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# Oral Therapy in Diabetes

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Oral therapy for diabetes came into general use in 1956 and tolbutamide was one of the first drugs used. Since then, this type of treatment has been extended by the use of other compounds in the sulphonylurea group and by the introduction of the biguanides (see Table 1).

There is convincing clinical and experimental evidence that the administration of the sulphonylureas in the short term leads to an increased output of endogenous insulin and so reduces blood sugar levels. However, this may not be the only action. It can be demonstrated in animals (Madsen, 1967) that the

sulphonylureas can exert a hypoglycaemic effect in the absence of the pancreas, provided that small amounts of insulin are present, suggesting a potentiating effect on the action of insulin.

The action of the biguanides has occasioned a great deal of interest because it at once became apparent that they did not stimulate the production of insulin. At least three sites of action have been demonstrated experimentally. Phenformin inhibits glucose absorption from the intestine (Czyzyk *et al.*, 1968), suppresses hepatic gluconeogenesis (Meyer *et al.*, 1967) and enhances glucose consumption by the muscles (Butterfield and Whichelow, 1962). Any of these effects could explain the fall in blood sugar following biguanide therapy, but it is not known which mechanism is most important or whether there is a summation of effects.

The clinical indication for tablets is now reasonably well-defined. Oral therapy is not a substitute for insulin in children or in the more severe type of adult diabetes where acetone is present. Tablets are of most value in the mild maturity onset diabetic who has failed to respond to simple dietary restriction. Of course, this begs the question as to what extent dietary restriction can be said to have failed before tablets are introduced. The age, weight, intelligence and willpower of the patient are all factors to be considered. The more Calvinistic the physician, the more vigorously is dietary restriction likely to be pursued but there must come a time when it is no longer reasonable to allow hyperglycaemia to persist, even though the suspicion remains that further prolonged and rigid dieting could restore near normoglycaemia. Here, too, difficulty arises, since the evidence is conflicting as to whether milder degrees of hyperglycaemia usually unassociated with symptoms are harmful even in the long term. When it has been decided that dietary advice has failed either to suppress symptoms or to restore the blood sugar to an acceptable level the choice of tablets will be influenced by the weight and age of the patient.

Patients with a tendency to obesity are best treated by phenformin or metformin, since these biguanides may help to reduce weight, partly because of an anorectic effect and partly because of delayed absorption of carbohydrate from the bowel. There is not much to choose between these two compounds. Phenformin is more effective than metformin as a hypoglycaemic agent but is more prone to upset the bowel.

Patients who are not overweight are usually prescribed one of the sulphonylureas (Table 1) since these compounds are better tolerated and less likely to give rise to gastro-intestinal symptoms. In patients who are old or frail, tolbutamide remains the tablet of choice. It has a short length of action and has to be taken two or three times a day but is unlikely to give rise to hypoglycaemia. In younger patients, glibenclamide or chlorpropamide are the

TABLE 1. Hypoglycaemic Agents

| Group | Approved name | Proprietary name | Daily dose |
|---|---|---|---|
| Sulphonylureas | Tolbutamide | Rastinon/Orinase | 1–3 g |
| | Chlorpropamide | Diabinese | 100–375 mg |
| | Acetohexamide | Dimelor | 250–750 mg |
| | Tolazamide | Tolanase | 100–500 mg |
| | Glibenclamide | Daonil/Euglucon | 2·5–15 mg |
| Sulphapyrimidine | Glymidine | Gondafon | 500 mg–1·5 g |
| Biguanides | Phenformin | Dibotin | 50–150 mg |
| | Metformin | Glucophage/Obin | 1–2 g |

most effective compounds and since each exerts its action throughout the day, a morning dose is sufficient. The action of the other drugs in this group is intermediate between tolbutamide and glibenclamide, and their choice will depend more on the experience of the physician than on clinical exigencies.

