Metabolic and Endocrine Studies with Phenethyldiguanide (DBI)

Thomas G. Skillman, M.D., Fred A. Kruger, M.D., and George J. Hamwi, M.D., Columbus

The recent report by Ungar and his colleagues[1] describing the hypoglycemic action of a nonsulfonamide compound has resulted in widespread clinical investigation of its possible use as an oral agent for the treatment of diabetes mellitus. This compound is the hydrochloride of phenethyldiguanide (N-beta-phenethylformamidinyliminourea hydrochloride) and has been designated DBI by the manufacturer and hereafter will be referred to as such. Although the mechanism of the hypoglycemic effect of the sulfonylurea compounds is not completely understood, it appears likely that it is predominantly an insulin effect, and that they act by stimulating the beta cells to secrete insulin. The hypoglycemic action of DBI does not appear to be mediated by insulin.

Since 1957, many investigators[2-6] as well as ourselves have conducted studies to assay the therapeutic efficacy and possible untoward effects of this compound in diabetics. Our experience with DBI has been gained from evaluation of hospitalized diabetic patients who presented specific problems in management. Particular emphasis was placed upon evaluation of the effects of the drug on thyroid, adrenal, hepatic, renal, gastrointestinal, and hematopoietic function as well as its influence upon the diabetic state. Studies also have been initiated to explore the mechanism of action of this type of compound.

Our findings, to date, indicate that DBI does not alter glandular physiology as reflected by the customary indices, and aside from its gastrointestinal side effects, does not influence the function of vital organs in an untoward fashion. DBI has been employed as the sole therapeutic agent to control hyperglycemia and glycosuria in the milder, obese diabetic whose disease is of short duration.

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From the Division of Endocrinology, Department of Medicine, Ohio State University, Columbus, Ohio.

METHODS

During a twelve-month period, twenty-nine selected diabetic patients were hospitalized on the metabolism service with the sole aim of evaluating their response to DBI. In each patient, control of hyperglycemia and glycosuria was not optimal prior to admission, either because the patient was a recently discovered diabetic, or because preadmission treatment with tolbutamide or insulin and diet presented problems in diabetes management.

A uniform plan of observation for evaluating the influence of DBI on hyperglycemia and glycosuria, endocrine function and vital organ function was adopted for all patients. A forty-eight- or seventy-two-hour control period preceded treatment with DBI in each instance. During this interval a diet believed optimal for control of diabetes was fed and the same diet was continued during the treatment period. Recently discovered diabetics and those not taking insulin were observed while treated with diet alone. In those patients who took insulin prior to study, the customary dose was continued during this period and then diminished or deleted during DBI therapy. Determinations of various functions made during the control period were then compared with similar findings made during the DBI treatment period. Daily fasting and two-hour postprandial blood sugar levels as well as twenty-four-hour urinalyses for volume and quantitative sugar were used to estimate the effect of the drug on carbohydrate metabolism. Paired values for serum cholesterol, protein bound iodine, and twenty-four-hour thyroidal I^{131} uptake were used to assay thyroid function. Estimates of adrenal physiology were made by daily twenty-four-hour determinations of urinary 17-ketosteroid, 17-hydroxycorticoid and creatinine excretion. Evaluation of liver function included cephalin flocculation, bromsulfalein retention, prothrombin concentration, serum alkaline phosphatase content and serum glutamic-oxaloacetic transaminase tests. Other indices included hemoglobin, hematocrit, white blood cell and differential counts. Blood urea

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nitrogen measurements and total urinary protein determinations were also performed.

DBI was administered orally with meals. Considerable variation in dose and in the timing of dosage occurred and was incident to attempts to avoid gastrointestinal side effects of the drug and to improve control of hyperglycemia. DBI was given for at least three days to all subjects and always was continued until a clear-cut appraisal of hypoglycemic response could be made. The criteria for response were rigid and included: (1) ability to stop insulin; (2) a drop in blood sugar resulting in levels consistently below 175 mg. per cent including postprandial values; (3) a drop in glycosuria to less than 5 gm. per day; and (4) tolerance to the drug of such degree that gastrointestinal effects were in no fashion disturbing to the patient.

