Diazoxide-induced Diabetes Mellitus in a Hypopituitary Dwarf

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SUMMARY

The successful application of the well-documented hyperglycemic effect of diazoxide to the management of hypoglycemic states has been previously reported. The present report describes the response of a hypopituitary dwarf to diazoxide administration. Diabetes mellitus, complicated by ketosis, was rapidly induced. Discontinuation of diazoxide therapy was followed by clearing of diabetes over the next five days. A comparison of the diazoxide response of this child to that of a child with leucine sensitivity is made. The possible mechanisms by which diazoxide induces hyperglycemia are discussed. DIABETES *15*:319-22, May, 1966.

The hyperglycemic effect of diazoxide has been documented in man and experimental animals.[1-6] The initial use of this compound in the treatment of clinical hypoglycemia was previously reported by the authors.[7] Our initial patient, a child with leucine-sensitive hypoglycemia, has been maintained normoglycemic during a period of over one year on diazoxide. Neither diabetes mellitus nor ketosis has been observed in this child. The only observed side effect has been mild hyperuricemia. Others have now confirmed the effectiveness of diazoxide in hypoglycemic management.[8,9]

The purpose of the present communication is to report the induction of transient diabetes mellitus which was complicated by ketoacidosis in a second child treated with diazoxide. In contrast to the first patient, the present child has hypopituitary dwarfism. The variability of response observed in these two children prompts consideration of the mechanism(s) of diazoxide-induced hyperglycemia.

CASE REPORT

M. S., a six-year-old, white female, has associated hypoglycemia and severe growth retardation. The initial hypoglycemic episode occurred at eleven months of age. Subsequently, she was hospitalized repeatedly for acute attacks of hypoglycemia which were associated often with mild systemic acidosis and ketonuria. At thirty months of age, when she had a height of 31.5 inches (height age, eighteen months) and a bone age of ten months, prednisone therapy was begun. Although 1.25 to 2.5 mg./day was administered continuously until the present admission, little or no change in the frequency of hypoglycemic reactions was observed.

On admission the height was 32.8 inches (height age, thirty-one months). The weight was thirty pounds, and the bone age three years. In addition to short stature, Cushingoid features secondary to prolonged steroid therapy were present. Hypopituitarism was suspected as the cause of hypoglycemia because of the severe retardation of linear and skeletal development which antedated steroid therapy.

Diagnostic studies clearly implicated pituitary deficiency. Fasting hypoglycemia, reactive hypoglycemia occurring secondary to oral glucose administration, increased insulin sensitivity, and increased tolbutamide sensitivity were demonstrated. Despite the presence of hypoglycemia, the fasting serum insulin levels (average 4 microunits per ml.) were consistently below the normal level of 15 microunits per ml., as determined by a modification of the radioimmunoassay of Morgan and Lazarow.[10] The expected hyperglycemic response to epinephrine and glucagon administration was observed, and the urinary catecholamines rose normally in response to insulin-induced hypoglycemia.

The basal urinary 17-hydroxycorticosteroid excretion was low ($<$ 0.5 mg./24 hours). There was no increase in urinary steroid excretion in response to a standard methopyrapone test. This is not surprising in the light of the prolonged adrenal suppression by exogenous steroids. However, nine months after complete cessation of steroid therapy she remained incapable of increasing the 17-hydroxycorticosteroid excretion during and following repeat methopyropone stimulation. However, the excretion increased normally with ACTH administration.

The initial PBI was 4.3 μg. per cent. The RAI uptake was 3.6 per cent at four hours and 11 per cent at twenty-four hours (low normal). The most impressive criteria for the diagnosis of hypopituitary dwarfism in this child was her extraordinary response to human growth hormone therapy. After nine months on human growth hormone, using physiologic doses (Wilhelmi SH-455A, 1 mg. daily) she has grown six inches and has had no recurrence of hypoglycemia.

