**ORAL HYPOGLYCEMIC DRUGS**

Oral hypoglycemic drugs are used only in the treatment of type 2 diabetes which is a disorder involving resistance to secreted insulin. Type 1 diabetes involves a lack of insulin and requires insulin for treatment. There are now four classes of hypoglycemic drugs:

* Sulfonylureas
* Metformin
* Thiazolidinediones
* Alpha-glucosidase inhibitors.

These drugs are approved for use only in patients with type 2 diabetes and are used in patients who have not responded to diet, weight reduction, and exercise. They are not approved for the treatment of women who are pregnant with diabetes.

SULFONYLUREAS – Sulfonylureas are the most widely used drugs for the treatment of type 2 diabetes and appear to function by stimulating insulin secretion. The net effect is increased responsiveness of ß-cells (insulin secreting cells located in the pancreas) to both glucose and non-glucose secretagogues, resulting in more insulin being released at all blood glucose concentrations. Sulfonylureas may also have extra-pancreatic effects, one of which is to increase tissue sensitivity to insulin, but the clinical importance of these effects is minimal.

Pharmacokinetics – Sulfonylureas differ mainly in their potency & their duration of action. Glipizide, glyburide (glibenclamide), and glimepiride are so-called second-generation sulfonylureas. They have a potency that allows them to be given in much lower doses.

Those drugs with longer half-lives (particularly chlorpropamide, glyburide, and glimepiride) can be given once daily. This benefit may be counterbalanced by a substantially increased risk of hypoglycemia.

Side effects – Sulfonylureas are usually well tolerated. Hypoglycemia is the most common side effect and is more common with long-acting sulfonylureas. Patients recently discharged from hospital are at the highest risk for hypoglycemia.

Patients should be cautioned about those settings in which hypoglycemia is most likely to occur. They are:

* After exercise or a missed meal.
* When the drug dose is too high.
* With the use of longer-acting drugs (glyburide, chlorpropamide).
* In patients who are undernourished or abuse alcohol.
* In patients with impaired renal or cardiac function or inter-current gastrointestinal disease.
* With concurrent therapy with salicylates, sulfonamides, fibric acid derivatives (such as gemfibrozil), and warfarin.
* After being in the hospital.

Other, infrequent side effects that can occur with all sulfonylureas include nausea, skin reactions, and abnormal liver function tests. Weight gain can also occur unless the diabetic diet and exercise program are followed. Chlorpropamide has two unique effects: it can cause an unpleasant flushing reaction after alcohol ingestion and it can cause hyponatremia (low blood sodium), primarily by increasing the action of antidiuretic hormone.

Clinical use – Sulfonylureas usually lower blood glucose concentrations by about 20 percent. They are most likely to be effective in patients whose weight is normal or slightly increased. In contrast, insulin should be used in patients who are underweight, are losing weight, or are ketotic despite adequate caloric intake.

The choice of sulfonylurea is primarily dependent upon cost and availability, because their efficacy is similar. However, given the relatively high incidence of hypoglycemia in patients taking glyburide or chlorpropamide, shorter acting drugs should probably be used in elderly patients

Repaglinide – Repaglinide is a short-acting glucose-lowering drug recently approved by the Food and Drug Administration for therapy of type 2 diabetes alone or in combination with metformin. It is structurally different than sulfonylureas, but acts similarly by increasing insulin secretion.

The clinical efficacy of repaglinide is similar to that of the sulfonylureas. The recommended starting dose is 0.5 mg before each meal for patients who have not previously taken oral hypoglycemic drugs. The maximum dose is 4 mg before each meal; the dose should be skipped if the meal is missed. Hypoglycemia is the most common adverse effect.

Natiglinide - Natiglinide (Starlix) is a very short-acting glucose lowering drug whose mode of action is similar to the sulfonylureas and is nearing approval by the FDA. A potential advantage of this drug is that it seems to have it's effect on the first phase of insulin release rather than the late phase of insulin release. The first phase of insulin release is brisk, of short duration and occurs within minutes of ingesting food. It is this first phase of insulin release that is abnormal in early diabetes & can often be found in patients with impaired glucose tolerance prior to the onset of diabetes. The usual dose is 120 mg before meals.

METFORMIN – Metformin has been used in Europe for over thirty years, and has been available in the United States since March 1995. It is effective only in the presence of insulin but, in contrast to sulfonylureas, it does not directly stimulate insulin secretion. Its major effect is to increase insulin action.

How metformin increases insulin action is not known but it is known to affect many tissues. One important effect appears to be suppression of glucose output from the liver.

