DBI (PHENETHYLDIGUANIDE) IN THE TREATMENT OF DIABETES MELLITUS

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The successful debut of the sulphonylureas, carbutamide and tolbutamide as oral hypoglycaemic agents was bound to act as a stimulus to the search for still more effective drugs in the treatment of diabetes mellitus.

In 1957 Ungar *et al.*[1] were able to report on the effectiveness of N-β-phenethyl-formamidinyl-iminourea (also called phenethyldiguanide or DBI) as a blood-sugar-lowering agent. Further experimental confirmation of this finding was provided by Williams *et al.*[2] and Tyberghein *et al.*,[3] and clinical reports of the successful use of DBI were soon presented by Pomeranze *et al.*[4,5] and Krall *et al.*[6]

All investigators have been unanimous in reporting frequent gastro-intestinal side-effects which have tended to limit the administration of DBI, and one of us[7] reported side-effects in 7 of 10 middle-old-age cases to which DBI was first administered. DBI is a white crystalline, water-soluble substance which is now available in the form of 25 mg. tablets, but was originally provided in both 25 and 50 mg. tablet size.

MATERIAL AND METHOD

The present investigation was undertaken to determine the effectiveness of DBI in 29 middle-old-age group diabetics

for periods of up to 1 year. They consisted of 25 females and 4 males whose ages varied from 39 to 75 years with an average of 56·3 years. The duration of diabetes varied between 2 and 24 years with an average of 9·8 years.

All the cases were proved diabetics and had been treated previously for varying periods of time with one or more regimens of treatment. Thus 9 cases had been on diet only, 18 on diet plus insulin, and 8 on diet plus tolbutamide.

The initial dosage of the drug was 25 mg. twice daily. This was increased by 25 mg. at weekly intervals or less until effective control was obtained or until side-effects precluded further increase. The maximum dosage administered was 250 mg., but usually no more than 150 mg. daily was given, because gastric irritation became marked above this amount. Insulin, where administered, was decreased slowly once the hypoglycaemic action of DBI had become manifest. It was found that administration during meals was better tolerated than either before or after, and in the later cases this method of administration was adhered to. The drug was always given in divided doses.

Fasting venous blood sugars (method of King and Garner[8]) were initially estimated at least at weekly intervals and at two-weekly intervals after the first month. Complete blood counts and erythrocyte-sedimentation rates were performed at fortnightly intervals and a battery of 12 liver-function tests[9] every 3 months.

Our clinical results have been evaluated as good, fair, or poor according to our previous criteria.[10]

RESULTS

The hypoglycaemic action of DBI is shown in Fig. 1. In this case 50 mg. of DBI was administered 3 times daily during meals. During the first 24 hours no real hypoglycaemic effect was noted, but the patient became aglycosuric from the fourth day onwards and frequent blood-sugar estimations showed a good hypoglycaemic effect on the tenth day.

Diet-only Group

Nine cases (2 males and 7 females) had previously been on a diet-only regimen. Five were obese and 4 medium in build. They had been known diabetics for periods of 2 - 13 years and their ages varied from 46 to 75 years. One was under good control, 3 under fair control and 5 under poor control.

The good-control diabetic was included in the hope that the blood sugar could be reduced to entirely normal limits. No such effect was noted, the blood sugars remaining at their previous levels.

Six cases improved to the good category, 4 having previously been under poor control and 2 under fair control. One of these cases, which had previously graduated from the poor to good category, has again deteriorated to the poor group after 10 months. One case improved from the poor to fair category on treatment with tolbutamide, 0·5 g. thrice daily plus 25 mg. of DBI 3 times daily. This case is of interest because neither diet only, nor diet plus tolbutamide, nor diet plus DBI were able to improve diabetic control, and only combined treatment was able to effect some improvement.

The remaining 'fair-control' case was unaffected by treatment.

