driven isolated rabbit auricle. It is approximately 16 times as active as quinidine in antagonizing acetylcholine-induced auricular fibrillation in the dog. It is slightly more active than quinidine in antagonizing aconitine-induced tachycardia in the same species. The safety margin of this drug, as measured by the ratio between minimal anti-fibrillatory doses and those producing marked blood pressure and ECG changes, is greater than that of quinidine.

1. Krayer, O., Uhle, F. C., and Ourisson, G., *J. Pharm. and Exp. Ther.,* 1951, v102, 261.

2. Margolin, S., Lu, G., Yelnosky, J., and Makovsky, A., *Science,* 1954, v120, 576.

3. Robson, J. M., and Trounce, J. R., *J. Physiol.,* 1955, v129, 10P.

4. Heer, J., and Hoffmann, K., *Helv. Chim. Acta,* 1956, v39, 1814.

5. Schallek, W., *J. Pharm. and Exp. Ther.,* 1952, v105, 291.

6. Schallek, W., *Arch. int. pharmacodyn.,* 1956, v105, 221.

7. Dawes, G. S., *Brit. J. Pharmacol.,* 1946, v1, 90.

8. Scherf, D., and Chick, F. B., *Circulation,* 1951, v3, 764.

9. Prinzmetal, M., Corday, E., Brill, I. C., Oblath, R W., and Kruger, H. E., *The auricular arrhythmias,* Springfield, Ill., 1952, p350.

10. Melville, K. I., *J. Pharm. and Exp. Ther.,* 1946, v87, 350.

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Effect of Tolbutamide (Orinase) on Plasma Non-Esterified Fatty Acids. (23244)

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Oral or parenteral administration of sulfonylurea derivatives produces hypoglycemia in normal subjects and in many diabetic patients(1,2). Since functioning pancreatic tissue is required for this action, it has been suggested that tolbutamide (1-butyl-3-p-tolylsulfonylurea) in some manner enhances the effect of endogenous insulin(3,4). On the other hand, there is evidence that tolbutamide may limit release of glucose from the liver into the blood stream(5,6) and thus reduce concentration of blood glucose in this manner rather than by promoting utilization. The close association between metabolism of carbohydrate and the level of plasma non-esterified fatty acids (NEFA) provides another way to test this question. Since an increased oxidation of carbohydrate appears to be associated with a fall of NEFA concentration, it should be possible to reveal any effect of tolbutamide on oxidation of carbohydrate by its action on the NEFA fraction of blood lipides.

Method. Tolbutamide was administered to 4 normal, 7 mild adult diabetic, and 3 severe juvenile-type diabetic patients, in a dose of 2 g dissolved in 20 cc saline and given intravenously over a 2-minute period. Venous blood samples, collected in duplicate before injection and at 20, 40, 60, and 120 minutes thereafter, were analyzed for glucose by a modification of the Nelson colorimetric procedure(7) and for NEFA by a method previously described(8). Urine samples for qualitative determinations of sugar and ketones were obtained at hourly intervals.

Results. Concentrations of blood glucose and NEFA observed in the normal and diabetic patients are given in Table I. In agreement with previous observations, tolbutamide produced hypoglycemia in normals and mild diabetics, but failed to lower blood sugar of the 3 diabetics with histories of recurrent ketosis. A decrease in NEFA occurred in every patient who responded with a reduction of blood sugar; no significant decrease was observed in the absence of a hypoglycemic effect. The correlation between changes in concentration of NEFA and blood sugar was highly significant ($p<0.001$).

TABLE I. Effect of Tolbutamide on Blood Glucose and Non-Esterified Fatty Acids.

			Glucose					NEFA				
			Initial value	% change Min.				Initial value	% change Min.			
Sex	Age	Wt (kg)	(mg %)	20	40	60	120	(mg %)	20	40	60	120
(A) Normal												
*♀	20	86	93	−11	−35	−37	−18	1215	− 9	−42	+ 6	+ 37
♀	33	75	78	−26	−42	−26	−15	774	− 5	−27	+10	+ 8
♀	22	84	71	−30	−23	− 1	− 3	1051	−16	−43	−47	+ 11
†♂	26	78	91	−31	−29	− 3	− 4	648	−31	+27	+41	+ 8
(B) Mild diabetic												
♂	54	104	160	− 8	−13	−13	−20	781	+ 2	−27	−35	− 20
♀	50	77	188	− 7	− 9	−19	−28	833	+ 4	−15	−25	− 29
♀	54	62	182	+ 4	+ 2	− 4	−14	1360	− 1	−17	−29	− 18
♀	35	94	157	−10	−15	−17	−29	758	+ 5	−13	−18	− 9
♂	48	74	159	−17	−35	−42	−52	532	− 3	−24	−30	− 35
†♂	50	55	179	−14	+ 6	+10	+27	1063	0	+ 5	− 9	− 13
♀	63	71	261	− 6	− 8	−12	−28	1148	−11	−17	−21	− 35
(C) Severe diabetic												
♂	27	66	107	+21	+46	+47	+61	758	− 1	+20	+20	+ 61
♀	31	69	330	+ 1	+ 3	+ 5	+ 4	1363	− 8	− 4	− 4	+ 7
♂	28	65	321	+ 4	+ 5	+ 6	+ 5	750	+22	+13	+93	+147

Dose = 2 g in all cases except as follows: * 3 g; † 1 g.

The average normal response to tolbutamide is shown in Fig. 1. In the 4 normal subjects blood glucose and NEFA reached a minimum approximately 40 minutes after injection. Thereafter the concentration of NEFA increased rapidly to a level above the control, while glucose returned more slowly toward the baseline value. Stable diabetics responding to tolbutamide showed a more protracted hypoglycemia with a parallel sustained reduction of NEFA concentration ($p = 0.003$) (Fig. 2).

