A CLINICAL ASSESSMENT OF THE ORAL ANTI-DIABETIC DRUGS *

T. SCHNEIDER, M.D. (RAND), F.R.C.P. (EDIN.) and I. R. YUDAKEN, M.B. (RAND), M.R.C.P. (EDIN.)

Diabetic Clinic, Johannesburg General Hospital

The introduction of the oral anti-diabetic drugs has opened a new era in the treatment of diabetes mellitus. While these drugs are seldom effective in the young insulin-deficient diabetic, their usefulness has been proved in the maturity onset or 'middle-old-aged' group.

Two main groups of these drugs have come into common usage, viz. the sulphonylureas and the diguanides. In the sulphonylurea group the two drugs most widely used are tolbutamide and chlorpropamide, while phenformin (DBI) and dimethyldiguanide ('glucophage') are those particularly used in the diguanide series.

ACTIONS

Various theories have been put forward to explain the action of sulphonylureas. Most of the work done supports the idea that they stimulate the beta cells of the pancreas with the release of greater quantities of insulin. Certainly the sulphonylureas require the presence of some functioning pancreatic islet tissue for their action.[1,2] While islet stimulation is probably the main action, other possibilities which have been suggested include inhibition of insulinase action,[3] interference with hepatic enzyme systems thus preventing glucose output,[4] and inhibition of glucagon production.[5,6]

During insulin action there is increased peripheral utilization of glucose, but this has not been found to be the case during administration of the sulphonylureas.[7] A further difference lies in the fact that insulin relieves acidosis, but the sulphonylureas do not. It follows therefore that they should not be used in those cases where ketosis is a feature.

The action of the diguanides is still under discussion. Williams *et al.*[8] have reported studies suggesting that gluconeogenesis is decreased with resulting diminished glucose output from the liver. Peripherally there is an increase in anaerobic glycolysis with increased glucose utilization by the tissues. Muscle glycogen is decreased in contradistinction to insulin action. More recently, it has been suggested that aerobic utilization of glucose peripherally may be the important action.[9,10] As with the sulphonylureas, acidosis is not relieved by the diguanides and in fact there have been reports of acidosis developing during effective control of blood-glucose levels with phenformin.[11] This has been attributed to a starvation ketosis and has necessitated a reduction of the drug dosage or the addition of food. In some cases at least the possibility exists that carbohydrate oxidation has not been completely rectified in spite of the effectiveness of the drug in returning blood glucose to normal.

The presence of pancreatic-cell tissue was not at first considered essential for the action of the diguanides, but recently Mehnert[12] has suggested that some insulin, whether endogenous or exogenous, must be present for effective lowering of blood sugar.

SELECTION OF CASES

Because of the abovementioned limitations, the oral hypoglycaemic agents are not as widely useful as insulin in the control of the diabetic state and in practice their usefulness has proved greatest in the 'middle-old-aged' group of diabetics whose disease had commenced above the age of 40 years and who were not acidosis-prone. The previous insulin requirements are usually not over 40 units a day, although this may be exceeded in occasional cases. In the case of the sulphonylureas, effective control is more likely to be achieved in those cases where pre-treatment blood-sugar levels do not exceed 300 mg. per 100 ml.

The juvenile ketosis-prone diabetic is usually insensitive to the action of the sulphonylureas. Occasional juvenile-onset diabetics and newly diagnosed diabetic children have been known to respond to the oral anti-diabetic drugs, more particularly to the diguanides.[13] Dolger[14] has called attention to patients with juvenile-onset diabetes with an atypical, insidious, mildly symptomatic onset lacking the explosive ketotic initiation characteristic of this age group and responsive to oral agents alone. Their ages ranged from 6 to 16 years. Eight out of 300 juvenile diabetics fell into this group.

THERAPY

Tolbutamide

The dosage of tolbutamide originally instituted was 1 G. *t.d.s.* post-prandially on the first day, with a reduction of 0·5 G. daily until 0·5 G. *t.d.s.* was reached. Most patients who responded required 1 - 1·5 G. daily as a maintenance dose. Later experience has confirmed the earlier impressions, but it has been found possible in many cases to commence therapy with a dosage of three 0·5 G. tablets daily. A maximum dose of 3 G. daily has been used, owing to the fear of toxic effects and because daily dosage in excess of 1·5 G. is, in most cases, unlikely to improve diabetic control to any marked extent.

Insulin, where used, may be discontinued completely on institution of tolbutamide therapy, provided that the dosage has been 20 units or less daily. Where, however, the dosage exceeded this amount, a daily reduction of 5 or 10 units is considered more appropriate. During withdrawal of insulin a careful watch should be kept for increased glycosuria or ketonuria, the occurrence of which might necessitate return to insulin therapy.