Insulin Group

Eighteen cases (2 males and 16 females) had previously been treated with insulin. Of these 11 were obese and 7 medium in build. They had been known diabetics for periods ranging from 5 to 24 years and their ages varied between 39 and 69 years. Control was good in 1, fair in 5 and poor in 12 cases. The dosage of insulin varied between 15 and 90 units daily. In one case DBI replaced the 15 units of protamine zinc insulin previously required to keep the diabetes under good control, while in another improved control (from fair to good) occurred while replacing the whole dosage of 10 units protamine zinc insulin. In 2 further cases improvement from poor to good control was achieved on DBI together with insulin, the latter being reduced by 10 units (Lente insulin 30 - 20 units and 35 - 25 units). Three cases improved from poor to fair control on DBI plus insulin, the daily dosage of the latter being 7 - 10 units less than previously (NPH 27 - 20 units, Lente 30 - 20 units, NPH 20 - 10 units). The remaining cases stayed in the poor category, but in 2 of these it was possible to reduce insulin by 20 and 30 units (70 to 50 and 90 to 60 units of Lente insulin) without producing any increase in blood sugar. Withdrawal of DBI was a signal for the return of insulin requirement to its previous level.

In 3 cases the side-effects were so severe as to necessitate abandonment of DBI treatment. One case which had failed on a regime of 40 units of Lente insulin plus 50 mg. of DBI thrice daily, improved to fair control when tolbutamide was substituted for both these drugs. The patient, a female aged 60 years, had been diabetic for 10 years and was originally under poor control on treatment with diet plus 40 units of Lente insulin. Contrariwise, a female aged 51 years who had been diabetic for 9 years and had been poorly controlled on both Lente insulin, 35 units, and this together with either tolbutamide or chlorpropamide, improved to the fair category on 25 units of Lente plus 75 mg. of DBI daily. Four poor-category cases were labile diabetics who had experienced both hypo- and hyperglycaemic coma. Administration of DBI did not in any way alter their lability, and they remained poorly controlled.

Tolbutamide Group

Eight cases (all females) had previously been treated unsuccessfully with tolbutamide. Their ages ranged from 41 to 69 years and the duration of diabetes from 2 to 19 years. Three were obese and 5 were medium in build. Transfer to DBI alone was sufficient to improve control to good in 1 case and fair in another. A further case improved to fair when DBI 75 mg. daily, was added to tolbutamide, 0·5 g., 3 times daily.

Two cases improved to the fair category on DBI plus insulin (20 and 10 units respectively), but showed no improvement on DBI alone.

The remaining 3 cases showed no alteration in control when switched to DBI therapy.

Side-effects

Twenty-one cases experienced side-effects. These were so severe in 6 cases as to necessitate discontinuation of treatment.

The side-effects noted were as follows: Dry mouth in 3 cases, bitter taste in 4 cases, abdominal discomfort and cramp in 3 cases, abdominal distention in 2 cases, nausea

in 7 cases, vomiting in 4 cases, hiccough in 1 case, diarrhoea in 4 cases, faintness and dizziness (not related to hypoglycaemia) in 8 cases, malaise in 4 cases, headaches in 3 cases, and loss of weight in 1 case.

In 6 cases the side-effects gradually disappeared despite a constant dosage. In 4 other cases reduction in dosage alleviated the side-effects, and in 1 other case these disappeared when dosage was reduced and did not recur when DBI was increased to its original dosage after a period of 1 month. The remainder were able to continue treatment in spite of side-effects.

Laboratory Investigations

Blood counts, erythrocyte-sedimentation rates and liver-function tests did not show any significant changes during the period of this trial.

