma glucose, i.e. the higher the glucose level the greater the insulin level irrespective of the tolbutamide value.

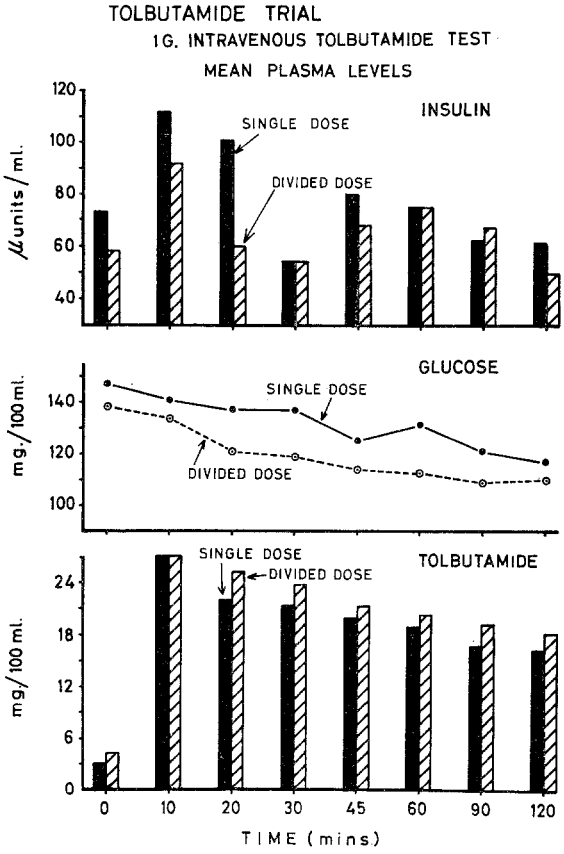

Fig. 3. Mean plasma insulin and tolbutamide values in relation to the plasma glucose response to intravenous tolbutamide 18 h (single dose) and 3 h (divided dose) after a previous oral dose

2. Intravenous Tolbutamide Test (Table 2)

Fig. 3 shows the mean values for all subjects during the two dose-schedules. Peak tolbutamide values in each were the same whether tolbutamide was given three hours (divided dose) or 18 h (single dose) after a previous oral dose (Fig. 3).

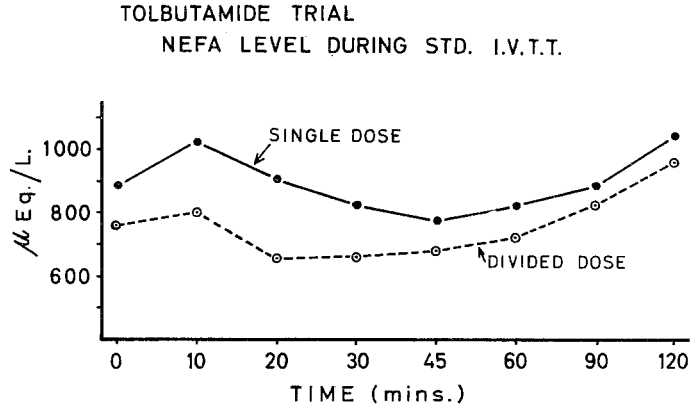

Fig. 4. Mean FFA levels after intravenous tolbutamide

The half-life of plasma tolbutamide after intravenous injection was measured from the straight portion of the curve when the plasma levels were plotted against time on a logarithmic scale. When intravenous tolbutamide was given 18 h after the last oral dose the mean half-life time was found to be 100 min; when given three hours after the oral dose it was 150 min.

Intravenously administered tolbutamide produced a further rise in plasma IRI when given either three or 18 h after oral tolbutamide. When tolbutamide was given intravenously 18 h after the oral dose the rise in IRI was significantly greater than that after three hours (Fig. 3). This contrasts with the lack of response seen with repeated oral doses, but the plasma tolbutamide level reached after intravenous administration was far greater than that attained with oral tolbutamide.

The mean plasma glucose levels were not significantly different in the two sets of tests, despite the higher insulin values attained when intravenous tolbutamide was given 18 h after the last oral dose (Fig. 3).