Chlorpropamide

This is in most respects similar to tolbutamide, except that it is effective in smaller dosage (125 - 500 mg.) and may be given in one daily dose owing to its more prolonged action (24 hours as against 9 - 10 hours). The maximum daily dose should not exceed 500 mg. owing to the greater possibility of hypoglycaemia and greater liability to side-effects than with tolbutamide.

Phenformin

Dosage at the outset should be 25 mg. twice daily, with increments of 25 mg. every fourth day until effective control is attained. The maximum dosage should not be more than 250 mg. and preferably not more than 150 mg. daily, owing to the frequent side-effects encountered with larger dosage. Insulin, where given, should only be decreased as the hypoglycaemic action of phenformin manifests itself. While insulin reduction can often be com-

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menced within a few days of institution of phenformin treatment, it may be necessary to persist with this therapy for 6 - 8 weeks before effective control is achieved.

Dimethyl-diguanide (Glucophage)

This has a similar effect to that of phenformin. The dosage at first is 500 mg. *t.d.s.*, preferably administered during meals. This may be increased to 1 G. *t.d.s.*, but larger dosages lead to more frequent side-effects and are to be avoided.

The diguanides may be used either alone or combined with insulin or the sulphonylureas. They may be used in combination with insulin in the juvenile diabetic, but the wisdom of such a course is open to question, since the patient must still receive an injection of insulin and the slight lowering of insulin dose usually achieved has little to recommend it. Diguanides have been recommended in combination with insulin in the treatment of the brittle diabetic,[15] but in our own experience only a proportion (1 in 4) have responded with improved control to the combined therapy.

The duration of action of the diguanides is 8 - 12 hours. Lately a long-acting, timed-disintegration capsule has been introduced which has an action lasting 14 hours and is believed to have the merit of more uniform control and less gastro-intestinal side-effects.[16] The recommended dosage is one 50 mg. capsule with breakfast and a further 50 mg. capsule in the evening where this may be necessary.

Side-effects

The earlier sulphonylureas gave rise to many side-effects: nausea, vomiting, malaise, headache, drowsiness, mental clouding, fever, rashes, jaundice, thrombocytopenia and agranulocytosis. Death occurred as a result of hepatic involvement and interstitial myocarditis. Carbutamide, which proved very effective in the treatment of the 'middle-old-aged' group, has been gradually withdrawn from clinical use as a result of its side-effects and there can be few who use it at the present time. Tolbutamide has shown an almost complete absence of severe side-effects and only occasional patients show intolerance in the form of nausea, vomiting and allergic rashes with, rarely, mild leucopenia. In our own series of cases an intermittent reversal of the neutrophil-lymphocyte ratio has been noted, but this has reverted to normal even while drug treatment was continued.

Chlorpropamide, which is more potent than tolbutamide, also seems to be more toxic.[17] Gastro-intestinal symptoms, such as bitter taste, anorexia, nausea, vomiting, epigastric pain, abdominal distension and eructations may occur, as well as lassitude, weakness, fulness in the head and generalized pruritis. Jaundice, maculopapular eruptions and exfoliative dermatitis have all been reported, but these have developed on higher dosages than are now recommended. Aplastic anaemia was discovered in one of our own patients receiving 1 G. daily. Cases of prolonged hypoglycaemia have occurred and it necessarily follows that care must be exercised in the administration of chlorpropamide.

The diguanides often produce gastro-intestinal side-effects, such as a metallic taste in the mouth, anorexia, epigastric fulness, nausea, vomiting, abdominal discomfort and diarrhoea. Lassitude has been noted, but no serious toxic manifestations have been encountered and liver-function tests and blood studies have shown no impairment.

RESULTS

The following criteria have been used in the classification of results into categories of 'good', 'fair' and 'poor'.

The *good* category consists of those patients in whom insulin, where used, has been discontinued; urine examinations at home and at the clinic have shown absence of sugar, or occasional glycosuria only; blood-sugar levels have been maintained at normal or near normal levels; and patients feel well and have suffered no side-effects.

The *fair* category consists of those patients in whom insulin, where used, has been discontinued; urine examinations have shown up to 0·5% glycosuria; blood-sugar levels have been reduced appreciably, but not maintained at normal levels; and patients have felt well without any side-effects.

The *poor* category consists of those patients who have shown little or no response.