DISCUSSION

DBI has a definite hypoglycaemic action which was found to occur after the administration of the first dose in some cases, but only after continued administration over a period of several days in others. This delayed type of reaction is shown in Fig. 1. Single doses of the drug have shown a hypoglycaemic response in 4 hours, maximal at 6 hours, and almost disappeared in 10 hours.[11]

Experimental studies have suggested that DBI lowers blood-sugar levels by promoting anaerobic glycolysis with increased glucose utilization by the tissue, and by causing decreased gluconeogenesis with decreased output of glucose from the liver. In contradistinction to insulin, DBI leads to a decreased muscle glycogen concentration.[12,13] While it produces a definite hypoglycaemia in depancreatized and in alloxanized animals,[1] it has a much greater effect in those in which the pancreas is present.[12]

The clinical studies reported here show that DBI has a mild blood-sugar lowering effect. Six out of 9 cases previously on a 'diet only' regime graduated to the good category while on DBI. Insulin-treated cases did not respond so well. In only 2 of these was it possible for DBI to replace the total 10 and 15 units of insulin which were required to control the diabetes effectively. Partial replacement of insulin by DBI was possible in a further 7 cases. Thus, 2 cases improved from poor to good and 3 from poor to fair while insulin requirement was reduced by not more than 10 units. Eight cases remained under poor control, but insulin requirement was 20 and 30 units less, while the blood sugar remained constant.

Thus, the maximum amount of insulin replaced, in this series, was 30 units. The effect of DBI must, therefore, be considered to be mild and owing to side-effects it was found impossible to continue treatment with dosages larger than 150 mg. daily; with this dosage no marked hypoglycaemic symptoms were noted.

Twenty-one of the 29 cases experienced side-effects—a high incidence for a drug which must be used over a prolonged period. In 6 cases these effects were so severe as to warrant discontinuation of treatment. The side-effects were mainly gastro-intestinal, but patients often felt depressed and 'miserable' as a result.

While reduction in dosage or the passage of time were sufficient to allow these symptoms to disappear in 10 cases, the frequent side-effects suggested that the drug could have only a limited use. On the other hand no haematologic, hepatic or renal complications were found in any patient in this group of cases treated for periods up to 1 year. Ketonuria has been reported coincidentally with the elimination of glycosuria, but this was not noted in our series. This

