Clinical and Metabolic Effects of Phenethylbiguanide

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Phenethylformamidinyliminourea hydrochloride (DBI) is a nonsulfonylurea compound capable of lowering the blood sugar when administered by mouth. Its hypoglycemic action has been demonstrated in human subjects in a variety of animal preparations including the eviscerate guinea pig,[5] alloxan-diabetic rabbits, rats and monkeys.[1] Death in animals following DBI administration has resulted from hypoglycemia[1] and cardiac arrhythmias[12] but, to date, no fatalities in man have been attributed to the drug and no cases of renal, hepatic or hematopoetic toxicity have been reported in patients receiving the drug.

MATERIALS AND METHODS

Forty-two patients with diabetes mellitus were treated with DBI for a minimum of one month, or until side effects precluded further administration of the drug. All patients were hospitalized, placed on a constant diabetic diet and evaluated for renal, hepatic and hematopoetic abnormalities. If they were on insulin, their current requirement was stabilized. Blood glucose was determined by the Somogyi-Nelson technic[13] and nonesterified acids by the method of Dole and his associates.[14]

The patients in this series ranged from sixteen to eighty-five-years in age. Four were juvenile-type diabetics, and nine showed marked changes in the level of their blood sugar from day to day and thus were considered to fall into the "labile" category. Duration of diabetes in these patients ranged from a few days to twenty-two years. Twenty-five of the group required 10 to 85 U. of insulin per day for control of hyperglycemia, while seven had unsuccessfully attempted dietary control. Response to DBI was graded as follows:

Good—fasting blood sugar 60-150 mg. per 100 ml., no glycosuria over two plus.

Fair—fasting blood sugar 150-200 mg. per 100 ml., no glycosuria over three plus.

Poor—fasting blood sugar over 200 mg. per 100 ml., frequent glycosuria over three plus.

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RESULTS

In twenty patients hyperglycemia was controlled by DBI alone, while thirteen patients (including six of the labile type) required less insulin than they had prior to DBI administration. In these patients diabetic control seemed to be stabilized by addition of the drug. Of the individuals who received DBI alone thirteen obtained good control, three fair control and four poor control according to the criteria already described. Ten of the thirteen patients receiving DBI and insulin maintained good and three fair control of their hyperglycemia.

Eight patients developed untoward side effects before significant control of hyperglycemia was attained and therefore no further DBI was administered. Sixteen patients who were successfully treated also developed side effects, as follows: nausea in ten, vomiting in six, diarrhea in two, metallic taste in one, and dizziness in one. Two patients showed intermittent acetonuria while taking DBI and maintaining adequate caloric intake. In ten patients who developed side effects, therapy was discontinued, while in six it was possible to minimize side effects and still control hyperglycemia by reducing the dose (table 1). Twenty-four of the series are currently receiving the drug. Nineteen are maintaining good control and five fair control. Two patients on insulin plus DBI have reported episodes suggesting hypoglycemic attacks. Unfortunately, chemical confirmation was not obtainable in either patient.

One patient in the series had undergone a total pancreatectomy for chronic pancreatitis. As can be seen in table 2, DBI appears to have reduced this patient's hyperglycemia despite lack of endogenous insulin and reduction in the dose of exogenous insulin. In this subject, twenty-four-hour urine glucose excretion decreased during DBI treatment, but on the last day of treatment marked anorexia developed, and since constant caloric intake could not be maintained the study had to be terminated.

In an attempt to elucidate the mode of action of the biguanides, the acute effect of DBI on plasma nonesterified fatty acids (NEFA) was studied in human subjects. NEFA levels are known to be lowered by ingestion of carbohydrate,[15,16] tolbutamide,[17] glucagon[14] and amino

TABLE 1
Results of therapy with DBI

	Number of patients		
Adequate period for evaluation	42		
DBI alone	20		
Control—good		13	
fair		3	
poor		4	
DBI and insulin	13		
Control—good		10	
fair		3	
Failures	9		
Side effects prior to therapeutic effect		8	
Total pancreatectomy		1	
Side effects (including failures)	20		
DBI stopped		14	
Loss of side effects on smaller dose		6	
Gastrointestinal			4
Acetonuria			2

TABLE 2
J.M—St. Luke's Hospital #358-573. Total pancreatectomy, April 1957

Date	Weight (lb.)	NPH Insulin (units)	Reg. Insulin (units)	DBI mg.	FBS mg. per 100 ml.	Total twenty-four hr. gm. glucosuria
7/8	133	40	10-20	none	287	67.2
7/9	133	40	15	none	150	36.9
7/10	135	40	20	none	188	52.2
7/11	136	20	15	50	206	5.1
7/12	—	20	10	75	200	73.2
7/13	136	20	5	75	287	64.0
7/14	—	15	15	125	—	11.7
7/15	—	15	20	175	312	25.0
7/16	136	10	10	175	250	9.7
7/17	—	10	5	225	262	5.9
7/18	136	40	15	Stop	300	—

acid administration.[18] It would appear that NEFA are mobilized from adipose tissue[19] to supply energy needs when glucose utilization is decreased.[14,20,21]