During the hospitalization, steroid therapy was discontinued over a two-week period. One week after complete withdrawal from prednisone, diazoxide therapy was initiated at a total dose of 9 mg./kg. of body weight per twenty-four hours given in three divided doses every eight hours.* This

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*Diazoxide was obtained through the kindness of Dr. J. Black of the Schering Corporation.

therapy was continued for seven days and the blood pressure remained normal. Fasting blood sugars remained in the low normal range for the first five days. The child ate poorly but otherwise appeared well. On the sixth day, following refusal of breakfast, she had a mild, documented hypoglycemic reaction. An acetone odor to her breath was noted, and the urine was strongly positive for acetone, but negative for sugar. Because of persistent refusal to eat, approximately 50 gm. of glucose as 10 per cent dextrose was administered intravenously over a twelve-hour period. Despite this therapy, ketosis persisted and glycosuria appeared. Over the next few hours the child became acutely ill with a temperature elevation of 39.5° C., had Kussmaul breathing, and vomited all fluids. Ten hours after discontinuing the intravenous glucose the blood sugar was 744 mg. per 100 ml.; CO_2, 16 mEq./L.; blood acetone, 25 mg. per cent; urine sugar, 4+; and urine acetone, strongly positive. Diabetic ketoacidosis was obvious. Diazoxide was stopped.

As our previous experience indicated that the hyperglycemic effect of diazoxide disappears within twenty-four to thirty-six hours after its discontinuation, specific diabetic therapy was initially withheld. Unexpectedly the diabetic state persisted for six days, necessitating therapy with tolbutamide, which was initially given on the third post-diazoxide day. After oral administration of 20 mg./kg. of body weight of sodium tolbutamide,* the blood sugar fell from an initial concentration of 220 mg. per 100 ml. to 66 mg. per 100 ml. in one hour and 52 mg. per 100 ml. at two hours. On the fourth and fifth post-diazoxide days, 250 mg. of tolbutamide was given once daily in the morning with adequate control of the hyperglycemia for ten to twelve hours, following which mild hyperglycemia and ketonuria recurred overnight. By the seventh post-diazoxide day the child had returned to a normoglycemic state and tolbutamide was no longer required. Fasting insulin levels obtained while on diazoxide and during the post-diazoxide hyperglycemic phase averaged 12 microunits per ml. This is a slight increase over the pretreatment level, but still below normal, and particularly inappropriate for the degree of hyperglycemia present.

Moderate fluid retention and hyponatremia occurred during the diazoxide period. Although fluid accumulation has been observed in association with diazoxide therapy, it may not have been the causal factor in this patient. Inability to excrete water efficiently is characteristic of the cortisol-deficient patient. As she had been off steroid therapy only two weeks at the time of diazoxide administration, it is reasonable to assume that this child was cortisol deficient.

Hypoglycemia spontaneously recurred approximately two weeks after discontinuating diazoxide, and management again became difficult. Investigative therapy with human growth hormone then was initiated. Her response to growth hormone administration, both from the point of view of marked acceleration in linear growth and maintenance of normoglycemia, has been gratifying.

DISCUSSION

Hypoglycemia may result from a variety of metabolic abnormalities. The etiology of hypoglycemia in the two children we have treated with diazoxide is basically different. The initial patient has leucine sensitivity with well-documented hyperinsulinism. The basic disease of the patient reported here is hypopituitarism with deficiency of both growth hormone and ACTH. Fasting insulin levels were below the normal range, a finding previously observed in hypopituitarism.[11]

The mechanism by which diazoxide induces hyperglycemia is not entirely clear. Possible mechanisms include (1) an increased rate of peripheral inactivation of insulin, (2) stimulation of the production or release of growth hormone, ACTH, or cortisone, (3) stimulation of glycogenolysis either through a direct action of diazoxide on the glycogen molecule or indirectly through either epinephrine or glucagon, (4) a block in the production and/or release of insulin from the pancreas, resulting from a direct action of diazoxide on the beta cells, and (5) a block in the production and/or release of insulin, resulting from diazoxide-induced catecholamine production or increased end-organ sensitivity to catecholamine metabolites.