Tolbutamide

We have treated 220 patients with maturity-onset diabetes with tolbutamide for periods up to 5 years. Their ages ranged from 38 to 84 years, and the duration of their diabetes from 1 month to 30 years. Their build varied from thin to obese. Success in therapy was shown in all groups. Good control was achieved in 102 cases (46·3%), fair control in 48 (21·8%), and the remaining 70 (31·8%) were not helped.

For some time it has been known that some patients have shown deterioration of control after initial stabilization. A disturbing feature which has emerged has been the continued accession of further failures, so that over a 5-year period complete loss of control has occurred in 23 originally 'good-category' patients. Twelve good-category

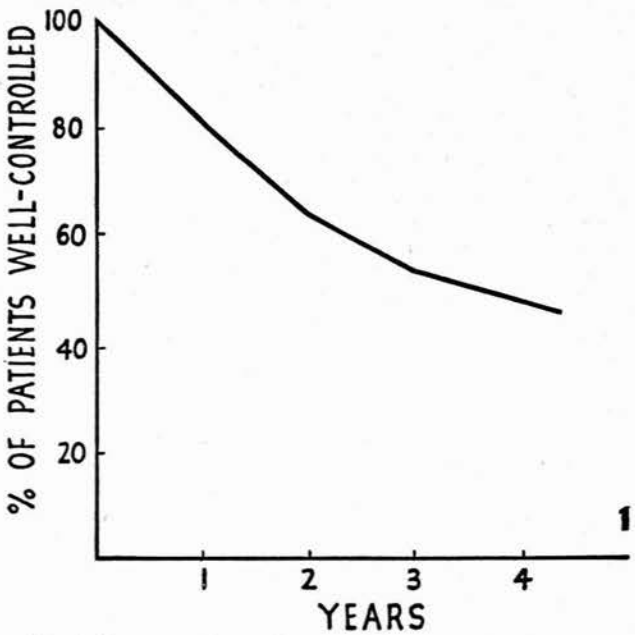

Fig. 1. Progress of a well-controlled group of patients on tolbutamide therapy. Over 4 years the percentage who were well-controlled dropped from 100% to 50%.

patients have deteriorated to fair control, and 7 originally 'fair-category' patients have deteriorated further to poor control.

Thus, 49% of those patients who had previously benefited from tolbutamide therapy have now lost that beneficial effect.

Fig. 1 demonstrates that secondary failures have shown themselves year by year since tolbutamide has been in use at the clinic. Contributing towards the development of failure were increases in weight, failure to keep to prescribed diet, infection, gangrene and pregnancy. However, in a proportion of cases no cause could be determined save a lack of response to the drug. It has been found that substitution of insulin therapy for 6 - 8 weeks has led to a return of responsiveness to tolbutamide in some cases, but this responsiveness may be only evanescent. Weight loss, disappearance of infection and the end of pregnancy have all contributed to return of tolbutamide effectiveness.

Chlorpropamide

Of 118 patients treated with this drug, 47 (40%) have shown good results, 12 (10%) fair results and 59 (50%) have not responded. Of these 118 patients, 59 had previously been unsuccessfully treated with tolbutamide; 13 of these improved on chlorpropamide, 11 graduating to the good category and 2 to the fair category. Ages, weights and duration of diabetes approximated closely to those found in the tolbutamide-treated series. Patients with successful results have been under treatment for periods up to 3 years. Seven secondary failures (15·2%) have developed in the good-control group during the past 2 years.

Combined Tolbutamide and Chlorpropamide

Forty-one patients who had failed on both tolbutamide and chlorpropamide separately, were subjected to combined therapy using both drugs simultaneously. The maximum dosages used were 1·5 G. of tolbutamide and 0·5 G. of chlorpropamide. Thirteen of these patients were effectively controlled in this way.

In view of the danger of serious side-effects developing on large dosage of sulphonylureas, this method of treatment cannot be recommended unless very careful clinical and haematological control is possible. Fortunately no serious side-effects developed among our patients.

Phenformin

In our first 50 patients on phenformin alone, our results, in contrast to other reported series, were comparatively poor. This is due to the fact that our patients were mainly those who had previously failed to respond to other oral therapy. To this extent they can be considered a selected group of patients. Of the 50 cases, only 10 (20%) showed good control, 2 (4%) were improved, and 38 (76%) proved refractory. Up to 36 units of insulin were replaced by phenformin. The main difficulty encountered was the high incidence of side-effects (24 cases). In 9 of these, discontinuation of therapy became necessary.

In view of the difference in the action of the diguanides and the sulphonylureas, it was decided to combine the treatment of these 2 types of oral drugs in those cases where treatment with sulphonylureas alone had been ineffective or where secondary failures had occurred. Sixteen further patients improved on this combined therapy (9 good and 7 fair). Thus, 28 of the 50 patients on phenformin alone or combined with a sulphonylurea showed improved control. An advantage of the combined therapy was the lower incidence of side-effects. This was probably related to the smaller dosage of each drug needed when they were used in combination.