In the poorly controlled diabetic patient, plasma NEFA tend to be abnormally elevated and, like the blood sugar, fall when insulin is administered.[14] Intravenous administration of tolbutamide, in responsive patients with diabetes mellitus, also induces a drop in plasma NEFA concentration.[17]

Accordingly, plasma NEFA levels were followed in diabetic patients (previously determined to be responsive to DBI) after administration of the biguanide. It was reasoned that a significant decrease in plasma NEFA after DBI might provide evidence for an increase in glucose utilization induced by the drug. These subjects all had mild diabetes mellitus and had received no DBI for one week, no depot insulin for forty-eight hours, and no crystalline insulin for at least twelve hours prior to the test. All were studied in the postabsorptive state and were given oral glucose (1.0 gm./kg. body weight) on a control day, and the same amount of glucose plus 50 to 100 mg. of DBI on the test day. Venous blood specimens were taken prior to administration of glucose and/or DBI one, two, three, four and five hours subsequently.

At the dose level of 50 mg. of DBI, the four patients tested showed no difference in NEFA or blood glucose response to the glucose load. When the dose of DBI was increased to 100 mg., an increase was noted in the rate of fall of NEFA concentration in plasma, although no consistent changes in the blood sugar occurred.

DISCUSSION

Numerous studies have indicated that the biguanides promote anaerobic glycolysis.[22-24] DBI may have such an effect by blocking one or more enzyme systems upon which the citric acid cycle depends.[24,25] The lack of any effect of DBI on plasma and urine steroid levels, or ACTH responsiveness[26,27] would seem to eliminate interference with gluconeogenesis as an action of the biguanides. Thus far studies with glucagon and epinephrine have been contradictory but neither hormone seems to be involved in the mode of action of DBI.[11,27]

The increased uptake of glucose by muscle that has been reported after DBI administration[1,5] suggests that phenethylbiguanide may increase peripheral glucose utilization under certain conditions.[28] Studies by Lundbaek[10] and Nielson et al.[5] have shown DBI to be effective in alloxan-diabetic and pancreatectomized animals. The results obtained in our patient with a total pancreatectomy must be considered inconclusive.

In the series presently reported, DBI helped in the control of hyperglycemia in approximately 60 per cent of the patients with diabetes mellitus who were given a therapeutic trial. If the patient does not develop side effects, there seem to be two main groups in which DBI may be a useful agent: patients requiring small amounts of insulin for regulation and patients who have wide swings in blood sugar from day to day. In this latter group the biguanides seem to smoothe the course.[7-9,11] In the present series, four patients were studied who fell into this category. One was controlled by DBI alone, two had their diabetic state stabilized by the drug, and the fourth was unable to tolerate it in a dose sufficient to alter his hyperglycemia.

The over-all incidence of side effects of DBI is between 35 and 60 per cent.[6-9] These symptoms are so unpleasant or occur at such low dosage in about 15 to 35 per cent as to preclude further attempts at DBI management. The use of the arylsulfonylureas and biguanides jointly, as suggested by Beaser[29] may circumvent some side effects, but until this handicap can be overcome, the extent of biguanide control of hyperglycemia cannot be fully evaluated.

SUMMARY

The effect of phenethylbiguanide on hyperglycemia was studied in forty-two patients with diabetes mellitus. Twenty were placed on the drug alone and of this group thirteen achieved good control of hyperglycemia, according to previously established criteria. Thirteen patients were given it as a supplement to insulin and, of these, ten obtained good control of their blood sugar levels. Fourteen patients developed gastrointestinal side effects which prevented further biguanide therapy, while six others with similar complaints were able to tolerate lower doses and maintain adequate control. The drug seems to be most effective in mild diabetes, or as an adjunct to insulin treatment in the labile patient.

SUMMARIO IN INTERLINGUA

Effectos Clinic e Metabolic de Phenethylbiguanida

Le effecto de phenethylbiguanida super hyperglycemia esseva studiate in quaranta-duo patientes con diabete mellite. Vinti recipeva solmente phenethylbiguanida. Dece-tres de illes obteneva un bon grado de stabilisation de lor hyperglycemia secundo previemente establite criterios. Dece-tres altere patientes recipeva phenethylbiguanida como supplemento de insulina. In dece de istes, bon grados de stabilisation del nivellos de sucro sanguinee esseva effectuate. Dece-quatro patientes disveloppava effectos secundari gastrointestinal que preveniva le continuation del therapia a phenethylbiguanida. Sex alteres, con simile gravamines, esseva capace a tolerar plus basse doses e mantener assi un stabilisation adequate. Phenethylbiguanida es le plus efficace in le patiente con leve grados de diabete mellite.

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