Phenformin in the Management of Diabetes Mellitus

Special Problems

Samuel B. Beaser, M.D., Boston, Moderator

Henry Dolger, M.D.
New York City
Barnett Greenhouse, M.D.
New Haven
Elmer Kleefield, M.D.
New York City
William Pearlman, M.D.
Wilkes-Barre
Frank Scott Perkin, M.D.
Detroit
Maurice Protas, M.D.
Washington, D.C.
Robert S. Radding, M.D.
Houston
Priscilla White, M.D.
Boston

Herewith are summarized eight discussions on the evaluation of DBI beyond its use as the sole therapeutic agent in the treatment of diabetes mellitus. These were presented by the panel on special clinical applications of DBI at the symposium on phenformin.

It is apparent from previous work that DBI lowers the blood sugar and controls the glycosuria in some cases of diabetes, but does not fully control some of the other interrelated metabolic factors.[1-5] Therefore, in the clinical application of the drug, DBI requires the presence of insulin, whether of endogenous origin, as in the maturity-onset type of diabetes, or exogenous origin, particularly in the juvenile diabetic. Thus, it is used in three basic ways:

1. Alone, to supplement the endogenous and avoid the need for exogenous insulin. In some patients reported in the symposium, the drug thus employed proved successful following failure of therapy with the arysulfonylureas. The use of DBI alone is especially effective in maturity-onset patients who have significant amounts of residual endogenous insulin.

2. In the same group and for the same purpose, as a supplement to the sulfonylurea drugs (Dolger, Pearlman).[1]

3. In the juvenile type of diabetes with a paucity of endogenous insulin, to supplement exogenous insulin, thus often reducing the insulin dosage. In the latter group, a further important action is that of decreasing the instability of the diabetes.

The studies here reported describe clinical experience using DBI in diabetic patients with especial attention to the last two actions above. In addition, two groups of patients presented the problem of the relatively more unstable diabetes of children (Pearlman, White) and another two groups comprised patients with non-diabetic complications upon whom unstable diabetes or poor regulation might have an adverse effect (Kleefield, Perkin). Finally, patients with severe and unstable diabetes were studied with respect to changes in blood electrolytes, with and without DBI therapy.

CASES AND METHODS

In all, these eight reports included a total of 280 diabetics, of whom *sixty-four were specified* as having the juvenile type of diabetes; an unspecified additional number probably had this type of diabetes also (table 1). All were ambulatory except for eleven hospitalized for tuberculosis (Kleefield) and six for metabolic studies (Perkin). Where an effect on instability or severity of diabetes was being studied, these factors were carefully defined, as were the criteria for clinical improvement (Kleefield, Perkin). The latter included blood and urine sugar determinations, as well as other clinical features, such as progress of complicating tuberculosis, electroencephalograms in patients with seizures,

TABLE 1

Author	Total number of patients	Number of juveniles
H. Dolger	100	Few
B. Greenhouse	30	Unknown
E. A. Kleefield	11	Unknown
W. Pearlman	57	14
F. S. Perkin	9	Unknown
M. Protas	29	12
R. S. Radding	6	Unknown
P. White	38	38
Total	280	64

Presented at the Symposium on "A New Oral Hypoglycemic Agent, Phenformin (DBI)" in Houston on Feb. 6, 1959.

and serial electrolyte determinations, depending on the study being reported.

RESULTS

Five discussants specifically reported on the reduction in insulin requirements of patients treated with a combination of DBI and insulin (Greenhouse, Kleefield, Pearlman, Perkin and White). DBI was given as a supplement to such patients when it could not entirely replace the insulin. Thirty-five of eighty-four patients (42 per cent) had a reduction in insulin needs of from 10 to 85 per cent as a result of the oral administration of 100-200 mg. DBI per day. Among an additional thirty patients, several were reported to have had similar reductions in insulin needs without detailed statistical evidence being furnished.

The same five investigators found a stabilizing effect of DBI upon "brittle diabetes" among 145 diabetic patients specifically studied for this purpose. The dose of DBI used was also 100-200 mg. per day in divided doses. Clinically, this most frequently took the form of the simultaneous absence or near absence of both glycosuria and hypoglycemic reactions in such groups of patients. In a small group, statistical evaluation showed that seventeen of twenty patients evidenced such an improvement.

