A New High-Potency Antidiabetic Sulfonylurea [N-(1-hexahydro-1-azepinyl)-N′-*p*-tolyl-sulfonylurea].* (26591)

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Since tolbutamide (Orinase†) was released for clinical use and its efficacy proven in treating maturity onset diabetics, an intense search has been conducted for compounds which offer advantages over tolbutamide. This report describes studies conducted with a new blood sugar lowering sulfonylurea, U-17835 ([N-(1-hexahydro-1-azepinyl)-N′-*p*-tolyl-sulfonylurea]) (Fig. 1), which has been found to be more potent than tolbutamide in rats and humans and better tolerated acutely than tolbutamide in both rats and mice.

Methods. Intact rats. Male rats (Sprague-Dawley) 140-160 g were used, following an overnight fast. They were injected subcutaneously with 100 mg glucose in 0.5 cc saline, immediately prior to oral administration of test compounds in 0.5 cc CMC vehicle(1). Blood was withdrawn 2 hours later from posterior vena cava while rats were under barbiturate‡ anesthesia. Blood sugars were determined by Autotechnicon which is a modification of a method described by Hoffman(2). Potency estimates were made by determining from dose-response curves doses of compounds which produced comparable blood sugar lowering.

Adrenalectomized rats. This method is as previously described(3) and measures ability of compounds to lower blood sugar in fasted adrenalectomized rats (7 days post-operative). The animals were injected subcutaneously with 100 mg glucose in 0.5 cc saline immediately prior to oral administration of compounds. Blood sugars were determined by Autotechnicon on blood taken from posterior vena cava, 2 hours following drug treatment. Potency ratios were determined by a standard USP method(4).

Duration of action—intact rats. Male rats (Sprague-Dawley) 140-160 g were used, following an overnight fast. Compounds were given orally in CMC vehicle (0.5 cc), immediately after a 0-time blood sample was taken. Blood was also obtained at 2, 4, and 6 hours following drug administration. Tail blood was taken by pipette from a razor-blade nick. Prior to bleeding, each animal was subjected to 5 min of 39°C temperature. Rats were maintained at room temperature between bleedings. Sugar was determined by Micro-Autotechnicon method.

Normal Humans. Normal, healthy, male prisoner volunteers, 150-180 lb were used to compare U-17835 with tolbutamide. Following an overnight fast, compounds were given orally as compressed tablets, immediately after a 0-time blood sample was obtained. Fasting continued during study. Blood was withdrawn from antecubital vein, 1, 2, 4, 6, 8, and 10 hr after treatment. Sugars were determined on Autotechnicon. All treatments were given on double-blind basis.

Diabetic humans. A preliminary study was conducted, using 3 diabetic prisoners treated with U-17835 for an 8-wk period. Daily fasting blood sugars, urinalysis, and body weights were obtained, together with urinary glucose estimates before each meal and at bedtime (using Tes-Tape). Complete blood counts were done at weekly intervals. Every 2 weeks, blood urea nitrogen, thymol turbidity, bromsulphalein retention, alkaline phosphatase, serum glutamic oxalacetic transaminase, cephalalin floculation, and erythrocyte sedimentation rates were performed by the usual clinical laboratory methods. The object of

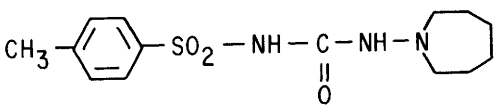
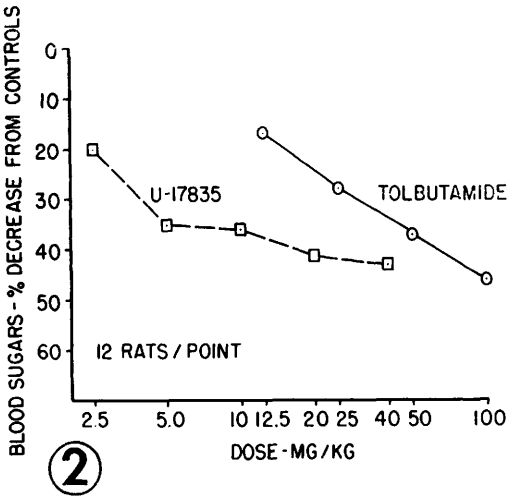


FIG. 1. Structure of U-17835.

* Synthesized and supplied for these studies by Dr. J. B. Wright, Dept. of Chemistry, Upjohn Co. A paper describing the synthesis and properties of this and related compounds will be published later.

† Registered Trademark, Upjohn Co.

‡ 5-(1-Cyclopenten-2-yl)-5-allylbarbituric acid, sodium.