Since the biguanides and the sulphonylureas have different modes of action, when given together their hypoglycaemic effect is additive (Beaser, 1958; Bloom and Richards, 1961). Consequently, patients who fail to respond to a sulphonylurea may be restored to normoglycaemia when a biguanide is added: glibenclamide 15 mg and phenformin 100 mg daily is an effective combination. The majority of patients developing diabetes over the age of 40 can now be controlled by oral therapy. Many newly diagnosed young adults can also be controlled by combined oral therapy for a time but in such cases relapse is likely to occur within a year or two, after which insulin becomes mandatory.

The incidence of adverse effects in patients taking oral hypoglycaemic agents is remarkably low. Harris (1971) reviewed the reports of toxic effects received by the Committee on Safety of Drugs and deduced the incidence to be no more than one reaction per 15,000 patients. Rarely, skin disorders, blood dyscrasias and jaundice occur with one or other of the sulphonylureas. More important in clinical usage are the dangers of hypoglycaemia with the more potent agents such as chlorpropamide or glibenclamide, particularly when enhanced by the effects of alcohol, mono-amine oxidase inhibitors or phenylbutazone. Chlorpropamide particularly, but other sulphonylureas as well, may give rise to an unpleasant flushing of the face when alcohol is taken, though the mechanism is obscure. In the main, the sulphonylureas are well tolerated and safe. Phenformin and metformin are prone to cause gastro-intestinal intolerance with nausea, a nasty taste in the mouth, gastric fullness,

and diarrhoea. However, when phenformin is mixed with shellac in capsule form, the large majority of patients will tolerate 100 mg daily without untoward effect. More serious, though fortunately rare, is the occurrence of lactic acidosis in patients taking phenformin, usually secondary to conditions associated with hypoxia such as myocardial infarction, haemorrhage or septicaemia (Tomkins *et al.*, 1972). It is as well not to use the biguanides in patients with chronic heart, lung or kidney disease and to discontinue it when patients fall ill for no obvious cause.

Throughout the sixties the percentage of diabetics treated with tablets steadily increased. In 1960, a few years after the introduction of the sulphonylureas, but before the biguanides came into general use, 42 per cent of patients at the Whittington Hospital clinic needed insulin. By 1968 only 26 per cent were on insulin, probably because 15 per cent were on combined sulphonylurea and biguanide therapy and would previously have needed insulin (Bloom, 1969). Over the same period, the percentage treated by diet alone had fallen from 40 per cent to 26 per cent due to an increased use of either sulphonylureas or biguanides as primary treatment when diet alone was insufficient (Fig. 1).

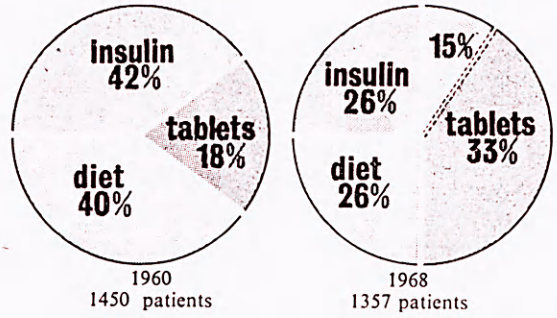


Fig. 1. Whittington Hospital Diabetic Clinic (Courtesy *Postgraduate Medical Journal*).

At least two reasons suggest themselves for this wider use of tablets. First, increasing familiarity with tablets showed them to be free from serious toxic effects and, secondly, evidence such as that provided by Keen *et al.* (1965) suggested that the higher the blood sugar the greater the incidence of arterial disease. Nevertheless, despite the continuing demonstration that tablets were both safe and successful in reducing hyperglycaemia, it had been realised from the beginning that the long-term effects in other directions were less certain. In particular, it could not be predicted whether these compounds would be able to delay the onset of the degenerative disorders that occur in longstanding diabetes.