When hypoglycemic reactions did occur during the adjunctive use of DBI with insulin, they were infrequent, usually mild, and never reached the stage of unconsciousness, in marked contrast to the frequency and severity of these reactions prior to the administration of DBI. The decrease in blood sugar variations corroborated these clinical observations. The absence of the usual hypoglycemic symptoms at low blood sugar levels was commented upon by two observers. Placebos were used by some as controls to establish the stabilizing effects of DBI.

These satisfactory features of DBI therapy were particularly noted by those dealing with childhood diabetes (Pearlman, White). In these patients, the duration of diabetes was shorter than in the adult groups, but the instability greater. Growth was normal in such children whether measured by the usual clinical criteria (Pearlman) or by the Wetzel grid (White). It was also stressed that such children could indulge in exercise and have greater latitude in meal scheduling with less danger of reaction (Pearlman).

Most authors observed that even under DBI therapy intercurrent bacterial or viral infections still adversely affect diabetes and increase its instability (Pearlman). Others reported an effect even upon this unsettling factor (White). Kleefield discussed the use of DBI in conjunction with insulin in eleven patients with tuberculosis and exceedingly unstable diabetes. Since the tuberculosis tends to add to the instability of the diabetes, and since it is clinically desirable for the healing of the tuberculosis to have as normal a blood sugar as possible, DBI was administered to such patients to minimize instability. In eight out of eleven of these patients, definite stabilization of the diabetes was effected.

A special group of unstable diabetic patients of the juvenile type complicated by seizures of central nervous system origin was studied by Perkin. All had electroencephalographic abnormalities, Grade III, and had been on Dilantin for extended periods of time. The latter drug decreased the frequency of seizures, which were sometimes mistaken for hypoglycemic reactions. However, the Dilantin did not affect the basic instability of the diabetes. Extensive experience had shown both the importance of preventing further cerebral damage by reducing the incidence of hypoglycemic reactions and the possibility of reversing mental changes already present as a result of such reactions. Accordingly, nine such patients were treated with DBI and insulin in an effort to stabilize the diabetes itself. A more stable blood sugar profile resulted, and the incidence of seizures decreased. In some patients, a parallel improvement in disposition, mental status and electroencephalogram resulted.

This beneficial effect of DBI was also noted by White in six children with seizures.

The previously reported additive effect of DBI and the arysulfonylureas in treatment of diabetes was confirmed by two investigators (Dolger, Pearlman). Dolger reported on such combined therapy in 100 maturity-onset diabetic patients, twenty-five with primary and seventy-five with secondary tolbutamide failure. The dose of tolbutamide had been 1.0 gm. per day and that of the DBI 50 mg. once daily. Satisfactory conversion of these patients from therapeutic failure on tolbutamide to success was obtained by the addition of DBI. Pearlman corroborated this finding in a smaller group of seven patients (included among his fifty-seven patients) with more conventional dosage levels of DBI (Pearlman) as had been reported previously.[1]

Gastrointestinal intolerance to the drug was noted in the present group of patients. Of seventy-seven patients reported in detail, ten (13 per cent) had to abandon therapy because of these symptoms (Greenhouse, Pearlman, Perkin). It should be noted that the incidence of significantly disturbing gastrointestinal symptoms was minimized in this series by the familiarity of these in-

vestigators with the drug and the policy of raising the dose slowly by small increments (25-50 mg. per day) over intervals of approximately a week each. Where the dose was only 50 mg. per day such symptoms were completely absent (Dolger). No toxic effects attributable to DBI were reported in any of these 280 patients.

Radding studied six unstable diabetics while in the process of regulation of DBI and insulin. In addition to blood and urine sugar determinations, blood sodium, chloride, CO_2, potassium, *p*H and lactic acid were measured over several days of change in regulation. Certain biochemical variations were encountered, but these were correlated solely with changes in blood sugar rather than with the DBI administration.

