TODAY'S DRUGS

With the help of expert contributors we publish below notes on a selection of drugs in current use.

Glymidine

This drug is marketed by Pharmethicals (London) Ltd. under the name Gondafon.

Glymidine (Fig. 1) is a hypoglycaemic agent which has been introduced as a possible alternative to the sulphonylureas and biguanides for the oral treatment of diabetes mellitus. It is one of a group of lipid soluble sulphapyrimidine derivatives synthesized by Gutsche *et al.*[1] and bears some structural resemblance to tolbutamide (Fig. 3). Its mode of action is similar to that of the sulphonylureas in that it appears to stimulate insulin release from the pancreas. Prolonged administration to animals results in beta-cell degranulation and increased numbers of islets,[2] whereas in pancreatectomized animals the drug has no hypoglycaemic effect. Behringer and Thaler[3] have suggested that glymidine has an additional effect on the liver, causing increased glycogen storage in diabetics when compared with insulin administration.

Figure 1

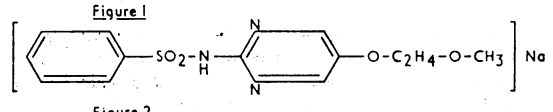

Figure 2

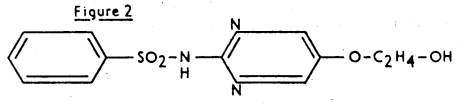

Figure 3

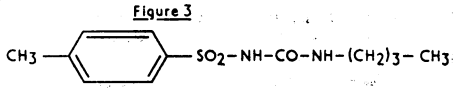

FIG. 1.—Glymidine: 2-Benzene-sulphonamido-5-methoxy-ethoxy-pyrimidine (Sodium salt). FIG. 2.—Glymidine—metabolite I: 2-Benzene-sulphonamido-5(β-hydroxy-ethoxy)-pyrimidine. FIG. 3.—Tolbutamide: *N*-Butyl-*N*-toluene-4-sulphonylurea.

Pharmacology

Glymidine has a rate of onset and duration of action similar to tolbutamide. Studies in man by Kramer *et al.*[2] have shown that it is rapidly absorbed following oral administration and causes a maximum fall in blood sugar within 30 minutes. Its duration of action is between 4 and 12 hours, being longer when very large doses are given. Blood levels of glymidine also reach a maximum within 30 minutes of administration, and the half-life in the blood has been estimated at 3.8 hours.[4] Maximum blood levels are about 4 mg./100 ml. after a dose of 0.5 g. by mouth and increase in proportion to the dose. When the plasma concentration is 10 mg./100 ml. 90% of the drug is protein-bound and 5 to 10% associated with erythrocytes, so that very little of it remains free in the plasma.

Most of the drug is excreted in the urine within 48 hours of oral administration. Within 24 hours 57–88% of glymidine metabolites appear in the urine, and by 48 hours 83–95%.[6] Only 1% appears as unchanged glymidine. Some 20–40% of the products excreted in the urine is made up of a demethylated compound designated metabolite I (Fig. 2), which is of interest in that it has hypoglycaemic properties greater than glymidine itself.

Clinical Experience

Although glymidine has been given to over 13,000 patients, mainly on the Continent, most of the published trials have been on relatively small numbers of subjects treated for a few weeks to a few months. The patients treated were mainly those with maturity onset diabetes of the type that was most likely to respond to existing oral antidiabetic therapy. From these studies, where adequate data are available,[5–10] it can be concluded that glymidine is as effective as tolbutamide or chlorpropamide in controlling diabetes, and in some instances is effective where other drugs fail. In early trials on the Continent the estimated late failure rate (after six months) of about 4%[11–13] is similar to that for tolbutamide. The potency of glymidine is possibly slightly greater than tolbutamide, the average dose being 0.5 g. given twice daily, with a range of from 0.5 g. to 1.5 g. daily.

Glymidine has been used in combination with biguanides in too few instances for valid conclusions to be drawn.

Toxic and Side Effects

Hypoglycaemic reactions have been mild and infrequent. However, it will be important to carefully observe diabetics with chronic renal failure in whom the excretion of glycodiazine products is impaired, since the hypoglycaemic action of metabolite I could lead to more severe reactions. The manufacturers report that leucopenia was seen in 0.53% of cases, but necessitated stopping the drug in only four out of the 13,000 patients receiving the drug. Skin allergies occurred in 1.2% of patients, and in half of these the drug was stopped. Two patients with rashes associated with the use of sulphonylureas were satisfactorily treated with glymidine.[7] One patient developed thrombocytopenia, which resolved when the drug was stopped. Mild gastrointestinal symptoms and malaise were described in 1.9% of patients. No instances of liver damage have yet been reported.

Conclusion

Glymidine appears to be a satisfactory drug for the oral therapy of diabetes mellitus as an alternative to the sulphonylureas; whether or not it will prove to be superior to them remains to be established. In its short duration of action it most resembles tolbutamide. Further observations are required to confirm that it is less toxic than the other drugs, and to establish how frequently it is effective where other oral drugs have failed. Most authors have limited the dose to 1.5 g. daily, but in the absence of side-effects it would seem reasonable to increase this dose when it has proved inadequate to produce good control.

Cost

Glymidine is available as Gondafon.

The basic N.H.S. cost of 100 0.5-g. tablets is 20s. 4d.

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