DIMETHYLDIGUANIDE ('GLUCOPHAGE', LA 6023) IN DIABETES MELLITUS

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Guanidine was known in 1918 to have a blood-sugar-lowering action.[10] A derivative, decamethylene diguanidine, was used in the treatment of human diabetes, but was abandoned because of its toxicity.[3] Since the sulphonylureas have successfully entered medicine as hypoglycaemic agents, there has been a resurgence of interest in guanidine derivatives — particularly in the diguanides.

These compounds were found to be virtually non-toxic, yet they retained a hypoglycaemic effect. Phenethyldiguanide ('DBI', 'phenformin') has been extensively used,[5]

but the high incidence of gastro-intestinal irritation has limited its use in diabetes.[6] It has been claimed that dimethyldiguanide produces fewer of these side-effects, but there are few reports on its use in the literature.[1,2,7,8]

In Groote Schuur Hospital the effects of dimethyldiguanide* have been observed in a selected group of diabetics, the majority of whom had previously been treated with other hypoglycaemic agents. Our early results and impressions are reported.

Mode of Action and Side-effects

The diguanides are generally believed to act by inhibiting certain enzymes which take part in oxidative glycolysis in the 'Krebs cycle'.[4] This has the effect of greatly stimulating anaerobic breakdown of glucose, and so promoting hypoglycaemia entirely independently of insulin.

One effect of this action is a tendency to build up ketone bodies and produce systemic acidosis at comparatively low blood-sugar levels.[9] Although we have not observed this phenomenon ourselves, the possibility should be borne in mind; and it is probably preferable not to combine diguanides with a diet which is very low in carbohydrate.

To counteract the gastro-intestinal side-effects of nausea, vomiting, and diarrhoea, it is advisable, where possible, to start therapy with 1 tablet daily, taken with or directly after a meal. The dosage is gradually increased to a maximum of 2 tablets 3 times daily, taken with meals (3 G. daily). Antacids or kaolin mixture may also help.

SUBJECTS AND METHODS

Glucophage was administered to 62 patients featured in this report, in doses ranging, as a rule, from 3 to 6 tablets daily (i.e. 1·5 - 3 G.), given as described above. In a few cases a smaller dose of 2 tablets daily sufficed. The response was assessed by fasting blood-glucose estimations and in some cases by glucose-tolerance tests as well. Semi-quantitative urine tests were carried out in all cases, and 24-hour quantitative glucose analyses in some.

Glucophage was tried in the following groups of patients:

1. In patients treated with sulphonylureas, where these agents were found to be ineffective or not tolerated. In some patients who had been on a variety of sulphonylureas, the comparative effect of glucophage was assessed.

Where only a partial response to the sulphonylureas or glucophage alone was obtained, the effect of treatment with a combination of these agents was tried.

2. In patients on insulin treatment (*a*) in the maturity-onset type, to whom glucophage was administered and insulin withdrawn slowly or abruptly; and (*b*) in some unstable juvenile diabetics, in an attempt to obtain better control.

All patients included here were observed for several weeks before a 'good' assessment was made.

* Hereafter called 'glucophage', the trade name used by Messrs. Rona Laboratories, and in the beginning kindly supplied to us for trial by Messrs. Westdene Products (Pty.) Ltd.

RESULTS

'Improved diabetic control' indicates:

(*a*) That fasting blood-glucose estimations fell to a normal level or a level below 140 mg. on glucophage alone, or

(*b*) a glucophage response which was distinctly better than that with the sulphonylureas, or

(*c*) a more satisfactory control obtained by the addition of glucophage to the treatment in patients previously treated with chlorpropamide alone or insulin alone, or a satisfactory reduction of the insulin requirement.

Maturity-onset Group

There were 47 patients in this group. The majority had failed to be properly controlled by any sulphonylurea drug. Improved diabetic control was obtained in 27

TABLE I. CONTROL OF DIABETIC PATIENTS

Type of diabetes	Total patients	Good response to: Glucophage alone	Gl. + chlor.	Gl. + insulin	Total: Good	Poor
Maturity-onset	47	20	5	2	27	20
Juvenile	12	0	—	6	6	6
Chronic pancreatitis	2	1	—	1	2	0
Total pancreatectomy	1	0	—	0	0	1
	62					

(Table I). In 20 of these, glucophage alone was satisfactory, in 2 glucophage was combined with a reduced dose of insulin, and in 5 it was satisfactorily combined with 1 or 2 tablets of chlorpropamide daily.

In 4 of the 'failed' cases, glucophage was actually found to be inferior to chlorpropamide in controlling the diabetes.

The following cases illustrate a good response to glucophage:

1. G.H., a middle-aged, non-obese European female, poorly controlled with insulin, was successfully managed on tolbutamide for 2 years, after which 'secondary tolbutamide failure' occurred.

At this stage there was a very good response (fasting blood sugar and urine tests) to chlorpropamide, but the patient complained of gastro-intestinal upset with this drug.