Tolbutamide administration resulted in no decrease of blood glucose or NEFA in the group of severe diabetics (Fig. 3). Their response differed significantly ($p<0.003$) from the effects seen in the combined groups of normal and mildly diabetic subjects. One patient, a juvenile diabetic in ketosis, had a marked elevation of both glucose and NEFA, which was unaffected by tolbutamide but responded promptly to insulin (Fig. 4).

Discussion. As indicated by the low p values, diabetics showed highly significant differences from normal in 2 respects: a prolonged fall of glucose and NEFA in mild diabetics, and absence of fall in the severe cases. Presumably these abnormal responses to tolbutamide were symptomatic of some metabolic disturbance in diabetes, but it must be emphasized that the sample size was small, and conceivably the diabetics might have been atypical.

The findings support the current theory that tolbutamide stimulates insulin discharge, but does not in itself promote oxidation of glucose. In general it appears that NEFA level rises when carbohydrate is being utilized at a reduced rate, and falls when carbohydrate oxidation is enhanced. The relation probably reflects actual utilization of glucose, rather than availability of sugar, because glucose is ineffective in lowering NEFA level under conditions of insulin deficiency. With diabetic ketosis, and to a lesser extent with simple fasting, NEFA level rises progressively. Insulin causes a drop of NEFA in either case(8,9), whereas glucose is effective only in the fasting subjects. If given to severe diabetics without supplementary insulin, glucose adds to the hyperglycemia without affecting NEFA level.* Summing the evidence, it seems likely that tolbutamide acts to relieve ketosis only when the pancreas is capable of responding with an increased output of insulin.

Summary. Tolbutamide (Orinase), given intravenously to normal and diabetic patients

* Unpublished observations.

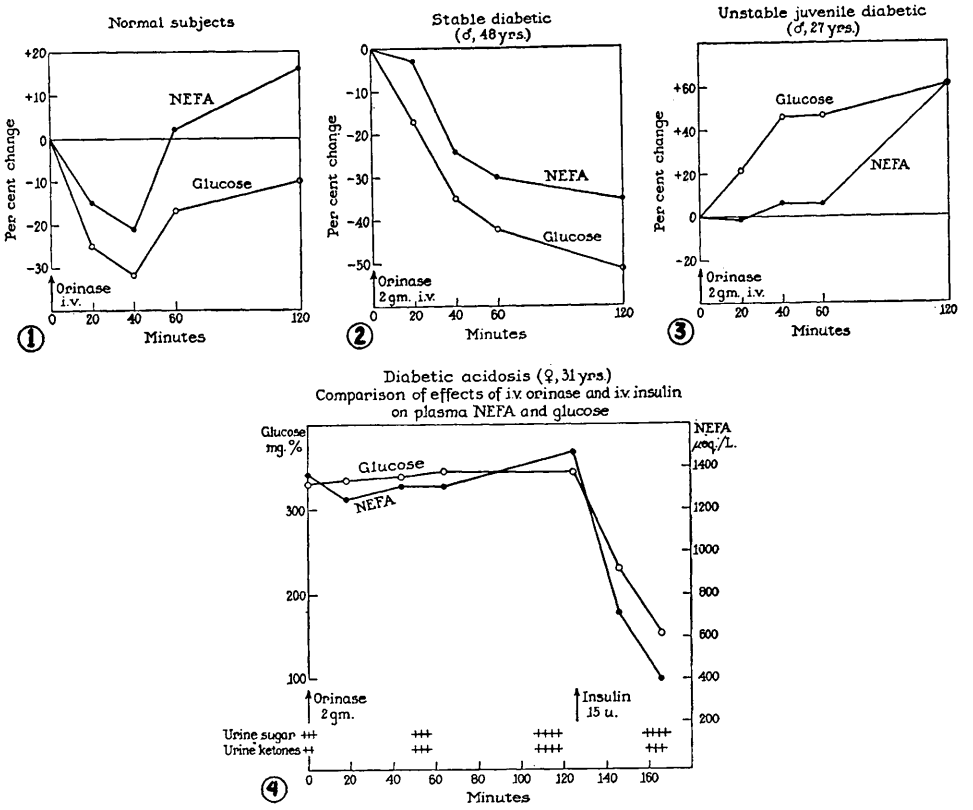

FIG. 1-4.

caused a reduction of non-esterified fatty acid concentration only in those subjects who responded with hypoglycemia. Diabetics responding to tolbutamide with a prolonged depression of blood sugar showed a comparably sustained reduction of the fatty acid fraction.

1. Symposium, *Metab.*, 1956, v5, 721.
2. 3rd Lilly Conference, *Diabetes,* 1957, v6, 1.
3. Levine, R., Duncan, G. G., *Metab.*, 1956, v5, 721.
4. Ricketts, H. T., Lukens, F. D. W.. Krahl, M. E., *Diabetes,* 1957, v6, 91.
5. Anderson, G. E., Perfetto, A. J., Monaco, R. N., Termine, C. M., *ibid.,* 1957, v6, 34.
6. Moorhouse, J. A., Kark, R. M., *Metab.,* 1956, v5, 847.
7. Nelson, N., *J. Biol. Chem.,* 1944, v153, 375.
8. Dole, V. P., *J. Clin. Invest.,* 1956, v35, 150.
9. Laurell, S., *Scand. J. Clin. and Lab. Invest.,* 1956, v8, 81.

Received March 18, 1957. P.S.E.B.M., 1957, v95.