Effect of Diphenylhydantoin on Glucose Tolerance in Patients with Hypoglycemia

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SUMMARY

Five patients with symptomatic hypoglycemia unresponsive to dietary management were treated orally with 600 mg. of diphenylhydantoin (DPH) daily administered in three divided doses. Treatment with DPH resulted in both subjective and objective improvement in all cases. Serum glucose and insulin levels were determined before and after DPH therapy, and the changes observed after treatment correlated with the clinical response. DPH treatment resulted in an over-all increase of 31 per cent in mean plasma glucose values and an over-all decrease of 76 per cent in plasma insulin levels. These changes are in accord with those previously reported in normal subjects, and they appear to reflect a direct effect of the drug. DIABETES *23*:679-83, August, 1974.

The conventional approach to the management of symptomatic hypoglycemia is dietary with a high protein, low carbohydrate diet divided into frequent small feedings. The reduced carbohydrate intake is believed to provide a decreased stimulus for insulin secretion, while the high protein diet facilitates gluconeogenesis.[1,2] In cases where dietary management has not yielded optimal control of the symptoms of hypoglycemia, drug therapy has been used. The administration of small quantities of soluble insulin immediately after each meal is partially effective in the management of hypoglycemia but is impractical.[3] Sulfonylurea and phenformin therapy have also been reported to improve both subjective symptoms and glucose tolerance in patients with hypoglycemia.[4,5] Anticholinergic drugs, by decreasing gastric emptying time and altering insulin response, may also alleviate hypoglycemic symptoms.[6] None of these forms of therapy, however, has provided more than marginal control in selected cases of hypoglycemia.

Corticosteroids and the thiazides are known to alter insulin levels and induce hyperglycemia, especially in persons with diabetes mellitus. For this reason the thiazides have been recently studied as to their potential for reducing the effects of pathologic hypoglycemia. More specifically the benzothiadiazine drugs, namely diazoxide, have been especially useful in controlling the severe hypoglycemia associated with islet cell tumors.[7,8] Similarly, diphenylhydantoin (DPH) administration has recently been reported to cause a marked change in the response to a glucose load and thereby potentially antagonize therapy for diabetes mellitus.[9] The effect of DPH on the glucose tolerance curve is a significant increase in the mean blood glucose response (+19 per cent) and a marked diminution of both early and late insulin responses (-60 and -39 per cent, respectively).

Because of this sustained effect of DPH on the glucose tolerance test, patients with symptomatic hypoglycemia poorly controlled by conventional dietary treatment were treated with DPH. DPH therapy in all cases resulted in marked subjective improvement. This study demonstrates that the subjective improvement in these patients can be correlated with a pronounced effect of DPH on blood glucose and insulin.

SUBJECTS AND METHODS

Three female (CB, NM, TL) and two male (PR and CH) patients with clinical signs and symptoms of hypoglycemia who were unresponsive to dietary treatment were selected for study. Their ages ranged from twenty to fifty-four and each weighed between 100 and 200 lbs. and varied no more than 10 per cent from ideal height/weight relationships[10] (table 1).

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TABLE 1

Clinical parameters of the subjects

	CB	TL	NM	CH	PR
Height (in.)	158.8	166.5	160	175	166
Weight (kg.)	46.4	56.8	58.8	75.2	59.6
Age	28	43	35	54	33
Sex	F	F	F	M	M
Glucose load (gm.)	60	65	65	75	65
Tolbutamide tolerance	normal insulin response*	normal insulin response	normal insulin response	normal insulin response	—
Pancreatic scan	normal	normal	normal	normal	patchy uptake-non-specific
Liver scan	normal	normal	normal	normal	normal
Pancreas and liver enzymes	normal	normal	normal	normal	normal
Laparotomy	—	normal pancreas	—	—	normal pancreas

*Response noted did not fulfill criteria to establish diagnosis for insulinoma.[14]

Each patient satisfied the criteria necessary to establish the diagnosis of hypoglycemia as recently reported.[11] During a standard glucose tolerance test, each subject's plasma glucose level fell below 50 mg. per 100 ml., corresponding to a value of 45 mg. per 100 ml. of blood glucose.[12,13] In all cases, the presenting symptomatology was produced at this level, and symptoms were relieved by the oral intake of food or sugar.