It is unlikely that diazoxide induces hyperglycemia by increasing the rate of peripheral insulin inactivation or blocking insulin-mediated glucose transport. It has been clearly demonstrated that normal responsiveness to exogenously administered insulin or tolbutamide persists in man and experimental animals during thiazide-induced hyperglycemia.[12] Our patient's prompt and marked response to tolbutamide confirms this observation.

Although there are contradictory findings regarding the response of the hypophysectomized animal to diazoxide, it is probable that diazoxide hyperglycemia is unrelated to either anterior pituitary or adrenal corticol stimulation. Hypophysectomy did not inhibit the hyperglycemic effect of diazoxide in animals studied by Wolff and Parmley.[12] The development of marked hyperglycemia in our second patient indicates that the anterior pituitary gland is probably not essential to the hyperglycemic effect of diazoxide. Others have found that hypophysectomy is associated with a relative resistance to the hyperglycemic effect of diazoxide. Tabachnick et al.[13] found a diminished hyperglycemic response to diazoxide in their animals. However, they suggested that this may have been nutritional, resulting from a depletion of glycogen stores rather than a primary relationship to the pituitary gland. In neither animal nor in human studies has there been clear evidence of adrenocortical stimulation by diazoxide. In neither of our patients has diazoxide administration been associated with an increase in urinary 17-hydroxy-

*Sodium tolbutamide was provided through the kindness of Dr. Thomas Vecchio, of The Upjohn Company.

corticosteroids or clinical evidence of increased cortisol production.

An increased rate of glycogen mobilization could conceivably produce the degree of hyperglycemia seen in association with diazoxide administration. Diazoxide appears to stimulate glycogenolysis. A decrease in hepatic glycogen stores has been observed in animals following treatment with diazoxide.[13] The possible mechanisms for glycogen mobilization include phosphorylase activation by either epinephrine or glucagon or a direct effect of diazoxide on the glycogen molecule. The evidence for an epinephrine effect will be discussed below. There is no evidence available for an effect of diazoxide upon glucagon or directly upon the glycogen molecule.

A number of workers have presented evidence suggesting that diazoxide hyperglycemia is produced principally, if not solely, by a block in insulin release. Samaan et al.[14] reported decreased insulin-like activity in the blood of four patients with thiazide-induced hyperglycemia. Others,[15,16] using normal adult subjects, found that the combination of diazoxide and a diuretic thiazide promptly induced carbohydrate intolerance as manifest by a diabetic glucose tolerance test in association with a decreased insulin response. In addition, several adults with hypoglycemia secondary to islet-cell adenoma or carcinoma have been successfully treated with diazoxide. In four of these patients the development of hyperglycemia was associated with a significant fall in circulating insulin concentration following diazoxide administration.[16,17] Our own observations with our initial patient are in agreement with these findings. While fasting insulin levels remained above normal, they were appreciably reduced below the prediazoxide level. Insulin response to leucine and glucose was significantly reduced in the child with leucine sensitivity while on diazoxide therapy.

However, other investigators have presented evidence suggesting that diazoxide hyperglycemia is not mediated through a direct effect on the pancreas. Tabachnick et al.[13] reported increased hyperglycemia in diazoxide-treated animals previously made diabetic by either alloxan or pancreatectomy. Others in studies on rats[18] and in humans[19] did not observe a decrease in the insulin-like activity associated with thiazide-induced hyperglycemia. The control of hypoglycemia in a patient with hyperinsulinism secondary to an islet-cell carcinoma using a combination of diazoxide and a diuretic thiazide has been reported[8] without a demonstrable fall in immunoreactive insulin.