DISCUSSION

The reduction in dose of exogenous insulin by addition of DBI in insulin-treated diabetics has been previously reported.[2,3]

The reduction of instability of the diabetes in so-called "brittle" diabetes is a unique action of DBI. Historically, it was only after more evenly acting types of insulin replaced crystalline insulin that the presence of other sources of metabolic instability became more clearly evident in treated diabetics. Of these various causes for instability, the least understood has been the "innate" lability that DBI affects. Various of the present authors have commented on the experience that, once the innate variability is minimized or removed, the other sources of lability become more readily recognizable. These include menses, exercise, fever, infection, etc. When the latter are isolated in this manner, measures can be taken to control them by anticipatory changes in diet or insulin available to the patient.

It is of theoretical interest to know whether the "stabilizing" effect of DBI in "brittle" diabetes is identical with an insulin-sparing action of the drug. Where details are adequate for evaluation, it seems that the "stabilizing" effect of DBI follows significant insulin-sparing, but is not always identical with it.

Less controversial is the relationship between diabetic instability and the occurrence of hypoglycemia and the clinical well-being of a subject prone to seizures of central nervous system origin (Perkin). The same may be said for degree of diabetic control and healing of tuberculosis or other infections in a diabetic (Kleefield).

The confirmation of the ability of DBI to add to the action of sulfonylureas is important (Dolger, Perkin). This principle widens the scope of each type of drug and increases the per cent of patients who can be controlled entirely by oral therapy.[1]

SUMMARY

1. A total of 280 diabetic patients, including sixty-four with juvenile diabetes, were treated with phenformin.

2. Beneficial effects upon the diabetes in the form of reduced insulin needs, stabilization of "brittle" diabetes, and the facilitation of the action of the arylsulfonylurea drugs were reported.

3. The drug could be used with success in control of the lability of diabetes in the presence of, and during treatment of, tuberculosis.

4. Secondary benefits from stabilization of diabetes were observed in the clinical course of patients with seizures of central nervous system origin.

5. No toxic effects were reported.

6. Gastrointestinal side effects were minimized by the method of gradual increase in dose of the drug to its effective level.

SUMMARIO IN INTERLINGUA

Phenethylbiguanida in le Manipulation de Diabete Mellite

1. Un gruppo total de 280 diabeticos, incluse sexanta-quatro con diabete juvenil, esseva tractate con phenformina (DBI).

2. Es reportate effectos benefic super le diabete, in le forma de reducite requirimentos de insulina, le stabilisation de diabete "fragile", e le facilitation del action de drogas arylsulfonylureal.

3. Le droga poteva esser usate a bon successo in le domination del labilitate de diabete in le presentia o durante le tractamento de tuberculose.

4. Beneficios secundari resultante del stabilisation de diabete esseva observate in de patientes con convulsiones de origine in le systema nervose central.

5. Nulle effectos toxic esseva reportate.

6. Effectos lateral gastrointestinal esseva reducite al minimo per le methodo del augmento gradual del dosage.

REFERENCES

[1] Beaser, Samuel B.: Therapy of diabetes mellitus with combinations of drugs given orally. New England J. M. *259*: 1207-10, 1958.

[2] Krall, Leo P., and Camerini-Davalos, Rafael: Clinical trials with DBI, a new nonsulfonylurea oral hypoglycemic agent. A.M.A. Arch. Int. Med. *102*:25-31, July, 1958.

[3] Odell, William D., Tanner, Donald C., Steiner, Donald F., and Williams, Robert H.: Phenethyl-, amyl-, and isoamyl-biguanide in the treatment of diabetes mellitus. Arch. Int. Med. *102*:520, October, 1958.

[4] Hardin, R. C., Jackson, R. L., Johnston, T. L., and Kelly, H. G.: Development of diabetic retinopathy: Effects of duration and control of diabetes. Diabetes *5*:397-405, 1956.

[5] McKendry, J. B. R., Kuwayti, K., and Rado, Peter P.: Clinical experience with DBI (phenformin) in the management of diabetes. Canad. M. A. J. *80*:773-78, May, 1959.