FDA CURRENT DRUG INFORMATION

NEWS AND REPORTS OF INTEREST TO PRACTICING PHYSICIANS. ISSUED BY THE FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

# Oral hypoglycemic agents

*Oral hypoglycemic agents should be used only in diabetics with adult onset, stable, disease, which cannot be controlled by diet alone and for whom insulin is unacceptable or impractical. A recently published study shows NO evidence that in diabetics with adult onset stable disease, therapy with a fixed dose of one such agent (tolbutamide) and diet is more effective in prolonging life than diet alone. The study also suggests that such a regimen may be less effective insofar as cardiovascular mortality is concerned than diet alone or than diet and insulin combined.*

## BACKGROUND

This Bulletin is a result of joint review of the University Group Diabetes Program (UGDP) study by the Council on Drugs of the American Medical Association, a committee of the American Diabetes Association, and the Food and Drug Administration. A complete report of the Study may be found in a supplement to *Diabetes:* The Journal of the American Diabetes Association published in November 1970.

Briefly, the study was started in 1961 and eventually included over 800 patients in 12 university medical-school clinics. Most patients have been followed at least five years and some as long as eight years. The study compared the results of various hypoglycemic treatment regimens in patients with recently diagnosed adult onset mild diabetes who were not insulin dependent and who were expected to live at least five years after entry into the study. All patients were placed on an antidiabetic diet. In one group, Orinase (tolbutamide) in addition to diet was given in a fixed dosage of 1.5 gm/day. Insulin in addition to diet was given in a fixed dosage (12-16 units U80 Lente daily according to body surface) to a second group and in varying dosage (dose required to maintain normal blood sugar) to a third group. A fourth group was treated with diet and placebo. (A fifth group was treated with diet and DBI (phenformin). Findings on this latter group will be presented in a subsequent publication.)

## FINDINGS

Despite a number of limitations in the study, the American Diabetes Association, the Council on Drugs of the American Medical Association, and the Food and Drug Administration agree with the University Group Diabetes Program's stated conclusions which are:

> "The findings of this study indicate that the combination of diet and tolbutamide therapy is no more effective than diet alone in prolonging life. Moreover, the findings suggest that tolbutamide and diet may be less effective than diet alone or than diet and insulin at least in so far as cardiovascular mortality is concerned."

For this reason use of tolbutamide has been discontinued in the study. At the end of an eight-year period, death rates from cardiovascular diseases were 2-1/2 times as high in the tolbutamide group (12.7% or 26 out of 204 patients) as in the placebo group (4.9% or 10 out of 205 patients). Though not statistically significant, mortality rates from all causes, including cardiovascular disease, were approximately 50% higher in the tolbutamide group (14.7% or 30 out of 204 patients) than in the placebo group (10.2% or 21 out of 205 patients). The mortality rates for the two insulin treatment groups were nearly the same as those for placebo treated patients. Preliminary analysis of data fails to show any significant differences among any of the groups in the incidence of non-fatal events.

Although this study considered only one sulfonylurea, tolbutamide, it raises serious questions as to the ultimate place of all oral antidiabetic agents in the treatment of diabetes mellitus. Further studies and analysis of other ongoing studies will be necessary to answer the many questions which now exist in diabetic therapy.

## RECOMMENDATIONS

**Pending results of such studies, the Food and Drug Administration recommends that the use of Orinase (tolbutamide) and other sulfonylurea type agents, Dymelor (acetohexamide), Diabinese (chlorpropamide), Tolinase (tolazomide), should be limited to those patients with symptomatic adult onset nonketotic diabetes mellitus which cannot be adequately controlled by diet or weight loss alone and in whom the addition of insulin is impractical or unacceptable. The oral hypoglycemic agents are not recommended in the treatment of chemical or latent diabetes, in suspected diabetes, or in pre-diabetes, and are contraindicated in patients with keto-acidosis.**