Most of the patients who met these criteria for response were then discharged from the hospital and followed at monthly intervals as outpatients. The study of all indices was continued.

RESULTS AND COMMENT

Hypoglycemic action. In twenty-nine instances an attempt was made to employ DBI as the sole hypoglycemic agent. In all instances fasting blood sugars exceeded 175 mg. per cent during the control period despite the administration of a carefully planned diet. In sixteen individuals insulin in suboptimal doses also was used during the control period.

Fourteen met the criteria for adequate hypoglycemic response while fifteen failed to do so. In the responsive group the fasting blood sugar levels fell from a mean of 240 mg. per cent during the control period to a mean of 135 mg. per cent during the fourth, fifth, and sixth day of DBI treatment. None of the patients responding received insulin during the treatment period. In the nonresponsive group, fasting blood sugars rose from a mean of 277 mg. per cent during the control period to an average of 350 mg. per cent on the fourth, fifth and sixth days of DBI therapy. These findings are summarized in figure 1.

Age. Only two true juvenile diabetic patients were included in the study, and neither was found to be responsive. One was a ten-year-old girl who had been symptomatic for only a few weeks. Dosage with 150 mg. of DBI daily was without effect, but subsequent insulin therapy in a dose of 20 units and ultimately 10 units daily resulted in excellent control. The other was a twenty-five-year-old man who had been diabetic for fifteen years, and two years prior to DBI treatment had undergone surgical hypophysectomy with the hope

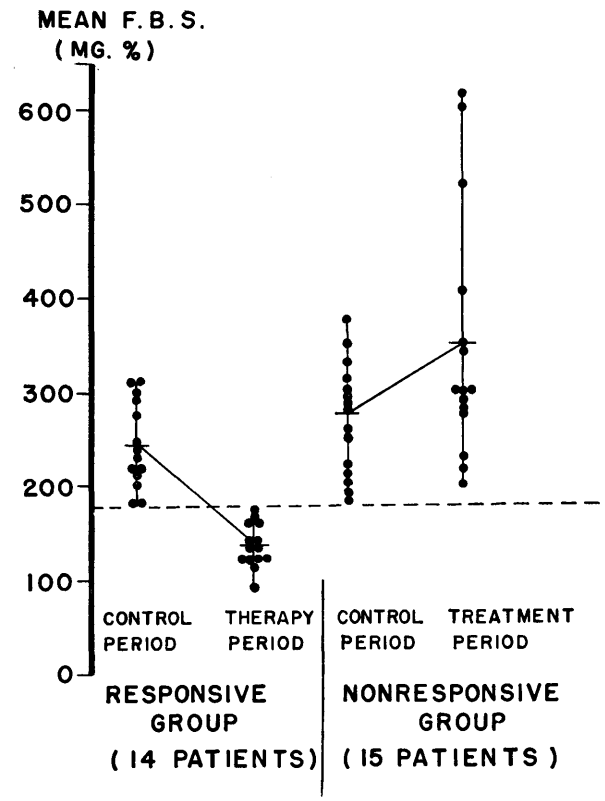

FIG. 1. Comparison of mean fasting blood sugar values measured during the control period and during the fourth, fifth and sixth days of therapy in the responsive and nonresponsive groups.

that his severe progressive retinitis proliferans might be controlled. This operation resulted in a decrease of his daily insulin requirement from 80 to 14 units per day. When DBI therapy was instituted, his NPH insulin dose was arbitrarily decreased from 14 to 8 units; but over a three-day period, his fasting blood sugar rose from 130 to 620 mg. per cent, and his glycosuria rose from 12 to 68 gm. daily. Aside from these two patients, age correlated poorly with responsiveness: Subjects as young as twenty-two and twenty-seven years of age responded, and those as old as sixty-one or sixty-two failed. The mean age of each group was essentially the same.