In 1959 a group of American clinicians and statisticians met to discuss methods of evaluating the efficacy of tablet therapy in preventing vascular

complications. By 1961 a co-operative prospective study was begun in six university centres, later expanded to twelve, under the title of the University Group Diabetes Program (UGDP). More than 800 recently diagnosed diabetics were recruited within five years. The diagnosis was confirmed by an oral glucose tolerance curve, and each patient was given an extensive series of base-line examinations at the time of entry. Follow-up was at three-monthly intervals and study forms were forwarded to a co-ordinating centre. Patients were randomly allocated into four groups and all were given the same dietary instructions. Two groups were given tablets, one a lactose placebo, and the other tolbutamide 1·5 g daily. Two further groups had insulin, one a fixed dose based on the patient's body surface and the other a variable dose depending on blood sugar levels. In 1962, a fifth group treated with phenformin 50 mg twice daily was added to the programme. There were approximately 200 patients in each group.

By 1969, when the majority of patients had been observed for more than five years, it became apparent that the overall mortality rate was highest in the tolbutamide and phenformin treated groups and, in particular, the cardiovascular mortality rate was significantly higher in these two groups as compared with the placebo and insulin groups (Table 2). The programme in this respect was therefore discontinued.

TABLE 2. University group diabetes program (UGDP)

| | | Diet and placebo | Diet and 1·5 g Tolbutamide | Diet and fixed insulin | Diet and variable insulin | Diet and 100 mg Phenformin |
|---|---|---|---|---|---|---|
| Mean fasting blood sugar at | Baseline | 143 | 149 | 142 | 142 | |
| | 12 months | 130 | 119 | 118 | 112 | |
| | 56 months | 148 | 139 | 141 | 115 | |
| % Cardiovascular deaths | | 4·9 | 12·7 | 6·2 | 5·9 | 12·7 |

This unpalatable and disturbing conclusion evoked considerable criticism (Feinstein, 1971), particularly as similar prospective studies in the same field yielded different results. Keen and Jarrett (1970) followed borderline diabetics for over five years and found a lower incidence of peripheral and cardiac arterial changes in patients treated with tolbutamide compared with controls, suggesting that tolbutamide had a protective effect on the vascular system. Paasikivi (1970) in Sweden made a random selection of patients who had suffered a myocardial infarct with an impaired glucose tolerance

curve. The mortality rate over the next 18 months was significantly less in the group treated with tolbutamide (Table 3) than in the control group.

TABLE 3. Tolbutamide trials

| | No. of cases | Type of case | Dose | Duration in years | Pathology | Placebo % | Tolbutamide % |
|---|---|---|---|---|---|---|---|
| UGDP (1970) | 823 | Mild maturity onset diabetics | 1·5 g | 5 to 9 | Cardiovascular deaths | 4·9 | 12·7 |
| Paasikivi (1970) | 178 | After infarct without overt diabetes | Up to 1 g | 1·5 | Mortality | 18·0 | 7·4 |
| Keen and Jarrett (1970) | 246 | Borderline diabetics | 1 g | 5 | Arterial events | 37·4 | 27·2 |

Although both these trials were concerned with somewhat smaller numbers than the UGDP, patients were followed by the same observers throughout. The American trial suffered the disadvantages of any multi-centre trial: numerous clinical investigators were involved and even patients attending a particular clinic were not always seen by the same clinician. Of the 12 centres, each contributed from 44 to 94 patients over several years. This slow rate of recruitment suggests that some selection must have taken place, and indeed randomisation appears faulty in that the patients selected are not representative of the diabetic population of that age group. Thus, 72 per cent of the patients were women and only 54 per cent were white. There was considerable variability in the results obtained in different centres. Two centres alone (Cincinatti and Minneapolis) provided no fewer than half the deaths, though contributing less than a quarter of the patients. There were no deaths in patients taking tolbutamide in St Louis but one-third of patients in Minneapolis taking tolbutamide died. The cause of death was often inferred, as postmortems were performed in only one-third of the cases.

