Acetohexamide and Tolbutamide Effects in Non-Diabetic and Diabetic Adults.* (28975)

T. S. DANOWSKI, M. E. SARVER, J. V. BONESSI, AND C. MOSES
Section of Endocrinology and Metabolism, and Addison H. Gibson Laboratory, University of Pittsburgh School of Medicine, the Medical Center and Shadyside Hospitals

The studies herein described indicate that in healthy subjects the hypoglycemic effect of intravenous sodium acetohexamide (N-p-acetylphenylsulfonyl-N'-cyclohexylurea) is, on a weight basis, as great as that of sodium tolbutamide (1-butyl-3-p-tolylsulfonylurea) but lasts longer. In patients with diabetes mellitus the two drugs administered intravenously appear to be of about equal potency in this respect, though in some the responses may be somewhat greater with the one or the other drug.

Materials and methods. One gram of sodium acetohexamide (2.5% solution in water with added sodium mono- and dibasic phosphate, sodium hydroxide, and phenol) or 1.0 g sodium tolbutamide (5% solution in water) was administered intravenously in the fasting state during a 3-minute interval to non-diabetic adults (14 prisoners, 1 adult with muscular dystrophy, and another adult suspected of diabetes mellitus but found to have a non-diabetic glucose tolerance) and to 6 patients with diabetes mellitus not under treatment with insulin or an oral hypoglycemic agent. Venous blood was withdrawn for blood sugar and serum inorganic phosphorus analyses prior to the injection and at 15- or 30-minute intervals thereafter for a total of 2 hours. The ability to dispose of a glucose load was used as an index of the presence of a non-diabetic or a diabetic state: 1.75 g/kg of body weight were ingested orally as a 50% solution in water and levels of blood sugar measured in the fasting state and during the succeeding 5-hour interval. In the non-diabetic group the 2 hour glucose tolerance blood sugar values ranged between 61 and 85, and in the diabetic group, between 211 and 584 mg%.

Results. The data in Table I indicate that the mean hypoglycemic responses of 16 non-diabetic adults to sodium acetohexamide and to sodium tolbutamide were of the same order of magnitude during the first 45 minutes (Table I). However, the hypoglycemic effect of sodium acetohexamide was more prolonged, as indicated by the significantly lower mean blood sugar values at the 60, 90, and 120 minute points.

In these adults without diabetes mellitus, the decrease in serum inorganic phosphorus after acetohexamide, an indirect index of carbohydrate metabolism(1), was no greater than that following tolbutamide, if the evaluation is based on changes from the mean concentration present at zero time (Table II).

It is to be noted, however, that the solution of acetohexamide contained phosphate buffer (79 mg percent of inorganic phosphorus by actual measurement). Hence the injection of 40 ml of the acetohexamide solution might be expected to raise the concentration of inorganic phosphorus by approximately 0.22 mg%, assuming that the inorganic phosphorus was distributed only within the extracellular fluid. In view of this the changes in serum inorganic phosphorus following acetohexamide and tolbutamide have also been calculated with the 15 minute value as the reference point. These calculations reveal that, compared to tolbutamide, acetohexamide produced a greater degree of hypophosphatemia at the 45, 60, and 120 minute points, *i.e.*, at time intervals generally coincident with its more prolonged hypoglycemic action.

There was no clear superiority of one drug over the other in inducing hypoglycemia in diabetes mellitus (Table I), but the number

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TABLE I. Comparison of Hypoglycemic Effects of Tolbutamide and Acetohexamide in Non-Diabetic and Diabetic Adults.

	Age range	Sex	#	Decrease in blood sugar (mg%) at: 15 min.	30 min.	45 min.	60 min.	90 min.	120 min.
Non-diabetic adults	20–66 yr	♂					†	*	†
Acetohexamide			16	24.2±10.0	40.1± 9.0	33.6± 9.1	26.9± 8.6	21.8± 8.6	17.6± 9.0
Tolbutamide			16	22.9±10.5	36.2± 9.9	30.0±12.2	16.8± 6.5	11.6± 8.3	7.0± 5.4
D. M. adults	42–60 yr	5♀ 1♂							
Acetohexamide			6	15.5± 9.6	37.2±21.1	37.0±23.3	38.3±20.0	31.0± 9.0	43.7±11.3
Tolbutamide			6	20.0±29.7	20.2±26.9	23.0±19.6	29.0±15.1	20.7±23.1	31.2±19.2

* p less than .01. † p less than .001.

TABLE II. Changes in Serum Inorganic Phosphorus from Zero Point in Non-Diabetic and Diabetic Adults Following Intravenous Acetohexamide or Tolbutamide.