Sex. Slightly fewer men than women were studied, but no sex difference was found between those who responded, (eight women and six men), and those who failed, (eight women and seven men).

Duration of diabetes. A high degree of correlation between the duration of the diabetic state and response to DBI was noted. In the responsive group the mean duration of the disease was 1.7 yr. and four subjects were recently discovered diabetics. No patient who had been

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diabetic for more than five years responded. The mean duration of the disease in the failure group was five times greater (8.6 yr.). Three of these patients were recently discovered diabetics. In this group persons having been diabetic 25, 20, 15, 12, and 11 yr. gave no evidence of responsiveness to the drug, while a few of those in whom the duration was less than ten years responded, but in a suboptimal fashion.

Insulin dose. With regard to the magnitude of insulin dose, differences between the responsive and nonresponsive groups could also be established. Among those responding, half took insulin prior to the trial of DBI while within the nonresponsive group, three fourths used insulin. The daily dosage of insulin averaged 10.2 U. per patient for all individuals in the responsive group, and averaged 25.3 U. per patient in the nonresponsive group. No patient who used more than 26 U. of insulin responded. It was noted that the insulin requirement could be diminished 10 to 25 per cent among some subjects classified as nonresponsive. However, the daily insulin dose of a fifty-eight-year-old man who had undergone a total pancreatectomy three years prior to study was not altered by the administration of as much as 225 mg. of DBI daily for a week.

Body type. Very definite differences were found when the incidence of overweight patients in each group was determined. If simple height and weight charts were employed to categorize those who were more than 10 per cent overweight, eight of the fourteen patients who responded could be so classified while only one of the fifteen who failed to respond fit these criteria. Although it was true that obese patients tended to respond as a group, body type alone could not be employed as a criterion to predict responsiveness, as certain lean subjects responded well.

History of previous diabetic ketosis. When a history of ketoacidosis was obtained, no patient was found responsive. Two thirds of the subjects within the nonresponsive group gave such a history. The relationship of ketosis to responsiveness was further extended as three nonresponsive subjects developed ketoacidosis during their trial of DBI therapy. One patient, a fifty-one-year old man, became ketotic after four days of therapy when his serum CO_2 content fell to 10 mEq./L. and blood sugar rose to 1,024 mg. per cent.

Magnitude of DBI dose. Considerable individual variation in response to DBI appeared to exist within members of the responsive group. Variations in daily dosage from 100 to 300 mg. were necessary to control different patients whose diabetes seemed equally severe. When blood sugars reached normal levels, it was usually possible to lower the dose so that the customary dose averaged 150 mg. daily. The magnitude of the dose was limited by side effects which were predominantly gastrointestinal and included nausea, anorexia, a metallic taste, and occasionally abdominal cramping, emesis, and diarrhea. Three individuals complained of severe generalized weakness. These reactions usually occurred as the dose approached 225 mg. daily and regressed or disappeared promptly as the dose was decreased or temporarily omitted. Aside from the actual size of the dose of DBI, a definite time factor seemed related to response. Among subjects reacting favorably, none displayed a significant decrease in hyperglycemia until the second treatment day, and none responded optimally until the third day. As a group, these patients required four days to respond; and in one person, normoglycemic levels were not reached until the sixth day. Our criteria for responsiveness were achieved with a mean dose of 195 mg. of DBI daily at this time. The observed delay in hypoglycemic response was also seen in nondiabetic subjects: When a dose of 100 mg. of DBI was given orally, no drop in fasting blood sugar was found in any of six subjects followed for five hours with hourly blood sugar determinations.