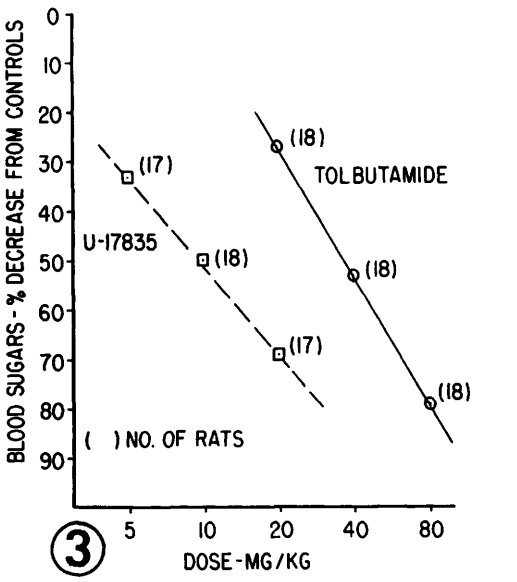


FIG. 2. Comparative blood sugar lowering effects of U-17835 and tolbutamide in glucose-primed, fasted, intact rats, 2 hr after oral administration. Data pooled from 2 experiments.

FIG. 3. Comparative blood sugar lowering effect of U-17835 and tolbutamide in glucose-primed, fasted, adrenalectomized rats, 2 hr after oral administration. Data pooled from 3 separate experiments.

this phase of investigation was to determine clinical efficacy and potency in diabetics, relative to tolbutamide, as well as any obvious side effects or toxicity.

Acute toxicity. LD_{50}'s were determined by intraperitoneal injection in the mouse or oral administration in the rat of a single dose of compound in CMC vehicle. Mice were of mixed sex of the Indianapolis laboratory strain, weighing 20-25 g. Rats were males of the Upjohn strain (Sprague-Dawley ancestry) weighing 150 g. Animals were observed for 7 days following drug. LD_{50} was calculated by method of Spearman-Kärber (5).

Results. Comparison of U-17835 with tolbutamide in intact rats shows that U-17835 was 4-6 times more active than tolbutamide (Fig. 2). A more exact potency determination is not possible since slopes of curves are shallow. In adrenalectomized rats, the ratio of U-17835 to tolbutamide was 4:1 (Fig. 3). This animal preparation gives steeper dose re-

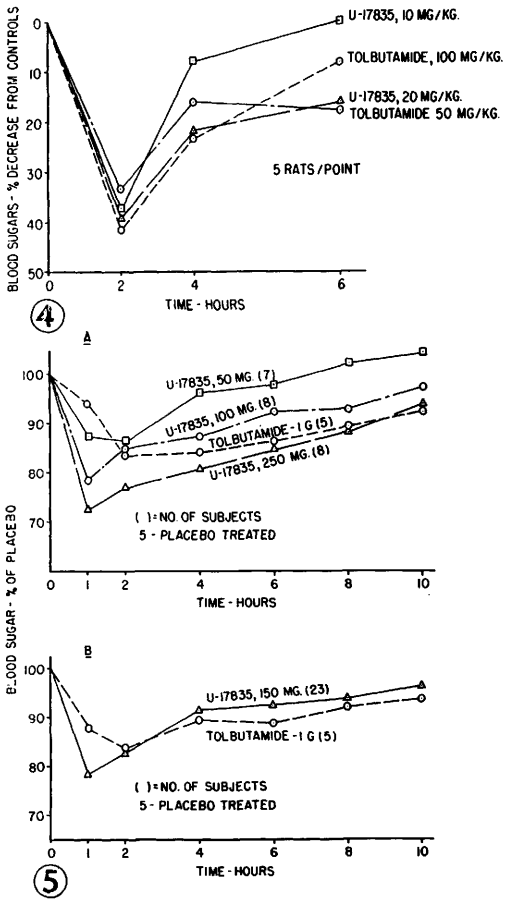


FIG. 4. Comparative duration of hypoglycemic effects of U-17835 and tolbutamide in intact, fasted rats.

FIG. 5. Comparative blood sugar lowering effect of U-17835 and tolbutamide in normal humans (prisoner volunteers) following single doses, administered orally.

TABLE I. Comparative Blood Glucose (Fasting) Responses to U-17835 and Tolbutamide in 3 Diabetics.

Treatment period	Drug	Dose, mg/day	Blood sugar, mg % Avg	(Range)
Pt. A.A.				
1958–59	Tolbutamide	1000		"Normal"
1959–60	"	500	89	(81–106)
11/19–12/18/60	U-17835	100	90	(80–115)
12/19–12/26/60	"	50	104	(88–126)
12/26– 1/18/61	"	100	84	(70–108)
Pt. H.C.				
1956–1960	NPH insulin	35 units		"Normal"
11/11–11/19/60	Tolbutamide	2000	96	(68–112)
11/19–11/26/60	U-17835	400	84	(69–109)
11/26–12/ 6/60	"	300	78	(72– 86)
12/ 7–12/13/60	"	100	132	(128–138)
12/22– 1/18/61	"	50	138	(130–146)
12/21– 1/18/61	"	200	85	(70–105)
Pt. A.U.				
1956–1959	PZI*	60 units		"Normal"
1959–1960	PZI	40 "	88	(71–105)
11/11–11/19/60	Tolbutamide	2000	109	(60–125)
11/19–12/ 5/60	U-17835	400	104	(86–123)
12/ 5–12/12/60	"	200	98	(80–116)
12/13–12/17/60	Placebo	—	148	(106–175)
12/17– 1/15/61	U-17835	200	93	(68–110)