Except in the case of PR, who had a previous history of pyloroplasty and vagotomy, no specific cause for the hypoglycemia could be demonstrated (table 1). NM and PR had high fasting insulin levels on several determinations, but no evidence for an insulin-secreting tumor or hepatic disease could be demonstrated. TL, who had a low fasting glucose, subsequently underwent a laparotomy for a left ovarian cyst at which time the pancreas was normal upon examination. CB, CH, NM and PR were considered to be reactive hypoglycemic with PR, perhaps more specifically, being alimentary hypoglycemic. TL, with a low fasting glucose and hypoglycemia at six hours, would be more characteristic of fasting hypoglycemia.

The base line glucose tolerance test was performed utilizing the following conditions. All subjects were placed on an adequate diet, including at least 200 gm. of carbohydrate daily for at least three days before the test. Subjects were fasted for twelve hours and a 5 ml. sample of venous blood for fasting glucose and insulin levels was obtained. Each subject was then given a glucose priming load using a single oral dose of 40 gm./m^2. A 5 ml. venous sample for blood glucose and insulin determinations was taken through an indwelling venous catheter at one-half hour and one hour thereafter for six hours. Spontaneously voided urine samples were collected with each venous sampling for determination of glucosuria.

After the initial glucose tolerance test, each patient was given two 100-mg. capsules of DPH orally three times daily for four weeks. The glucose tolerance test as described was then repeated and comparable blood and urine samples were obtained. On the morning before the test the usual 200 mg. of DPH was administered orally.

Plasma glucose measurements were performed on the Technicon AutoAnalyzer, utilizing the alkaline potassium ferricyanide method of analysis. Plasma insulin was measured by the radioimmunoassay method using the Sephadex coupled antibodies technic.[15] Serum levels of DPH were measured by gas liquid chromatography involving the formation of trimethylsilyl (TMS) derivatives of plasma extracts.[16] Data before and after treatment were compared, matched pair t-tests being used, and 0.05 or less was chosen as the accepted level of significance.

RESULTS

The untreated plasma glucose and insulin levels for each subject are shown in figure 1. Figure 2 shows the plasma glucose and insulin levels following treatment with DPH. An obvious improvement in both glucose and insulin levels resulted. Both levels approached that reported for normal subjects.[12] In these five patients, the symptoms due to hypoglycemia, which were observed during the base line glucose tolerance test, were not observed with the tolerance test after DPH therapy. This marked change in glucose and insulin responses after DPH is further demonstrated by comparison of the mean values for the five subjects (figure 3). The administration of DPH resulted in an over-all increase of 31 per cent above untreated mean glucose values, i.e. from 86 ± 6.8 mg. per 100 ml. to