Long-term studies. Of the fourteen patients who exhibited optimal response to DBI, nine were followed as outpatients for periods ranging from seven to thirteen months; and the remaining five could not be followed, either because they lived at distances too great from the hospital for intensive sequential study, or because they chose not to take part in this phase of the experimental program. The nine who were followed provided eighty-three patient-months of study. The daily dose averaged 150 mg. Control of hyperglycemia in eight of these patients could be classified as excellent, as each reported total absence of glycosuria during the entire period; and none was found to have a blood sugar exceeding 200 mg. per cent at any time. The remaining patient, who thus may be classified as a secondary DBI failure, was an obese thirty-seven-year-old housewife who was well controlled symptomatically until the seventh month of therapy. At this time, she developed a pelvic infection, and diabetes control deteriorated: DBI was discontinued and treatment with insulin was begun. She now takes 30 U. of NPH insulin daily, but hyperglycemia and glycosuria are still not optimally controlled. DBI treatment was discontinued in one other patient. This subject was a twenty-seven-year-old engineer who was ideally controlled with 150 mg. of DBI daily. Dosage was stopped after seven months to challenge the need for the drug. During five months, since discontinuation

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of DBI, blood sugar levels have remained within normal limits and aglycosuria has persisted. It appears most likely that a natural temporary remission of diabetes has occurred.

Careful scrutiny was given to all subjects to elicit signs of possible toxicity to the drug. Mild complaints of a metallic taste sensation, frequent defecation, and intermittent nausea were occasionally registered, but in no instance was withdrawal of the drug necessary. Other complications beset two of these patients, but in neither instance could these events be ascribed to DBI. One patient, who was known to have coronary heart disease, developed congestive failure which responded to the customary measures while DBI was continued, and another suffered from pelvic inflammatory disease. No change in weight of significant magnitude was observed; consequently, if an anorexogenic effect of DBI was operative, it was not sufficient to decrease caloric intake.

STUDIES ON ENDOCRINE AND VITAL ORGAN FUNCTION (SEE TABLE 2)

Thyroid function. Values of thyroid function obtained during treatment with DBI were not found to deviate substantially from control levels. Serum PBI concentrations averaged 6.91 μg. per cent during the control period and 6.69 μg. per cent after five to twenty days of DBI therapy. Random studies done after six to twelve months of treatment indicate no effect of DBI on protein bound iodine levels. Iodine^{131} uptake studies before and after five to twenty days of treatment also indicated that DBI does not influence this function. A mean increase in uptake from 16 to 23 per cent was recorded, but in no instance was uptake elevated beyond the upper limit of normal (37 per cent); and some individuals displayed a drop in uptake. No major changes in serum cholesterol were recorded; and nearly all values were found to be within normal ranges both before and after treatment.

Adrenal function. Data obtained by measurement of twenty-four-hour urinary excretion of 17-hydroxycorticoids and 17-ketosteroids suggest that DBI administration exercised no appreciable effect on adrenal function. Values for the former averaged 19.5 mg. during the control period, and as a mean fell to 17.7 mg. during therapy while average levels of the latter fell from a mean of 10.8 to 10.2 mg. per day. Although variations of steroid excretion typical of the uncontrolled diabetic were seen, no trend suggestive of an effect of DBI on adrenal function could be established.

Liver function. Short-term estimations of the effect of DBI upon various tests reflecting liver function showed no change when values were compared with control

TABLE 1

Comparison of characteristics of diabetic patients responding and not responding to DBI

Factor	Responsive group (14)	Nonresponsive group (15)
Age (years)*	45.9 (22-68)	46.4 (10-62)
Per cent women	57	54
Duration of diabetes* (years)	1.7 (1-4)	8.6 (1-25)
Usual daily insulin dose* (units)	10.2 (0-26)	25.3 (0-50)
Per cent of group calculated to be more than 10 per cent overweight	57	7
Per cent of group in whom a prior history of ketosis was obtained	0	67
Daily dose of DBI at the time* of response or discontinuation (mg.)	195 (100-300)	196 (150-300)
Number of days of DBI therapy until response or discontinuation*	4.1 (3-6)	6.2 (3-13)
Per cent of group developing significant gastrointestinal symptoms	36	100

*Figures given as mean and range.

