Tolbutamide Loading in the Initial Therapy of Diabetes Mellitus

Ravindra S. Arora, M.D., Patrick Hardy, M.D., and Gerald T. Perkoff, M.D.
St. Louis

SUMMARY

A controlled study has been made comparing a loading dose schedule of tolbutamide with a maintenance dose schedule in the initial therapy of fourteen patients with maturity-onset diabetes mellitus. No advantage of one dose schedule over another was found. Since hypoglycemia may occur when large doses of tolbutamide are used, these results provide supporting evidence for those who recommend use of low doses of this drug in the initial therapy of patients with diabetes mellitus. DIABETES *15*:279-80, April, 1966.

Tolbutamide* is used widely as an oral hypoglycemic agent in the treatment of patients with maturity-onset diabetes mellitus. Although the side effects from this agent are minimal, hypoglycemic reactions have been reported when the drug was given to some patients with diabetes mellitus, particularly when the patients were elderly or when they had diseases other than or in addition to diabetes.[1-5] It is generally accepted that the maintenance dose of tolbutamide is 0.5-2.0 gm. per day, with an average of about 1.0 gm. per day. However, the amount used in initial treatment varies. Some[6-12] recommend an initial loading dose of three grams on the first day, followed by two grams on the second day and one gram daily thereafter. Others use 0.5-1.0 gm. per day as the initial dose,[13-17] but a controlled study of the merits of these two schedules has not been reported. Since the incidence of hypoglycemic reactions may be greater when the larger dose of drug is used, the present study was conducted to evaluate the necessity of the loading dose in the initial management of diabetes mellitus.

MATERIALS AND METHODS

Fourteen patients with maturity-onset diabetes mellitus who had never received oral hypoglycemic agents were studied. The patients were placed in the study successively as they appeared in the clinic. Two patients had received small doses of insulin previously, but in neither case had insulin been given for at least a week before the beginning of the study. Diabetic diets were prescribed for all patients according to their weights and activity, using standard exchange tables. Fasting and two-hour postprandial (p.c.) blood glucose levels were measured for two days (control days). On the third day of study, each patient was given one of two kinds of unlabeled tablets of tolbutamide. One set was formulated so that the total dose of tolbutamide was one gram per day, even though different numbers of tablets were given on days 1, 2, and 3 of therapy (Group A, seven patients), while the other was the standard 0.5 gm. tolbutamide tablet (Group B, seven patients). Both kinds of tablets were identical in appearance. Thus the same number of tablets could be given whether the loading dose schedule (3.0, 2.0, 1.0 gm.) or the maintenance dose schedule (1.0 gm.) was used. On Day Three, three tablets were given before breakfast and supper. On Day Four, each patient received two tablets before breakfast and supper. On Day Five and each day thereafter, each patient received one tablet (0.5 gm.) before breakfast and supper. Neither the patient nor the physician knew which tablets were being used; alternate patients merely received the tablets for Group A or B as the case may have been. Blood studies were repeated on Days 3, 4, 5, 7, 14, 21, and 28. Glucose was determined by the Nelson-Somogyi method.[18] Statistical analyses were made by the method of covariance in the statistical laboratories of The Upjohn Company. The differences between the means of the blood glucose levels for each treatment group were adjusted for differences in the mean control values of the various groups using regression analysis and analysis of variance.[19]

RESULTS AND DISCUSSION

The results are given in table 1 and figure 1.

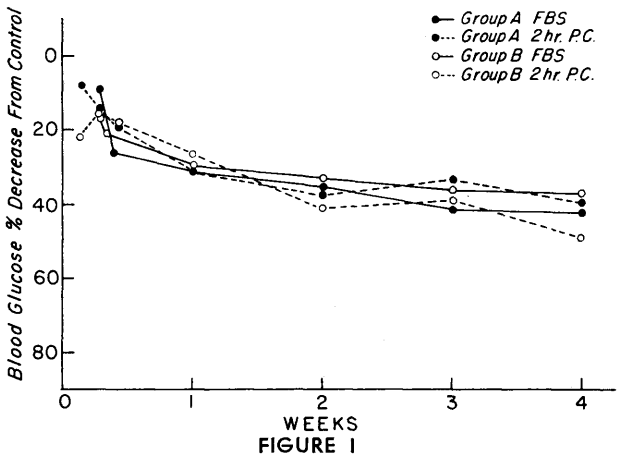

FIGURE 1

From the Unit I (Washington University) Medical Service, St. Louis City Hospital, and the Department of Medicine, Washington University School of Medicine, St. Louis, Missouri.

*Orinase, The Upjohn Company, Kalamazoo, Michigan.

TABLE 1

Mean blood glucose values (mg. per 100 ml.)

Days of study	Control	3	4	5	7	14	21	28
Group A	241.2	254.1	229.4	182.8	169.6	162.4	148.0	149.1
FBS	±12.0*	±16.2	±25.1	±20.6	±35.3	±14.9	±20.6	±19.6
Per cent decrease†	—	—	9	26	31	35	41	42
2-hr. p.c.	316.1	293.8	258.6	247.4	221.3	177.1	191.3	181.5
	±19.7	±30.3	±28.6	±37.1	±32.0	±31.04	±24.9	±32.0
Per cent decrease	—	8	14	19	31	37	33	39
Group B	241.6	233.8	194.7	192.3	171.0	159.6	151.0	150.6
FBS	±11.1	±14.9	±23.2	±19.0	±32.0	±14.1	±20.6	±17.5
Per cent decrease	—	—	17	21	30	33	36	37
2-hr. p.c.	314.2	245.3	278.6	266.9	232.6	204.1	208.9	164.5
	±17.9	±27.5	±26.0	±33.8	±28.3	±29.0	±23.0	±32.0
Per cent decrease	—	22	16	19	27	41	39	49

*Adjusted mean ± standard error of the adjusted mean (ref. 19; see text).
†Per cent decreases calculated from unadjusted means.

Except for the fact that the control two-hour post cibum blood glucose values were somewhat higher for Group B (Loading Dose) than for Group A, the results of the blood glucose analyses were similar for the two groups. There were no statistically significant differences between the two groups on any day of study. The degree of diabetic regulation achieved in the two groups was the same, both in terms of the time at which maximal reduction in blood glucose levels occurred, and in terms of the absolute and percentage decreases in blood glucose level. This is seen best in figure 1, where per cent fall in fasting and two-hour post cibum blood glucose levels is shown for both groups.

Although the number of patients evaluated in this study was quite small, the data obtained are remarkably consistent and show that similar results were achieved in both groups. Under the conditions of this study the loading dose schedule had no advantage over the maintenance dose schedule. Hypoglycemia from tolbutamide was not observed in any patient studied. These results suggest that doses of tolbutamide larger than 1.0 gm. daily are unnecessary in the initial therapy of diabetes. They are not pertinent, however, to those cases of diabetes known to require doses of tolbutamide larger than 1 gm. per day for maintenance of diabetes regulation later in therapy.

ACKNOWLEDGMENT

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