* Protamine zinc insulin.

sponse curves than intact rats, allowing more exact potency calculations. U-17835 was not longer acting than tolbutamide in fasted intact rats (Fig. 4) since blood sugars returned to placebo levels at the same time following equipotent doses.

In normal human subject 150 mg U-17835 was as potent as 1 g tolbutamide (Fig. 5), *i.e.*, U-17835 was about 6-7 times as potent as tolbutamide. These results agree surprisingly well with those obtained in intact rats. No difference in duration of hypoglycemic action of the two drugs is apparent from this study in normal humans.

Three diabetic humans were studied for a 8-wk period (Table I) and it was found that in one (H.C.) 200 mg U-17835 gave control equivalent to that obtained with 2 g tolbutamide. In the second (A.A.) 100 mg U-17835 was equivalent to 0.5 g tolbutamide while in the third (A.U.) 200 mg U-17835 was comparable to 2 g tolbutamide. These results suggest that U-17835 is 5-10 times more effective than tolbutamide in diabetic subjects. No evidence of intolerance or toxicity was observed in these 3 patients.

Oral LD_{50} of U-17835 and tolbutamide in rats was $>$ 5000 mg/kg and 2344 mg/kg, respectively. LD_{50}'s by intraperitoneal injection in mice were 2239 mg/kg for U-17835 and 1288 mg/kg for tolbutamide. Therefore, on a single-dose basis, U-17835 is better tolerated than tolbutamide in mice and rats.

Discussion. Sulfonylureas have been chemically modified in various ways in attempts to achieve some advantage over tolbutamide. Carbutamide and metahexamide are examples of modified sulfonylureas which were more potent but, because they were also more toxic, were unacceptable for clinical use in the U.S.(6,7,8). Chlorpropamide is a more potent sulfonylurea which has been accepted for clinical use in maturity onset diabetics(9). Whereas some of the more active compounds differ structurally from tolbutamide in the aryl portion of the molecule (carbutamide and chlorpropamide), others were modified in both the aryl and alkyl portions (metahexamide). U-17835 is one of the first compounds substituted on only the alkyl portion of the molecule, which exhibits increased potency, and is better tolerated in mice and rats.

West(9) has suggested that true clinical

potency of sulfonylureas in diabetics can be predicted from acute hypoglycemic potency in normals and metabolic half-life. If this is true, then it should be possible to predict half-life from potency in normals and diabetics. Since U-17835 has been found (relative to tolbutamide) to be about as potent acutely in normals as it is clinically in diabetics, it suggests that U-17835 may prove to have a half-life similar to that of tolbutamide.

Although U-17835 may have a half-life similar to tolbutamide, it should be emphasized that duration of action and/or potency can be affected by rates of intestinal absorption. This is supported by observations in other areas of biological activity where pharmaceutical alterations of absorption rates can result in maintenance of effective blood drug levels and increased duration of action(10, 11).

Although U-17835 has a greater potency in man than tolbutamide, extensive clinical trial will be necessary to establish the significance of these findings with U-17835 regarding increased efficacy or fewer side effects compared to tolbutamide.

Summary. U-17835 ([N-(1-hexahydro-1-azepinyl)-N'-*p*-tolyl-sulfonylurea]), a new blood sugar lowering sulfonylurea, was 4-6 times more active than tolbutamide in intact rats and 4 times more active in adrenalectomized rats. At equipotent doses it was not longer acting than tolbutamide in intact rats. Normal human subjects showed U-17835 to be 6-7 times more effective than tolbutamide in lowering blood sugar after a single dose. In 3 diabetic patients, U-17835, given for 8 weeks, was found to be 5-10 times more active than tolbutamide, and it showed no signs of intolerance. This compound was also better tolerated than tolbutamide in both rats and mice.

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Special Tubes for Total Bile and Pancreatic Juice Collection in the Human.* (26592)

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Soft rubber and plastic tubes were designed, which, when implanted in the post-operative wound in patients operated on for biliary and pancreatic disease, permitted physiologically significant measurements of total human bile and pancreatic juice. The rubber tube for bile collection† was constructed like a T-tube, but the long arm was composed of 2 tubes, one draining the liver, the other connected to the lower limb, which was of small

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† These tubes were manufactured by C. R. Bard, Inc., Summit, N. J.