TABLE 2

Short-term studies of endocrine and vital organ function in twenty-nine DBI-treated patients

	Test	Before* DBI	After DBI
Thyroid function	Serum PBI (μg. per cent)	6.91 (4.8-8.8)	6.69 (5.2-7.5)
	Twenty-four-hr. Thyroidal I^{131} uptake per cent	16 (13-22)	23 (8-30)
	Cholesterol (mg. per cent)	191 (135-260)	172 (113-220)
Adrenal function	Twenty-four-hr. 17OHCS Excretion (mg.)	19.5 (7-29)	18.7 (11-27)
	Twenty four hr. 17KS Excretion (mg.)	10.8 (5-17)	10.2 (6-16)
Liver function	Cephalin flocculation	0-1 plus	0-1 plus
	Bromsulphalein retention per cent	1.7% (1-4)	1.6% (0-4)
	Alkaline phosphatase (Bodansky units)	5.5 (4-8)	5.1 (4-7)
	Prothrombin concentration per cent	75 (68-100)	79 (65-100)
	S.G.O.T. (units)	34 (25-58)	34 (10-47)
Peripheral blood	Venous hematocrit per cent	45 (41-52)	42 (37-49)
	WBC Hundreds/mm.^{3}	9.2 (5.4-11.5)	9.5 (4.7-15.1)

*Values given as mean and range.

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levels. Observations of these same indices over a six- to twelve-month period were the same. Bromsulfalein excretion values averaged 1.7 per cent after forty minutes during the control period and 1.6 per cent during treatment. Alkaline phosphatase, cephalin flocculation tests, one-stage prothrombin times, and levels of serum oxaloacetic transaminase also did not deviate from normal.

Peripheral blood. Frequent measurements of the percentage of packed red cells and total and differential white blood cell counts were made during the hospital period in all patients, and after prolonged DBI treatment in the responsive group. These data suggest that the drug does not influence these indices of hematopoietic function.

SUMMARY AND CONCLUSIONS

DBI was given to twenty-nine patients with uncontrolled diabetes mellitus. Fourteen demonstrated an adequate hypoglycemic response and became aglycosuric. This group was characterized by having mild diabetes of short duration, frequently associated with obesity. A patient with a total pancreatectomy, two juvenile diabetics, and patients who gave a history of ketosis did not respond. Reactions to DBI, other than occasionally encountered generalized weakness, were entirely gastrointestinal and included epigastric discomfort, metallic taste, nausea, vomiting, and frequent defecation. All reactions were transient and regressed promptly with cessation of therapy.

DBI in the doses given did not influence thyroid or adrenal function as measured by the usual indices. No evidence of untoward effects upon renal, hepatic, or hematopoietic function was observed during a period of one year's study.

SUMMARIO IN INTERLINGUA

Studios Metabolic E Endocrin Con Phenethyldiguanido

Phenethyldiguanido (DBI) esseva administrate a vintinove patientes con non-coercite diabete mellite. Decequatro monstrava un adequate responsa hypoglycemic e deveniva aglycosuric. Iste gruppo se distingueva per le facto que in illo le diabete esseva leve e de breve duration, frequentemente associate con obesitate. Un patiente previemente subjicite a pancreatectomia total, duo patientes con diabete juvenil, e un patiente con un historia de cetosis non respondeva. Le reactiones lateral provocate per DBI—a parte le occurrentia de debilitate generalisate in certe casos—esseva exclusivemente gastrointestinal. Illos includeva disconforto epigastric, gusto metallic, nausea, vomito, e frequentia de defecation. Omne le reactiones esseva transitori e regredeva promptemente con le interruption del therapia.

DBI, in le doses usate in le presente studio, non influentiava le functionamento thyroide o adrenal, secundo le indices in uso general. Nulle signo de effectos adverse super le functionamento renal, hepatic, o hematopoietic esseva observate in le curso del studio que habeva un duration de un anno.

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