Treatment of Diabetes With Oral Hypoglycemic Drugs

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Oral hypoglycemic drugs now available are of two types. The biguanides, of which phenformin (DBI) is the only one available, increase glucose utilization by muscles. The sulfonylureas, tolbutamide (Orinase), acetohexamide (Dymelor), and chlorpropamide (Diabinese), stimulate the pancreas to produce and release more insulin. All three sulfonylureas have the same effect in responsive patients, but they differ in potency and in duration of action.

THE SULFONYLUREAS

Tolbutamide is rapidly metabolized into an inactive chemical that is promptly excreted in the urine. Because the blood half-life is six hours, this drug should be given two to four times each day. On cessation of treatment the hypoglycemic effect is promptly dissipated.

Acetohexamide has a blood half-life of six hours, but the metabolic product has hypoglycemic activity that lasts for several hours before it is excreted in the urine. In patients with poor renal function, the metabolite may accumulate in the blood and cause prolonged hypoglycemia after a small dose. This drug is usually given twice daily.

Chlorpropamide is not metabolized but is excreted in the urine over a period of four days. Because the blood half-life of this drug is 36 hours, the entire daily dose can be given at breakfast. Since there are occasional reports of cholestatic jaundice after large doses, chlorpropamide should not be used in patients with known or suspected liver disease.

Comparative studies of these three drugs shows that chlorpropamide has the greatest overall effectiveness with the best diabetic control, the smallest number of secondary failures, and the lowest cost to the patient. The difference between the three drugs is so small that each physician should routinely use only one but learn to use that one well.

The sulfonylureas are most effective in patients who develop diabetes after the age of 30, who have few diabetic symptoms, and who are near normal weight. Younger patients and those who have ketonuria, weight loss, and the classical symptoms of diabetes usually require insulin. A few symptomatic patients who require insulin for initial control may later respond to a sulfonylurea.

The sulfonylureas are usually of no value in juvenile patients. On rare occasions when diabetes was detected during the asymptomatic phase, it has been possible to achieve satisfactory control for several months with the sulfonylureas. Because this response is always temporary, it is essential that the patient be followed closely so that insulin may be started promptly when needed.

FAILURES OF ORAL HYPOGLYCEMIC AGENTS

"Primary failure" refers to lack of response to the oral agent from the beginning of therapy. "Secondary failure" describes the loss of
diabetic control after initial satisfactory control for more than a month on an oral drug. The exact incidence of secondary failure will depend upon how freely the drug is used initially and how strict are the criteria of control. If the drug is used only in those patients expected to have an excellent diabetic response, the incidence of primary and secondary failure will be low. If the drug is used in younger patients with moderately severe diabetes, there will be a higher incidence of failures. Some patients classified as secondary failures initially were not under good control and should be classified as primary failures. Many obese patients follow their diet initially, but later eat excessively, gain weight, develop hyperglycemia and are classified as a secondary failure. Some patients develop poor control during a transient period of stress and must be changed to insulin. If the sulfonylurea is continued with supplemental insulin during the period of stress, the oral drug may later be successful. In our series, the clinic patients who had a fasting blood sugar over 200 mg per 100 ml after being on the maximum dose of the drug for one week were classified as secondary failures. The highest incidence of failure is in the first few months, but true secondary failure may develop after several years of excellent diabetic control. A patient who is under excellent control is less likely to develop secondary failure than is one who is under fair control. Patients who required large doses of insulin have more secondary failures than do those who require no insulin. The longer the duration of diabetes, the greater is the incidence of secondary failure. The true incidence of secondary failure is probably about 0.25% during each month of treatment with a sulfonylurea. The exact rate makes little difference, as long as physicians are aware that this condition can occur at any time.

**CONTRAINDICATIONS TO SULFONYLUREAS**

When they were first introduced, the sulfonylureas were not recommended for patients with infection, surgery, pregnancy, or neuropathy. These precautions are still included on the package inserts. However, many patients have successfully undergone major surgical procedures while taking these drugs. Excellent diabetic control was maintained in the post-operative period, but a few patients required supplemental injections of insulin for two or three days. In the presence of infection, the insulin requirements rise and supplemental insulin may be needed until inflammation has subsided. In a group of 20 pregnant patients treated with oral drugs, there was no evidence of any deleterious effect that could be attributed to the drugs, even though there were only 13 live babies in the group.

Many physicians have used the sulfonylurea drugs in patients with very mild diabetes. Theoretically, if hypertrophy and hyperplasia of the \( \beta \)-cells is produced, the eventual use of insulin could be postponed. However, sufficient data to substantiate this is not yet available. Patients with minimal diabetes are more responsive to the sulfonylurea drugs, and may easily develop hypoglycemia. There is little justification for the use of any drug in patients who have a normal fasting blood sugar, even though the post-prandial blood sugar is elevated.

