

Oral Hypoglycemic Agents

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The pharmacology of the two general groups of oral anti-diabetic agents, namely the sulfonylureas and biguanides, are briefly discussed here. The sulfonylureas have a common hypoglycemic core. These sulfonylurea compounds can be divided into short, intermediate, and long-acting agents, with varying half-lives, and duration of action. Therapeutic doses of sulfonylureas have produced wide variations in serum levels depending upon the rates of absorption, rates of metabolism, renal clearance, and degree of protein-binding. Tolbutamide is a short-acting agent metabolized by the liver to inactive compounds which are excreted by the kidney; it has a half-life of four to five hours, a duration of action of approximately six to ten hours, and is given in divided daily dosage. Acetohexamide and tolazamide, the intermediate-acting compounds, are metabolized by the liver. Approximately 75% of acetohexamide is metabolized to another hypoglycemic compound, and tolazamide is metabolized to several hypoglycemic products. The duration of the action of these agents is approximately 10 to 16 hours; they are administered either once or twice daily. Chlorpropamide is only slightly altered, less than 1% being metabolized, probably in the liver; it is firmly bound to protein, is dependent on renal excretion for clearance, and, as it has a duration of action varying from 35 to 72 hours, it is given only once daily.

Sulfonylurea compounds appear to exert their primary action through direct stimulation of pancreatic insulin secretion. Peripheral insulin levels correlate with blood sugar levels during acute therapy,

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but do not appear to correlate with blood sugar-lowering effect of chronic drug therapy. Hence, important extra-pancreatic actions may be responsible for the hypoglycemic effects of these compounds, that is, induced hepatic glycolytic enzymes, impaired insulin sensitivity, increased membrane receptors, lowered insulin resistance, or other as yet undefined mechanisms.

Phenformin, a biguanide, is metabolized to some extent by the liver, but approximately 65% may be excreted unchanged by the kidneys. The hypoglycemic effect of the "short-acting" tablet lasts six to eight hours. In contrast, the timed disintegration capsule has a duration of action from 8 to 14 hours because of prolonged gastrointestinal absorption of the drug. The mode of action of these agents is not completely understood. There is evidence that phenformin lowers blood sugar levels by accelerating anaerobic glycolysis and delays the absorption of glucose from the gastrointestinal tract. Phenformin also decreases hepatic gluconeogenesis of diabetic animals, but this has not been confirmed in man. It is also quite possible that the anorexigenic effects of this agent may lower caloric intake, and help exert its hypoglycemic action in this manner.

Side effects and toxic effects are relatively rare with the sulfonylureas. Hematologic, hepatic, and dermatologic reactions have been described. An "antabuse" effect has been noted with chlorpropamide. Rare cases of hypersensitivity angitis have been described. Dilutional hyponatremia has been noted with chlorpropamide, and very occasionally with tolbutamide. In contradistinction, tolazamide and acetohexamide appear to have a proximal tubular diuretic effect.

Side effects of phenformin consist primarily of

gastrointestinal reactions. Lactic acidosis, however, is a serious problem, particularly in the phenformin-treated diabetic with liver or renal disease, who is vulnerable to a variety of medical conditions which may lead to tissue hypoxia, that is, myocardial infarction, peripheral vascular disease with gangrene, and gastrointestinal bleeding. In addition, alcohol and phenformin are a particularly dangerous combination.

There are a number of drugs which may interact and potentiate the effects of the sulfonylurea compounds. These include phenylbutazone, probenecid, alcohol, salicylates, and monamine oxidase inhibitors. The list is growing, and the clinician treating the diabetic with sulfonylureas must be constantly on the alert.

The indications for oral agent therapy are relative, depending upon the patient's age, weight, fasting and postprandial blood sugar levels, and intensity of symptoms. Oral agents have a place in the management of the maturity onset diabetic. The aim of therapy of the diabetic patient is to produce normal weight for frame and height, to obtain as close to normal fasting and postprandial blood glucose levels as possible, to maintain normal lipid levels, and to keep the patient free from hypoglycemic episodes. Diet or insulin therapy or both are the bases of treatment for the non-obese patient with fasting blood glucose values above 160 mg/100 ml. A weight reduction regimen, however, is the mainstay of management of the obese maturity onset diabetic. This requires constant dietary counseling by the physician, the dietician, and the nurse-educator. In most cases, if weight reduction is successful, plasma glucose and lipid levels will approach normal values, and the patient will usually become asymptomatic. If the plasma glucose still remains high, and particularly if the patient is still symptomatic, the sulfonylurea agents may be tried. If hyperglycemia is not controlled within a short period of time, by either short- or intermediate-acting agents, as well as long-acting sulfonylurea compounds, then insulin should be administered; the "uncontrolled" patient may also have been taking other drugs during this period which may antagonize

the action of the oral agents, for example, corticosteroids in pharmacologic doses, excessive doses of thyroid hormones, diuretics which may produce moderate to severe hypokalemia, oral contraceptives, and nicotinic acid in pharmacologic doses. More significantly, the patient must be warned against increasing weight gain during the administration of these oral agents. All these factors must be borne in mind in the consideration of "secondary failures." Hypoglycemia during oral therapy may result from overdosage (that is, failure to titrate dosage downward), poor choice of the oral therapeutic agent, omission of meals, renal or hepatic insufficiency, and interaction with other drugs, or alcohol.

In conclusion, comment is made on the findings of the University Group Diabetes Program (UGDP). The purpose of the UGDP was to determine whether or not control of blood glucose levels would help to prevent or delay vascular disease in non-insulin-requiring diabetics. After 8½ years of follow-up at 12 university-affiliated treatment centers, "The findings of the 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 diet and insulin, at least insofar as cardiovascular mortality is concerned." The debate on the validity of this study still rages. A number of the criticisms leveled against the study by diabetologists, other clinicians, epidemiologists, and statisticians are discussed. These include inappropriate patient selection and randomization, higher risk factors at the outset of the study, manipulation of electrocardiographic data, risk factors such as smoking and hypertension not measured or monitored, use of fixed dosage of drug, clinic preponderance regarding mortality (it has been alleged that the bulk of tolbutamide mortality occurred in four clinics, Birmingham, Boston, Cincinnati, and Minneapolis), use of "patient data" against "computerized data," neglect of appropriate "vascular" history, neglect of "co-morbidity," contradictory clinical studies here and abroad, and the danger of extrapolation of the UGDP findings to other sulfonylurea agents.