A further important criticism emerges from study of the cardiovascular morbidity figures. Although mortality was higher in the tolbutamide group, the reverse was true of morbidity. In the placebo group 14·1 per cent of the patients developed significant electrocardiographic changes compared with 8·2 per cent in the tolbutamide group. Indeed, the placebo group seemed unusually fortunate in this respect; 205 middle-aged diabetics in the group were observed for nearly nine years and only one developed an infarct. Despite its importance in the aetiology of cardiovascular disease no mention was made of cigarette smoking.

The changes in blood glucose levels in the American trial provide great interest. As can be seen (Table 2), all patients showed a lowering of fasting blood sugar levels after 12 months, even the placebo group. But after 56 months the fasting levels had returned to those recorded before treatment in the placebo and fixed insulin groups. Only in the variable insulin group was there a significant reduction in fasting blood sugars. More arresting still, and surprising in view of the findings of Keen *et al.* (1965), the mortality rate from cardiovascular causes bore no relation to the blood sugar levels.

Although these comments and criticisms of the UGDP have substance, it should be emphasised that the whole concept and conduct of the American trial displayed great foresight, ingenuity, and a vast expenditure of resources for which those concerned deserve great credit. Some of the statistical methods now open to criticism were devised more than ten years ago. Unfortunately, a prospective multicentre trial of this sort is so expensive and time-consuming that it is unlikely to be repeated, and this is particularly unfortunate when, like a double blind Samson, it brings down the temple around our ears. For despite all the doubts and criticisms, there remains a salient conclusion. There was no obvious benefit in the long term from treating mild borderline diabetic patients with oral hypoglycaemic agents.

In 1956, when we first conducted trials with tolbutamide, we were worried lest the tablets should give rise to toxic effects and for this reason patients were treated for six weeks only (Crowley *et al.*, 1957; Bloom, 1959). We were able to demonstrate a marked amelioration of the glucose tolerance curve taken a few weeks after the discontinuation of six weeks' tolbutamide on the same diet that had been manifestly unsuccessful before the introduction of tolbutamide. This demonstration that the sulphonylureas could lead to a remission was lost sight of in the ensuing years as we became more confident of the safety of this type of treatment. When the results of the American trial were made public, we decided to investigate to what extent the maintenance of long-term continuous tablet therapy was necessary to sustain diabetic control. With this in mind, oral hypoglycaemic tablets or capsules were replaced by placebos in patients attending a diabetic clinic and the effects observed at regular intervals on blood sugar levels taken at the same time of day (Tomkins and Bloom, 1972). As can be seen (Table 4), about two-thirds of patients relapsed within a few months and tablet therapy was successfully reintroduced. In one-third, however, diabetic control was as good on placebo as on oral agents during the period of observation from eight months to a year. It has always been the practice in this country to introduce tablets only when simple dietary restriction has failed to restore normoglycaemia. Our findings suggest that the dosage of tablets, even in these patients, should be reduced and discontinued

TABLE 4. After discontinuation of oral therapy

| Group | Number of cases | Number relapsed at | | Mean blood glucose | |
|---|---|---|---|---|---|
| | | 3 months | 6 months | before trial | at relapse |
| 1. Combined therapy | 16 | 14 | 14 | 132 | 257 |
| 2. High dose sulphonylurea | 16 | 10 | 11 | 120 | 251 |
| 3. Low dose sulphonylurea | 16 | 10 | 11 | 122 | 212 |
| 4. Phenformin | 14 | 6 | 7 | 103 | 212 |
| Overall | 62 | 40 (64·5%) | 43 (69·3%) | | |

if normoglycaemia is maintained. Should hyperglycaemia recur it seems reasonable in the present state of our knowledge to reintroduce tablet therapy at the previous effective dose level. There is no firm evidence that insulin is more or less effective than oral therapy in preventing the degenerative complications in diabetics who cannot be controlled on simple dietary restriction.

In summary, then:

1. Dietary restriction is the most important aspect of treatment in mild diabetes.
2. In patients who cannot be controlled by diet, there is no evidence that tablets are more or less successful than insulin in delaying or preventing degenerative changes.
3. Tablet therapy need be neither permanent nor continuous.

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