**PHENFORMIN**

Phenformin (DBI) is a different type of chemical that acts on muscle and liver cells in an undetermined manner to increase glucose uptake. This drug will lower the blood sugar of any diabetic if a large enough dose is given, but it does not lower the blood sugar of non-diabetics. It is effective in many patients who do not respond to a sulfonylurea. It is also used to increase the effectiveness of both sulfonylureas and insulin.

Obese patients taking phenformin usually lose one pound each month. Because no other method of treating diabetes causes such consistent weight loss, this is the preferable drug for obese diabetics. The average therapeutic dose is slightly less than 1 mg per lb of body weight, but there is a narrow therapeutic margin. If the dose is raised too high in an effort to produce anorexia, the patient may interpret nausea as hunger and overeat. When an excessive dose is given, any patient will develop such side effects as metallic taste, foul breath, anorexia, vomiting, diarrhea, abdominal cramps, and malaise.
These side effects are readily controlled by stopping the drug, or reducing the dose. The incidence of side effects is less with the use of the time dispersal (TD) capsules than it is with the tablets. Severe side effects are now rare, and true toxic effects are of little consequence. The tablets have a four-hour duration of action and are usually given three to four times daily. The TD capsules have a longer (12 hours) effect, and are usually given at breakfast and supper.

There have been reports of lactic acidosis in patients taking large doses of phenformin. These patients usually had hepatic, renal, or severe cardiac disease with shock and tissue hypoxia. They were seen only after symptoms of toxicity had been present for several days. In our experience lactic acidosis has not been a problem. It is essential that all diabetic patients be followed closely regardless of the method of treatment used.

COMBINED USE OF ORAL HYPOGLYCEMIC DRUGS

There are some patients who improve but do not attain good control with a sulfonylurea drug with phenformin alone, but who achieve satisfactory diabetic control on both drugs together. The average dose for the combination is 500 mg of chlorpropamide and 150 mg of phenformin each day, but the dose of either drug must be varied in order to produce the desired control in each patient.

INSULIN PLUS PHENFORMIN

There have been reports stating that brittle diabetics can be stabilized if they are given one of the oral drugs in addition to insulin. In our study using tolbutamide with insulin, and then a placebo with insulin, there was no difference between the two groups. Most diabetics are made unstable by physicians who prescribe too much insulin, resulting in hypoglycemia and rebound hyperglycemia. When the insulin dose is reduced, there is less hypoglycemia and consequently less rebound hyperglycemia. If the patient is given another drug at the same time the insulin dose is reduced, the new drug is credited with the improvement actually produced by the insulin reduction. Some authors who have reported good results with this combination have not used placebo controls. The combination of insulin plus a sulfonylurea is worthless, but the supplemental use of insulin in patients taking a sulfonylurea is helpful during transient stress.

The combination of insulin and phenformin has been widely advocated to stabilize brittle diabetics. In our study only 2 out of 37 patients on this regimen showed improvement. The other 35 were no better controlled than they were on insulin plus a placebo. The two patients whose control improved possibly ate less because of the mild anorexia produced by phenformin. Patients who need insulin usually do best when they are given nothing but insulin.

Following the introduction of oral drugs, the fear was expressed that the simplified treatment would result in an epidemic of degenerative complications. This fear has not been borne out, and as long as satisfactory control is achieved, there is probably no contraindication to the use of oral hypoglycemic drugs.

CONCLUSION

The sulfonylurea drugs stimulate the pancreas to produce more insulin and are effective in patients with mild diabetes. Because it is excreted more slowly, chlorpropamide is four times more potent, and acetohexamide twice as potent, as tolbutamide. Chlorpropamide gives the most effective and most economical diabetic control. Phenformin increases the use of glucose in the muscle cells and is effective in many patients who do not respond to the sulfonylurea drugs. The average dose of phenformin is slightly less than 1 mg per lb body weight. If excessive phenformin is given, the patient will develop reversible gastrointestinal side effects. Phenformin is the only drug associated with consistent weight loss, and therefore is the drug of choice in the obese diabetic. Continued use of phenformin and chlorpropamide is effective in many patients who do not achieve satisfactory control with either drug alone. A combination of sulfonylurea and insulin is worthless, and a combination of phenformin and insulin is rarely valuable. Surgery, pregnancy, infection, or degenerative complications are not absolute contraindications to oral drugs, as long as the diabetes is well controlled. There is no evidence of increased incidence of degenerative complications in patients controlled by oral hypoglycemic drugs.