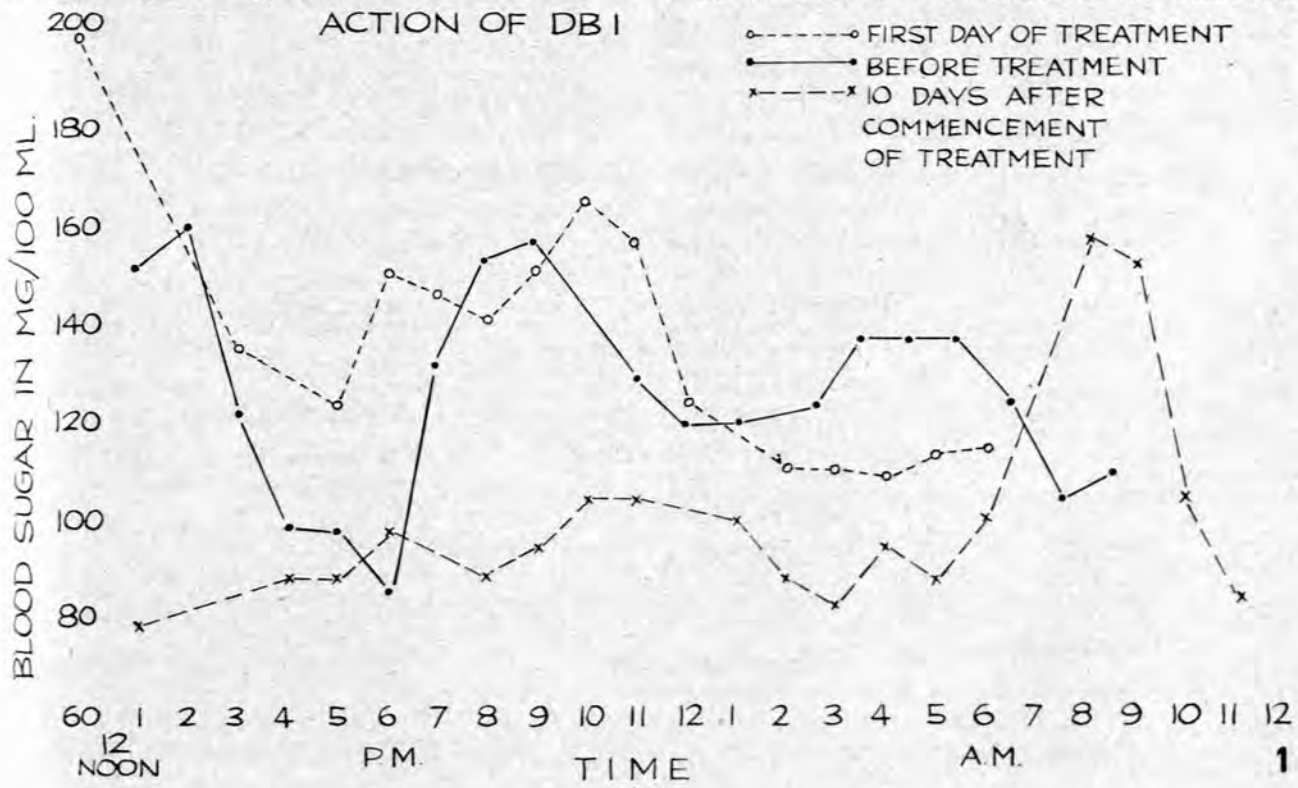

Fig. 1.

type of ketonuria has been referred to as 'starvation ketonuria' and can be eliminated by reduction in DBI dosage or by a liberal intake of carbohydrate. Hall *et al.*[11] have suggested that carbohydrate oxidation is not completely rectified even when the drug has reduced the blood-sugar level to normal.

It has been suggested that one of the uses of the drug is control of the labile diabetic by means of DBI and insulin.[6] In the 4 cases studied no such stabilizing effect was noted, the lability being uninfluenced.

In 1 of 8 cases where tolbutamide had failed, DBI was able to improve control to such an extent that the case could be placed in the good category. DBI plus insulin was able to take over effective control in several other cases, but a slightly larger dose of insulin alone could have done this.

Where tolbutamide alone was ineffective, a combination of DBI with tolbutamide improved control to the fair category in 1 case. This is one use of DBI which merits further investigation in the patient who would prefer oral diabetic therapy.

CONCLUSIONS

Our experience in a middle-old-age group of diabetics points to DBI being a mild hypoglycaemic agent which is prone to give rise to side-effects, mainly gastro-intestinal in type. While reduction of blood sugar to normal limits is possible in mild cases, DBI alone is unable to control the severe diabetic. In the latter type a combination of DBI and insulin can allow of smaller doses of insulin being administered, but in most cases this would have no advantage over giving larger doses of insulin alone. We have been unable to substantiate the claim that DBI is useful in stabilizing labile diabetes. The possibility, however, exists that a combination of tolbutamide or chlorpropamide with DBI may improve control in some stable cases, and particularly where control deteriorates after initial successful stabilization with tolbutamide. It is apparent that DBI has only a limited use in the treatment of diabetes.

SUMMARY

1. Twenty-nine diabetics in the middle-old-age group were treated with phenethyldiguanide (DBI) for periods up to 1 year.

2. Side-effects, mainly gastro-intestinal, were noted in 21 cases. In 6 cases these side-effects necessitated discontinuation of treatment.

3. DBI was able to replace a maximum of 30 units of insulin.

4. DBI alone was unable to control severe diabetes although reduction in insulin dosage was possible by means of combined therapy.

5. In 4 cases of labile diabetes DBI did not exert any stabilizing effect.

6. The suggestion is made that combined therapy with other oral anti-diabetic drugs may prove useful.

7. DBI has only a limited use in the treatment of diabetes mellitus.

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