Recent studies suggest a relationship between diazoxide and catecholamine metabolism. A recent report demonstrates a reduction in diazoxide hyperglycemia in animals previously treated with beta-adrenergic blocking agents.[18] In a study on the effect of intravenous diazoxide in dogs, it was demonstrated that hypotension preceded the onset of hyperglycemia and the magnitude of hyperglycemia appeared to be related to the severity of induced hypotension, suggesting an epinephrine effect.[20] The previously stated effect of diazoxide on glycogen mobilization suggests a possible epinephrine effect. In addition, diazoxide has been shown to stimulate free fatty acid mobilization. Both increased glycogenolysis and free fatty acid mobilization are characteristic responses to epinephrine stimulation.

From a clinical point of view there are a number of points against diazoxide stimulating an increase in catecholamine production. Our patients have had neither significant changes in their blood pressure nor signs of epinephrine excess such as tachycardia, nervousness, increased perspiration, etc., during periods of diazoxide hyperglycemia. Urinary catecholamines have not been elevated in either of these children. Total urinary catecholamines per twenty-four hours have been well under 30 μg. under basal conditions. There has been no appreciable increase in this level during diazoxide administration.

It would appear that diazoxide can affect carbohydrate metabolism through an inhibition of insulin release as well as by stimulation of glycogen breakdown. Evidence has recently been presented that epinephrine can directly block the release of insulin from the pancreas.[21] It is possible that this mechanism can help explain some of the apparent contradictions in diazoxide action. Some relationship between diazoxide and catecholamine metabolism appears likely, either via an increased epinephrine production, for which there is no clear evidence at this time, or an increased end-organ sensitivity to epinephrine. Such an effect would be consistent with the evidence for an increase in glycogenolysis and free fatty acid mobilization. In addition, the block in insulin release might be mediated through the same mechanism. Further studies to clarify the relationship between catecholamine metabolism, insulin production, and diazoxide are clearly in order.

In view of the possible different mechanisms of action, it is of interest that the effect of diazoxide in our two patients may have been qualitatively, rather than quantitatively, different. The child with leucine sensitivity and hyperinsulinism became normoglycemic

on diazoxide. The elevation in blood glucose in this child was associated with a decrease in circulating insulin levels but not a complete return to the normal insulin range. This child never became ketonuric. It is possible that the persistence of a slightly increased insulin level prevented the release of free fatty acid, thus eliminating the possibility of the development of ketosis.

The second patient characteristically became ketotic in association with hypoglycemia. In addition, she developed ketosis before becoming hyperglycemic while on diazoxide. Her serum insulin levels were persistently below the normal range. Several investigators, in addition to ourselves, have observed that patients with hypopituitarism have diminished insulin production. Luft et al.[22,23] have demonstrated that HGH administration increased circulating insulin levels.

It is not unreasonable to assume that the rapid development of diabetic ketosis in this child resulted from an increased sensitivity to diazoxide because of initially low insulin levels. On the other hand, the primary effect of diazoxide in this patient may have been in terms of glycogen and lipid mobilization rather than further suppression of an already low insulin level.

The need for caution in the future use of diazoxide is emphasized by the transient but marked diabetic syndrome induced in this patient. Particular care must be taken in hypoglycemic patients whose disease is not secondary to hyperinsulinism. The production of ketosis might be anticipated in these patients. It is recommended that careful monitoring of blood electrolytes, blood glucose, and urine glucose and ketones be routine in every patient placed on this therapy.

ACKNOWLEDGMENT

We wish to express our appreciation to Dr. Milton Grossman who referred the patient, and to the nursing staff of the Pediatric Clinical Research Unit without whose help these studies could not have been completed.

This work was supported in part by a grant from the Joseph P. Kennedy Junior Fluid Research Fund, NIH Grant AM 04499, USPHS Research Grant HD-00126-02, National Heart Institute, Grant HEO-8463-01 (SRC). Dr. Wolff is a Career Scientist of the Health Research Council of the City of New York (1-342). The growth hormone was supplied by the National Pituitary Agency (NIAMD).

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