

13418 COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

The usual daily dose of tolbutamide is 1000 mg, while 2000 mg is the maximally effective total dose; corresponding dosages are 500 and 1500 mg for acetohexamide. Tolazamide and chlorpropamide are usually administered in a daily dosage of 250 mg, while 750 to 1000 mg is maximal.

Therapeutic Uses. *The sulfonylureas should be used only in subjects with diabetes of the maturity-onset type who cannot be treated with diet alone or who are unwilling or unable to take insulin if weight reduction and dietary control fail.* The physician must realize that he is using these agents only to control symptoms associated with hypoglycemia, and that dietary control with or without insulin is more effective for this purpose. There is no evidence that the oral hypoglycemic agents prevent cardiovascular complications from diabetes, and the best data available suggest that the incidence of such complications is increased in patients taking these drugs. This is obviously too high a price for the convenience of an oral agent, unless all other measures have been exhausted.

In general, the likelihood of adequate control with an oral hypoglycemic agent is inversely proportional to the dose of insulin required to maintain the patient. When the insulin requirement is in excess of 40 units per day, the chances of success are relatively low. The sulfonylureas are of no value in the juvenile-onset type of diabetes, in which the pancreas has lost all or nearly all of its capacity to secrete insulin. However, whatever the age of onset, in unstable, ketoacidotic diabetes, sulfonylureas will not provide adequate control. *Such patients require insulin, and attempts to control them with oral therapy are dangerous and doomed to failure.* Deaths from acidosis and dehydration have occurred in patients with unstable ketotic diabetes in whom regulation was attempted with sulfonylureas.

There is no fixed dosage of sulfonylurea to be used in diabetes mellitus. Treatment is guided by the individual patient's response, which must be frequently monitored with chemical determinations, because the requirements change from time to time.

The mildly diabetic patient, whose insulin requirement is fewer than 20 units daily, can be started on the usual dose of the agent chosen, and at the same time all insulin is discontinued. The dose is then adjusted up or down, depending on the patient's response. In the instance of chlorpropamide, about 3 days is required to attain steady-state concentrations in blood. Consequently, upward adjustments of dose should be made at 3-day intervals. Patients of advanced age should begin with about half the usual daily dose, for some are very responsive to sulfonylureas and may develop severe hypoglycemia after usual doses. During the period of initiating treatment, all patients should test their urine four times daily and communicate the results to the physician daily.

The patient who requires more than 20 and fewer than 40 units of insulin daily should be started on the usual dose of the chosen agent and his insulin dosage should simultaneously be reduced by 50%. Thereafter, guided by the patient's response, insulin dosage is progressively reduced and eventually discontinued. Sulfonylurea dosage may need adjustment.

The patient requiring more than 40 units of insulin daily should be given the usual dose of the agent chosen and his insulin dosage should be reduced by 25%. Insulin is then cautiously withdrawn and eventually discontinued, and sulfonylurea is adjusted according to the observed response. It is to be emphasized that the chance of success is relatively poor. In the patient who requires more than 40 units of insulin daily, it may be desirable to carry out the attempted transfer to the sulfonylurea therapy in the hospital to provide assurance against development of dehydration and acidosis.

Stimulation of the pancreas of the maturity-onset diabetic can often maintain these subjects under ordinary circumstances. However, when insulin requirements are increased, as fever, surgical interventions, or trauma, the sulfonylureas are inadequate and the patient must be given insulin to carry him through such critical situations.

Weight reduction is of the greatest importance in the treatment of diabetes. A vigorous effort must be made by the patient and the physician to reduce the patient's weight as an integral part of diabetic treatment, irrespective of the drug chosen.

Patients whose diabetes is not controlled by sulfonylureas from the initiation of treatment are said to experience "primary failure." Patients whose diabetes is regulated for a month or more after beginning sulfonylurea treatment, fol-