	#	Decrease in inorganic phosphorus (mg %) at: 15 min.	30 min.	45 min.	60 min.	90 min.	120 min.
Non diabetic adults							
Acetohexamide	15	.16 ± .5	.56 ± .5	.90 ± .6	.96 ± .5	.85 ± .5	.74 ± .5
Tolbutamide	15	.38 ± .3	.65 ± .4	.85 ± .4	.81 ± .4	.78 ± .4	.70 ± .5
D. M. adults							
Acetohexamide	6	.08 ± .3	.16 ± .3	.18 ± .4	.34 ± .4	.23 ± .6	.21 ± .5
Tolbutamide	6	.15 ± .6*	.40 ± .2	.30 ± .3	.24 ± .2	.27 ± .3	.15 ± .3

* = increase.

of patients is limited. Nonetheless, in 3 of these the hypoglycemic effects were of the same order of magnitude, in 2 others acetohexamide produced a greater effect, while in the sixth patient the hypoglycemia induced by tolbutamide was more pronounced. The inorganic phosphorus changes were of the same order of magnitude whether calculated with reference to either the zero or the 15 minute concentration in serum (Table II).

Discussion. The molecular weights of acetohexamide and of tolbutamide are 324.3 and 270.3, respectively. Hence the more prolonged hypoglycemic effect of acetohexamide in healthy subjects cannot be attributed to higher molar concentrations.

Data from human subjects which might identify variables in this more prolonged hypoglycemic action of acetohexamide compared to tolbutamide are lacking. Studies in dogs and rats suggest, however, that in these species the more protracted effect of acetohexamide cannot be attributed to higher levels or to longer survival of the drug. Indeed, the serum levels of acetohexamide shortly following intravenous injection are lower than those obtained with the same dosages of tolbutamide(2,3), suggesting a volume of distribution in body fluids greater than that of tolbutamide. Also, in animals the urinary excretion of acetohexamide appears to be some 75% more rapid than that of tolbutamide. If these findings apply to human subjects, the longer duration of the hypoglycemic produced by acetohexamide cannot be attributed either to a longer chemical or biological half-life. However, the suppliers of acetohexamide have pointed out that the chief metabolic product of acetohexamide, produced by hydrogenation of the acetyl group of the parent compound, has a hypoglycemic potency comparable to that of the precursor(2,3). On the other hand, the metabolic products of tolbutamide are inert in this respect. This difference between the two drugs could account for the more prolonged action of acetohexamide.

The lack of a clear demonstration that, compared to tolbutamide, acetohexamide has a more profound hypophosphatemic effect makes it impossible to estimate the relative roles of increased insulin secretion and dimin-

ished hepatic and other glucose output in the observed hypoglycemia. The calculation of phosphorus changes using the 15 minute rather than the starting value as the reference point may not be valid. If it is valid, then acetohexamide would appear to exert most and perhaps all of its additional hypoglycemic effect through an increased secretion of insulin.

The lack of consistently greater hypoglycemic effect of one drug or the other in diabetes mellitus suggests that individual susceptibilities to these two agents vary. This may be of import in their clinical applications in specific patients with or without a poor response to tolbutamide or sulfonylureas, though the impression to date is that the therapeutic effectiveness of acetohexamide and tolbutamide is comparable, and that control of hyperglycemia with the former requires less drug and perhaps only a single daily dosage (3-9).

Summary and conclusions. 1. Intravenous injection of one gram of the sodium salt of acetohexamide or of tolbutamide produced the same degree of hypoglycemia in human adults without diabetes mellitus but the acetohexamide-induced hypoglycemia was more prolonged. 2. In patients with diabetes mellitus the blood sugar and inorganic phosphorus decreases following acetohexamide and tolbutamide were of the same order of magnitude, though in some patients one or the other drug had a greater effect.

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A Study of Rabbit Antibody Against Rous Sarcoma Virus.* (28976)

MARY ALEXANDER FINK

Laboratory of Viral Oncology, National Cancer Institute, Bethesda, Md.

The effect of antibodies against chicken tissues on the neutralization of Rous sarcoma virus (RSV) has most recently been reviewed by Rubin(1). Previous investigators used either antisera prepared against normal chicken tissues, or antisera prepared with much less potent RSV preparations than are available today.

The present work was undertaken to determine whether or not the more potent preparations of RSV available in this laboratory could engender a good antibody response in the rabbit; and to measure the reactivity of this antibody by complement-fixation and neutralization techniques before and after exhaustion of antibody reactive with Forssman antigen and with the antigens of normal chicken tissue.

Materials and methods. Preparation of antigens. The RSV used to immunize and as antigen in the complement-fixation tests was prepared from wingweb tumors in chickens. The microsomal fraction was obtained by differential centrifugation in a manner which yielded a preparation with an infectivity titre 100 times greater than previously standard preparations. The method was essentially the same as that previously used(2), except that the ultracentrifugation was carried out at 30,000 *g*. One ml of this preparation rep-

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