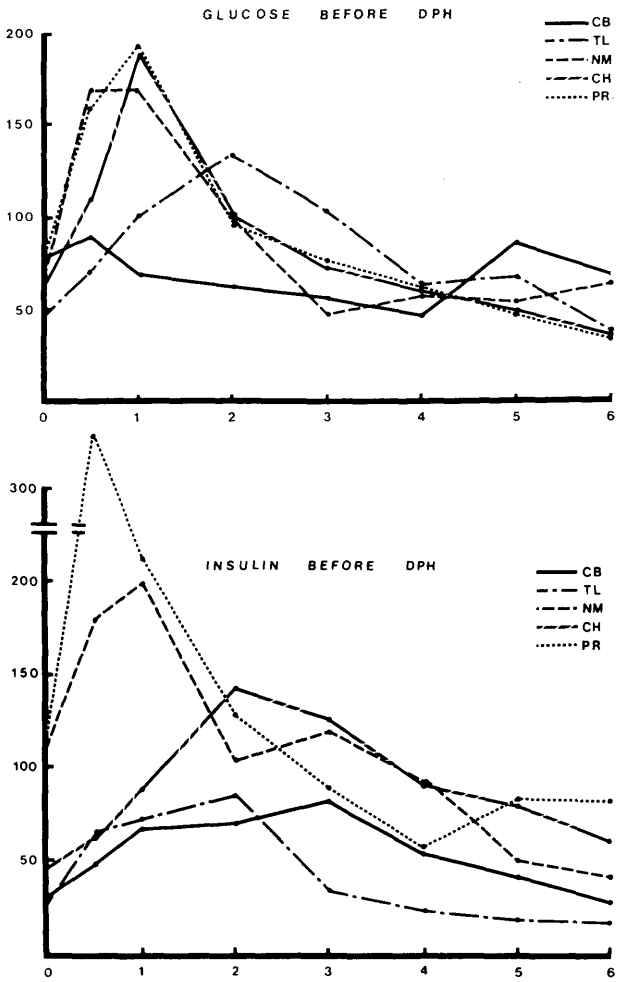

FIG. 1. Plasma glucose (mg./100 ml.) and insulin levels (μU./ml.) vs. time (hours) in patients with hypoglycemia following an oral glucose load of 40 gm./m².

113 ± 5.9 mg. per 100 ml. ($P < .001$). Fasting glucose levels rose 42 per cent following DPH treatment, and the mean glucose values during the hypoglycemia portion of the curves (three to six hours) indicated a rise at each hour of 40 to 60 per cent over untreated levels ($P < .05$). Similarly, DPH treatment resulted in an over-all decrease in plasma insulin levels by 76 per cent, i.e. from 88 ± 10 μU. per milliliter to 21 ± 2.0 μU. per milliliter ($P < .001$). Fasting insulin levels were reduced following DPH treatment by 74 per cent and mean plasma insulin levels at each hour were similarly decreased by 70 to 80 per cent ($P < .01$).

Plasma DPH levels were in the range reported both for effective anticonvulsant activity (7 to 33 mg.)[17] and for DPH interference with insulin release by the pancreas.[9] Urinary glucose levels were insignificant both before and after DPH treatment.

DISCUSSION

The observed effect of DPH on both plasma glucose and insulin levels in these patients with hypoglycemia was the same as that previously reported for normal subjects—plasma glucose levels increased and insulin levels decreased.[9] The quantitative effect in these patients, however, was much greater than that observed in normal subjects throughout the entire curve, but especially during the periods of hypoglycemia. This might imply that the mechanism responsible for the production and/or release of insulin in these patients is more sensitive to DPH than it is in normal subjects.

In this study both the fasting insulin levels and the reactive phase of insulin release were reduced after DPH therapy. The fasting insulin levels were only reduced, however, by taking DPH before the tolerance test, which supports the hypothesis that the effect of DPH is a direct inhibition of insulin release by

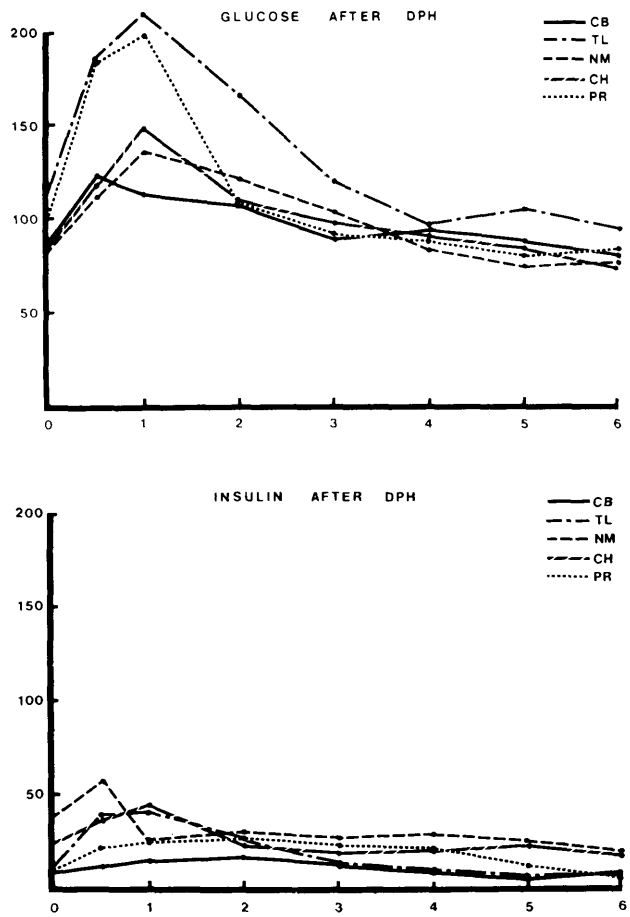

FIG. 2. Effect of oral DPH (200 mg. three times daily) on plasma glucose (mg./100 ml.) and insulin levels (μU./ml.) vs. time (hours) in patients with hypoglycemia following an oral glucose load of 40 gm./m².