Isobuzole (a thiadiazole derivative) failed to control the hyperglycaemia (fasting blood sugar 200 - 300 mg.). Glucophage, 2·5 G. daily, has produced a satisfactory response. Fasting blood-sugar levels have remained near normal over the past 10 months.

2. C.v.N., a middle-aged European male, failed to respond to all the sulphonylureas — tolbutamide, chlorpropamide, metahexamide, and isobuzole.

For the past 8 months his control on glucophage alone (1·5 G. daily) has been better than with 35 units of insulin. The fasting blood-sugar levels have been normal and urine tests sugar-free at all times. There has also been an improvement in general well-being.

Juvenile Group ('Ketosis-prone')

Twelve patients with the 'juvenile' type of diabetes were given glucophage, most being inpatients of Groote Schuur Hospital at the time. Assessment of the value of glucophage in this group may be extremely difficult, but there was

virtually no doubt that the drug had a considerable effect in allowing a reduction in insulin dosage and an improvement in control in 6 cases. In no case was glucophage alone satisfactory. Two of the 'successful' patients might have been classed as 'brittle' before glucophage was given.

Example. U.M., a Coloured girl of 20 years, had been diabetic for 7 years. Her control on 140 units of insulin per day in divided doses was poor (blood-sugar levels frequently over 300 mg.). On the addition of glucophage, 1·5 G. daily, the control with the insulin dosage, halved to 70 units, was much improved as judged by repeated urine tests and estimations of blood-sugar levels. Previous reduction of insulin dosage had proved impossible.

Chronic Pancreatitis

Glucophage was tried in 2 patients with chronic calcific pancreatitis and diabetes. In both, sulphonylureas had been unsuccessful. In one case, 2 tablets of glucophage very satisfactorily replaced 22 units of lente insulin. In the other patient the maximum of 6 tablets, added to his previous dose of 60 units of insulin, reduced the mean early morning blood-sugar level from 266 to 160 mg. and the level of the 24-hour urinary sugar from 90 to 21 G.

Total Pancreatectomy

In this single case, glucophage had no discernible effect.

Toxic Effects

No serious toxic effects were seen.

Symptoms of gastro-intestinal irritation were encountered by about 25% of patients and precipitated discontinuation of tablets in 6 of the 62 patients.

There appears to be no tendency for patients to gain weight on glucophage. This may be an advantage, particularly in the obese, and is possibly due to some interference with the appetite.

DISCUSSION

The addition of glucophage to the current therapy for diabetes has made it possible to treat an additional number of maturity-onset patients satisfactorily with oral agents alone.

Certain patients who failed to respond to the sulphonylureas showed a satisfactory response to glucophage or to a combination of glucophage and chlorpropamide.

In many patients the use of the oral agents has improved diabetic control. It is still too early to judge whether oral therapy will influence the late complications, but it is hoped that the better control achieved may reduce the liability to diabetic vascular disease.

The administration of glucophage may improve the control in some 'brittle' diabetics of juvenile type, and allow a lesser dose of insulin to be taken. It may thus render these patients less liable to the hazards accompanying hyperglycaemia and ketosis on the one hand, and hypoglycaemia on the other hand. The failure rate in this group of patients is likely to be high, and the trial is best performed in hospital.

It was noted that control of diabetes with glucophage was not always better than that with the sulphonylureas; in fact it was sometimes worse.

Glucophage was found to enhance the hypoglycaemic effect of chlorpropamide in some cases which were not satisfactorily controlled by either of these agents alone.

We feel it necessary to reiterate that, in the mild, 'maturity-onset' diabetic, dietary control, with weight reduction if necessary, remains the first line of attack. Secondly, no oral drug should be continued over the trial period unless it has been shown to be of definite benefit. Thirdly, it must be clear that the patient is out of control when treated by diet alone, before any oral agent is administered. Finally, mixed therapy should only be given after thorough trial of each agent singly, and also, of course, of dietary measures.

CONCLUSION

Glucophage is an effective blood-sugar-lowering agent in many maturity-onset diabetics. It may be effective when the sulphonylurea hypoglycaemic agents have failed; on the other hand patients who have responded to chlorpropamide may fail to respond to glucophage. It appears to be reasonably safe and to produce considerably less gastro-intestinal irritation than its analogue, phenethyldiguanide. It may be effective in some patients in the absence of endogenous insulin.

SUMMARY

The effect of dimethyldiguanide (glucophage) in 62 selected diabetic patients attending the Groote Schuur Hospital is described. Satisfactory control of the diabetic state was obtained in 27 out of 47 'maturity-onset' patients, in many of whom the sulphonylurea drugs had previously failed.

Of 12 juvenile-type diabetics, glucophage appeared to assist in obtaining better control, and allowed a reduced insulin dosage, in 6. Glucophage was of value in patients with chronic calcific pancreatitis, but had no effect in 1 patient who had undergone total pancreatectomy.

No serious toxic effects have been encountered, though symptoms of gastro-intestinal irritation occurred in about 25%, and necessitated stopping the drug in a small number.

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