Dimethyl-diguanide (Glucophage)

As a result of our favourable experiences with combined therapy it was decided, when dimethyl-diguanide became available, to use this drug mainly in combination with a sulphonylurea in those cases where the latter alone had failed. Thus, of 34 patients 14 showed good results — 11 of these were on combined therapy. Fair results were shown in 4 patients, of whom 3 were on combined therapy; 16 patients failed to improve. Nine patients showed side-effects. One, poorly controlled on chlorpropamide alone, developed a prolonged hypoglycaemia lasting 2 days, about 2 weeks after dimethyl-diguanide was added. Up to 30 units of insulin daily were replaced by this drug.

DISCUSSION

There is no doubt that the oral anti-diabetic drugs have proved a boon to the 'middle-old-aged' diabetic. The absence of daily injections, the ease of administration, the smooth control achieved in successful cases, have all contributed to a more optimistic outlook in their treatment. The success of combined therapy has added to the number of patients who can be treated by the oral drugs. Such treatment with a sulphonylurea and a diguanide should certainly be attempted in the case of those patients who are considered suitable for treatment with oral therapy, but who have failed to respond to one or other drug alone.

Certain disadvantages have become evident with the passage of time. None of the oral drugs has proved generally useful to the young diabetic or the ketosis-prone older patient. The brittle diabetic still presents a problem in treatment. While the occasional patient has been found to respond to combined treatment with insulin and diguanides, our own experience has not been impressive. Side-effects occur in a larger proportion of cases than were evident when insulin was the only drug used. With greater experience and the use of smaller drug dosage these effects have been markedly reduced, but the diguanides, particularly, still present a problem in this regard. Infections and operative interference often necessitate the temporary abandonment of oral therapy and the return to insulin. This, however, need not necessarily always happen, and our patients on these drugs have successfully undergone cataract extractions without recourse to insulin.

Pregnancy has been found to be a bar to continuation of treatment with these drugs, often the result of the greater insulin requirements during this period. In addition, the occurrence of foetal abnormalities in pregnant animals treated with sulphonylureas, e.g. anophthalmia, cleft palate, and brain abnormalities,[18] has cautioned against their use during pregnancy. Further investigation is awaited in this field.

The problem of secondary failure is beginning to loom large over this realm of therapy. Our own results suggest an ever-increasing number of failures the longer treatment

is continued. Certainly, the combination of sulphonylurea and diguanide has proved heartening in avoiding the need for a return to insulin therapy in many cases, but whether failure with combined therapy will present a later problem remains to be seen.

There is no doubt that the high rate of secondary failures experienced by ourselves and other authors[19-21] is aggravated by various contributory factors, the chief of which is non-adherence to diet. Strict attention to diet should therefore decrease the number of these failures. Infection, gangrene and pregnancy are some other contributory factors which may only prove temporary. A certain number of true secondary failures without evident cause have still to be explained. Interestingly enough, return of these patients to insulin does not appear to have increased their requirements for that drug. It is sometimes possible at a later date to reinstate successful oral therapy with the sulphonylureas, suggesting that secondary failure is not due to permanent exhaustion of the pancreas. If this is indeed so, the possibility of treating the prediabetic patient with the oral drugs to prevent diabetes becoming overt is a speculation which opens a fertile field for future investigation. Similarly, newly diagnosed diabetes in the young has been satisfactorily controlled with these drugs for varying periods of time before insulin administration has become necessary.

One great problem which remains is the prevention of the late manifestations of the disease. The development of retinopathy has already been reported in patients well-controlled on tolbutamide,[22] but sufficient time has not yet elapsed to allow workers in this field to assess fully whether good control with the oral drugs will substantially reduce the incidence of these vascular changes.

SUMMARY

1. The oral anti-diabetic drugs, both sulphonylureas and diguanides, have been found useful in the treatment of maturity-onset or 'middle-old-aged' diabetic subjects.

2. Actions, usage, dosage and side-effects of the various drugs are discussed.

3. Detailed results of treatment with these drugs for periods up to 5 years are presented.

4. Combined treatment with a sulphonylurea and a diguanide has helped to stabilize patients who were unsatisfactorily controlled on either alone.

5. Loss of control after initial good stabilization has become a feature of treatment with sulphonylureas. Causes for this are discussed.

6. It is still too soon to assess whether the incidence of late manifestations of the disease will be affected by the use of the oral drugs.

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