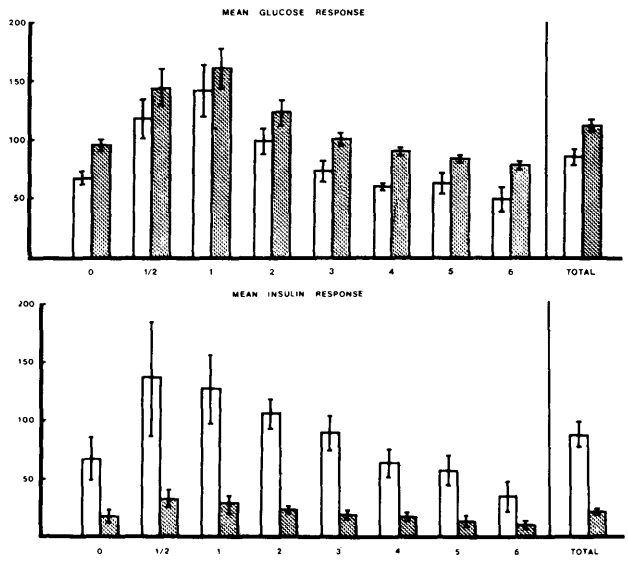

FIG. 3. Effect of oral DPH (200 mg. three times daily) on mean plasma glucose (mg./100 ml.) and serum insulin (μU./ml.) curves vs. time (hours) (vertical bars indicate the mean ± S.E.M. of the five subjects; shaded bars reflect the effect of DPH on glucose and insulin levels).

interfering with an enzyme-related cation flux.[9,18-20] Further support of this direct inhibitory effect of DPH was suggested by the changes in clinical and laboratory parameters observed following a change in either dosage schedule or total daily doses. Although the patients were instructed to take DPH every eight hours, in one patient (CH) the dose schedule had to be periodically adjusted to compensate for his changing work and meal schedules. In another patient (TL) the prolonged administration of the 600 mg. dose resulted in reversal of the glucose tolerance and the onset of neurologic symptoms due to DPH toxicity. Decreasing the daily dose to 400 mg. resulted in a loss of symptoms and a normal glucose curve; eventual stopping of the dosage due to mild gum hyperplasia resulted in the return of the initial hypoglycemic curve and associated symptomatology.

With a larger group of subjects the 600 mg. dose will only be suitable for a proportion of the patients, and adjustment of dose and dosage schedules may be necessary to achieve optimum results. In addition, since toxic serum levels of DPH show marked variation among subjects it is reasonable to assume, as in TL, that toxicity may delimit the degree of response observed.[17] DPH therapy should be especially monitored since it may aggravate underlying diabetes mellitus[9] or produce a diabetic-like tolerance curve at toxic doses as in patient TL.[21,22]

Doses greater than 600 mg. of DPH have been used in three patients with hypoglycemia due to neoplasm. Since adequate base line tolerance tests could not be obtained due to the severity of the hypoglycemia, these patients could not be included in this study. The dose of DPH was increased in each patient to the point of early signs of toxicity. One patient with a pancreatic neoplasm and two patients with soft tissue sarcoma associated with hypoglycemia were studied, and all three patients responded partially to therapy. The over-all improvement in glucose response and clinical parameters was not as complete as in those patients presented in the paper. However, the response was adequate to prevent severe hypoglycemic episodes while antitumor therapy was instituted.

From this study it appears that DPH may be of value to control select cases of hypoglycemia which are unresponsive to dietary or other therapeutic measures. Whether DPH should be used as the primary treatment of hypoglycemia with dietary management serving as an adjunctive therapy cannot be answered from this study due to the limited number of patients treated and the possibility that the clinical response observed was a placebo effect rather than the result of an effect on blood glucose. The effect of DPH on severe hypoglycemia, especially that related to underlying causes such as malignant neoplasm, is probably not adequate for long-term management. The toxicity associated with the higher doses necessary in these patients for complete control is the limiting factor but lower doses may be temporarily useful until specific corrective therapy can be instituted.

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