Clinical use – Metformin is most often used in patients with type 2 diabetes who are obese, because it promotes modest weight reduction or at least weight stabilization. This is in contrast to the increased appetite and weight gain often induced by insulin and sulfonylureas.

Metformin typically lowers fasting blood glucose concentrations by approximately 20 percent, a response similar to that achieved with a sulfonylurea.

Metformin given in combination with a sulfonylurea lowers blood glucose concentrations more than either drug alone.

In addition to causing modest weight loss, metformin has two other advantages as compared with sulfonylureas. They are:

* It is less likely to cause hypoglycemia.
* It has prominent lipid-lowering activity, producing a significant reduction in serum triglyceride and free fatty acid concentrations, a small reduction in serum low-density lipoprotein (LDL) cholesterol concentration, and an elevation in serum high-density lipoprotein (HDL) cholesterol concentration.

There are, however, two disadvantages to metformin: the risk for lactic acidosis described below and its prominent gastrointestinal side effects.

Pharmacokinetics – Metformin should be taken with meals and should be started at a low dose to avoid intestinal side effects. The dose can be increased slowly as necessary to a maximum of 2550 mg/day (850 mg TID).

Side effects – The most common side effects of metformin are gastrointestinal, including a metallic taste in the mouth, mild anorexia, nausea, abdominal discomfort, and diarrhea. These symptoms are usually mild, transient, and reversible after dose reduction or discontinuation of the drug.

A rare problem is lactic acidosis, which may be fatal in as many as one-half of cases. The risk is much less than with another biguanide, phenformin, which was withdrawn from use in the United States in the 1970s because of this complication. Serious lactic acid accumulation usually occurs only in the presence of a predisposing conditions including:

* Renal insufficiency.
* Current liver disease or alcohol abuse.
* Heart failure.
* Past history of lactic acidosis.
* Severe infection with decreased tissue perfusion.
* Hypoxic states
* Serious acute illness
* Hemodynamic instability
* Age 80 years or more

Drug interactions – A potential drug interaction exists between metformin and cimetidine (Tagamet) resulting in an increase in metformin blood levels. This interaction could increase the risk of hypoglycemia in patients taking metformin plus a sulfonylurea or insulin, and could increase the risk of lactic acidosis in those with impaired renal function. These risks could increase now that cimetidine is available over-the-counter. Other H2-blockers are less likely to cause this problem.

The manufacturer also recommends discontinuing metformin for 48 hours after any radiologic procedure involving the administration of iodinated contrast material into the blood. The rationale for this recommendation is to avoid the potential for high plasma metformin concentrations if the patient develops contrast-induced acute renal failure

THIAZOLIDINEDIONES – The thiazolidinediones such as Avandia (Rosiglitazone) and Actos (Pioglitazone) reverse insulin resistance by acting on muscle, fat and to a lesser extent liver to increase glucose utilization and diminish glucose production.

The mechanism by which the thiazolidinediones increase insulin action is not well understood but they may be acting by redistributing fat from the visceral compartment to the subcutaneous compartment. We know that visceral fat is associated with insulin resistance.

Efficacy – In one large study of 284 patients with type 2 diabetes treated with Rezulin, the fall in mean fasting blood glucose concentration was significant but not dramatic over 12 weeks; patients treated with placebo had a fall in blood glucose concentration of only 4 mg/dL. The HbA1c value in the troglitazone group fell from 8.6 to 8.1 percent.

Thiazolidinediones are also effective when given in combination with metformin, although they are not currently approved for this purpose.

Safety – There have been reports of severe liver injury in small numbers of patients receiving Rezulin and this product has now been removed from the market. Most cases of liver damage occured early in treatment with the drug and were reversible when it was stopped but there have been some deaths. The newer agents such as Actos and Avandia have a much lower incidence of this side effect.

ALPHA-GLUCOSIDASE INHIBITORS – The alpha-glucosidase inhibitors include acarbose (Precose) & Miglitol (Glycet) and are available in the United States. They inhibit the upper gastrointestinal enzymes that converts dietary starch and other complex carbohydrates into simple sugars which can be absorbed. The result is to slow the absorption of glucose after meals.

As in patients with type 2 diabetes, patients with type 1 diabetes have a reduction in the amplitude of glucose excursion and HbA1c and a possible reduction in nocturnal hypoglycemia with alpha-glucosidase inhibitors.

The main side effects of alpha-glucosidase inhibitors are flatulence and diarrhea. These symptoms are usually mild and do not necessitate cessation of therapy.