# Hypoglycemic Potency in Man of a New Sulfonylurea Derivative (Chlorpropamide).* (24163)

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Previous studies have dealt with a comparison of carbutamide analogs, chlorpropamide and tolbutamide, with respect to hypoglycemic potency, as well as acute (Pan—personal communication) and chronic toxicities in mice, rats and or dogs. The present studies were designed to compare the hypoglycemic potencies of chlorpropamide and tolbutamide in man at various times after single oral doses.

*Methods.* In the first experiment, 10 normal adult male subjects were studied who had been in a fasting state after 7:00 p. m. except for 8 ounces of milk at midnight. Venous blood glucose determinations were carried out using the method of Nelson(1) on specimens drawn at 7:00 a. m. Each subject then received by mouth either tolbutamide, 1 g., chlorpropamide, 1 g., or a placebo (sodium bicarbonate, 1 g). The subjects continued in fasting state on sedentary activity and blood glucose samples were drawn 1, 2, 3, 4 and 6 hours after each drug was administered. At weekly intervals, the tests were repeated on each subject using an alternate drug until each subject had received all 3 drugs. The order in which the drugs were administered was randomized, and the technician performing the tests did not know which drug had been administered. In a second experiment, 10 normal adult subjects who had supper at 5:00 p. m. received by mouth at 7:00 p. m. either tolbutamide, 1 g, chlorpropamide, 1 g, or sodium bicarbonate, 1 g. At 11:00 p. m. each subject drank 16 ounces of milk. Sedentary activity was permitted. At 7:00 a. m. the following day, 12 hours after the drugs were given, blood glucose samples were drawn, followed by a standard breakfast containing 52 g carbohydrate, 18 g of protein and 26 g of fat. At 1:00 p. m. (18 hours after the drug and 6 hours after the last feeding) another blood glucose was drawn. This procedure was repeated until each subject had been tested with each drug. The order of testing was randomized and the technician who performed the tests was unaware of which drug had been administered.

*Results.* Table I shows the mean changes in levels of blood glucose during a 6-hour period following administration of the 2 drugs and of the placebo. At 1, 2, 3, 4 and at 6 hours, mean blood glucose levels were significantly lower after chlorpropamide than after placebo ($p<.05$). On the other hand, after tolbutamide, values were significantly lower than placebo only from the second through the fourth hour. It may be seen that on the average, chlorpropamide produced greater hypoglycemic responses than tolbutamide at 1, 2, 3, 4 and 6 hours. At the third hour after medications, the differences between hypoglycemic responses to chlorpropamide and those seen with tolbutamide were statistically significant ($p<.05$, paired control t-test). The observation that chlorpropamide repeatedly led to lower blood glucose levels than did tolbutamide at all 5 periods of measurement lends weight to the evidence that the former does induce a greater hypoglycemia. This observation would be expected to occur by chance only once in 32 trials ($p<.05$).

Table II shows mean blood glucose levels of 10 subjects at 12 and 18 hours following administration of each drug and of the placebo. These data were analyzed using a paired controls t-test. The analyses indicated that a significant hypoglycemic effect was produced by chlorpropamide at 12 hours ($p<.02$) and at 18 hours ($p<.02$). On the other hand, the effect produced by tolbutamide was not statistically significant at 12 or at 18 hours although the mean blood glu-

* Chlorpropamide was supplied by Charles Pfizer and Co., as *Diabenese.*

TABLE I. Mean Changes (± S.D.) in Blood Glucose Levels after Placebo, Chlorpropamide and Tolbutamide in 10 Normal Subjects.

| Drug | | Control in mg % at 7 a.m. | 1 hr | 2 hr | 3 hr | 4 hr | 6 hr |
|---|---|---|---|---|---|---|---|
| $NaHCO_3$ | 1 g | 76 ± 7.9 | − 2 ± 3.9 | − 3 ± 4.0 | − 4 ± 6.3 | − 5 ± 6.8 | − 6 ± 7.0 |
| Chlorpropamide | " | 76 ± 5.6 | −12 ± 11.0 | −15 ± 5.3 | −17 ± 7.4 | −15 ± 8.4 | −12 ± 6.7 |
| Tolbutamide | " | 77 ± 4.7 | − 5 ± 8.2 | −11 ± 6.4 | −13 ± 6.3 | −10 ± 7.4 | −11 ± 7.3 |

See text for degree to which differences statistically significant.

cose values were slightly lower after tolbutamide than after the placebo at both 12 and 18 hours.

None of the subjects exhibited significant toxic effects from either chlorpropamide or tolbutamide, although in a few instances subjects reported symptoms which could have been on the basis of mild hypoglycemia, such as headache and tremulousness. In 2 instances these symptoms occurred 1 to 2 hours after chlorpropamide at which time the levels of blood glucose were less than 55 mg %.

*Discussion.* It is evident that chlorpropamide is a potent hypoglycemic agent. It is not possible on the basis of these data to define clearly its time-action curve. It has been shown that the blood levels of chlorpropamide 24 hours after single doses are greater than blood levels of tolbutamide after equivalent doses of tolbutamide(1). This suggests that the greater potency of chlorpropamide might be due to slower degradation or slower excretion of that drug. On the other hand, it does not seem likely that a slower rate of degradation or excretion could account entirely for the increased potency in man of chlorpropamide as compared to tolbutamide since differences in potency were impressive as early as 1 to 3 hours after administration of the drugs (Table I).

TABLE II. Mean Changes in Blood Glucose Levels of 10 Normal Subjects 12 and 18 Hr after Chlorpropamide and Tolbutamide.

| At 7 a.m., 12 hr after drug | | | At 1 p.m., 18 hr after drug | | |
|---|---|---|---|---|---|
| Control,* | Chlorp. | Tolb. | Control | Chlorp. | Tolb. |
| 73 ± 4.0† | −6 ± 4.7 | −2 ± 6.8 | 73 ± 3.6 | −5 ± 5.6 | −2 ± 7.0 |

* Blood glucose at 7 a.m., 12 hr after a placebo.
† Stand. dev.

See text for degree to which differences statistically significant.

In the diabetic patients whom we have treated with daily doses of chlorpropamide, the fasting blood glucose level gradually declined during the first 4 to 7 days of treatment before stabilizing, suggesting that daily administration produced a cumulative effect. This suggests that the half-life of this drug is similar to that of carbutamide, which is approximately 33 hours(2). The biologic half-life of tolbutamide is approximately 4 hours(2).

The degree to which chlorpropamide will be useful in the treatment of diabetes will depend also, of course, on its toxicity in man which we are not yet able to evaluate adequately.

*Summary and conclusions.* A single oral dose of 1 g of chlorpropamide produced a significant hypoglycemic effect in normal subjects at 1, 2, 3, 4, 6, 12 and 18 hours after administration by mouth. At each of these hours the hypoglycemic effect produced was greater than that produced in these subjects by an identical dose of tolbutamide.

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