In seven subjects a rebound rise in plasma insulin was observed one hour after the intravenous administration of tolbutamide. This was associated with a fall in plasma glucose (Table 2).

An unexpected rise in the (mean) levels of plasma FFA was observed ten minutes after intravenous tolbutamide, followed by the expected fall (Fig. 4).

Discussion

CROWLEY [8] compared the control of diabetes attained by single and divided doses of tolbutamide in two different groups of subjects with the control off treatment, and obtained results similar to ours.

It is not clear how tolbutamide, a substance with its short half-life, produces prolonged effects. MIRSKY [25] postulated two phases of tolbutamide action, an early insulin-dependent phase and a late phase thought

to be due to decreased insulinase activity and prolongation of insulin action. However VOLK [6] has shown that tolbutamide does not prolong the ^{131}I-insulin half-life. Our studies do not support a prolonged insulin survival as the mechanism of the prolonged hypoglycaemic action of tolbutamide, since low blood glucose values obtain when insulin levels are also low.

Prolonged action of tolbutamide may occur in elderly subjects [9, 13], renal failure [2] or, rarely in subjects with an inability to destroy tolbutamide [3]. None of these apply to our cases, because tolbutamide (intravenously administered) was shown to disappear from the blood stream with a half-life of 100—150 min.

It has been asserted that tolbutamide may potentiate the action of insulin [20], but this was only apparent with large doses.

Differences in the action of tolbutamide and insulin [8, 17, 11] have been disputed [31], and the suggestion that tolbutamide direcly inhibits hepatic release of glucose [21, 22, 10, 1] may be accounted for by differences in measureable portal and systemic insulin levels [26, 36]. Certainly no increase of peripheral glucose utilization occurs with tolbutamide in the absence of insulin [4].

There is a natural fluctuation in blood sugar in diabetics [14], which tolbutamide appears, from our data, to set at a lower mean level. Our finding that plasma insulin levels vary with the blood glucose rather than with tolbutamide is in keeping with that of YALOW and BERSON [36], who suggest that the sustained insulin response to tolbutamide is partly dependent on the raised glucose levels rather than the tolbutamide *per se*.

It has been suggested [27] that large doses of tolbutamide stimulate the pancreas to release all preformed insulin and that it is then refractory for about four hours in normal subjects and up to 24 h in diabetics. Our present investigations show that certainly within three hours of standard oral doses a further insulinotropic response can be obtained with intravenous tolbutamide in maturity-onset diabetics, but not with a further oral dose. An oral dose of 500 mg thus appears to produce a relative refractoriness for several hours, which can be overcome if the blood level of tolbutamide is raised to sufficient height as by intravenous administration.

Of interest are the rebound or secondary peaks in plasma insulin levels seen at one hour after intravenous injection (Table 2) of tolbutamide, associated with a fall in blood sugar. Possibly the pancreas is refractory for only one hour, and in the face of adequate tolbutamide levels, is restimulated. Alternatively a negative feedback system may exist in which circulating insulin inhibits the pancreas, and on falling to a threshold level in the presence of circulating tolbutamide the pancreas is restimulated.

If glucose can decrease synalbumin antagonism to insulin [34] it is possible that tolbutamide may act similarly.

Finally we found an unexpected early rise in FFA after intravenous tolbutamide (observed also in MAINGAY's report [23] but not commented upon).

Tolbutamide when added to plasma *in vitro* in a concentration of 30 mg % raised the FFA measurement from 900 μ Eq/Litre to 1000 μ Eq/Litre and from 750 μ Eq/Litre to 890 μ Eq/Litre on estimations done in triplicate. We feel however that this may be only part of the explanation for the early rise in plasma FFA, and have engaged in further exploratory studies.

We can conclude that single doses of tolbutamide usually afford control as good as divided doses. This may be related to the maintenance of effective blood levels of tolbutamide for 24 hours, despite the short half-life of plasma tolbutamide. Tolbutamide does not appear to produce its prolonged hypoglycaemic effect by increasing the plasma insulin levels after the first few hours; in fact the mechanism of this phenomenon remains obscure.

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