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Short Communications

Improvement of metabolic control in diabetic patients during mebendazole administration: preliminary studies

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Summary. After the observation of decreasing insulin resistance in a diabetic patient during treatment with mebendazole for nematosis, we investigated the effect of mebendazole on metabolic control in six Type 1 (insulin-dependent) and six Type 2 (non-insulin-dependent) diabetic patients, eight of whom were chronically resistant to conventional treatment. Before and after mebendazole treatment for 1 month, plasma glucose and serum C-peptide concentrations were determined both fasting and 4 h after a mixed breakfast. Improvements in fasting blood glucose concentrations occurred in Type 1 (12.83 ± 1.11 versus 6.56 ± 0.56 mmol/l; $p < 0.05$) and Type 2 (10.22 ± 0.56 versus 7.56 ± 0.67 mmol/l; $p < 0.05$) diabetic patients and were associated with increases in post-cibal C-peptide responses in Type 1 and Type 2 diabetic patients. Following discontinuation of mebendazole, metabolic control deteriorated in five out of the six Type 1 diabetic patients and in all the Type 2 diabetic patients. We conclude that mebendazole increases insulin secretion, and decreases plasma glucose concentration in Type 1 and Type 2 diabetic patients. However, these beneficial effects may be transient.

Key words: Mebendazole (Vermox), insulin secretion, C-peptide, Type 1 and Type 2 diabetes.

Through serendipity, we observed the resolution of an insulin immunoresistant state [1] in a Type 1 (insulin-dependent) diabetic patient following the use of mebendazole (Vermox), a benzimidazole, for the treatment of intestinal trichuris trichiura (whipworm), and considered the possibility that mebendazole may be an insulin secretagogue. Therefore, we treated this initial patient and recruited other diabetic patients to investigate the effect of mebendazole on metabolic control and to delineate its mechanism(s) of action.

Subjects and methods

Subjects

Twelve diabetic patients were admitted to the General Clinical Research Center of the Temple University Hospital. The nature, purpose and possible risks involved in the study were explained to the subjects before obtaining their written consent. The study was approved by the Institutional Review Board of Temple University School of Medicine.

The initial studies were conducted in six Type 1 diabetic patients. Their mean ± SEM age was 30 ± 3 years, and their mean ± SEM body weight was 114 ± 10% of ideal weight. Two had acquired insulin immunoresistant states [1]; both developed severe diabetic ketoacidosis while taking between 160–200 units insulin/day [1]. One patient was studied several months and another one week after treatment for diabetic ketoacidosis. The additional four subjects were Type 1 diabetic patients of recent onset with the classic symptoms of polyuria, polydypsia, and polyphagia, with accompanying weight loss and laboratory findings of hyperglycaemia and hyperketonaemia [2].

The mean ± SEM age of the six Type 2 diabetic patients was 42 ± 4 years, and their mean ± SEM weight was 160 ± 12% of ideal body weight [2]. All were treatment failures, having persistent fasting hyperglycaemia despite taking oral chlorpropamide (500–750 mg daily) and receiving repeated diet and exercise counselling. In addition to chlorpropamide and diet prescriptions, four of these patients received supplementary subcutaneous insulin daily to aid in controlling their symptomatic hyperglycaemia. However, none of the Type 2 diabetic patients was dependent on insulin for the prevention of ketonuria.

All patients were free of acute illnesses and were taking no medication other than insulin or chlorpropamide. Stools from every patient were negative for ova and parasites.

The mean ± SEM age of six lean non-diabetic volunteers, who served as controls, for the Type 1 diabetic patients was 29 ± 1 years, and their mean ± SEM weight was 104 ± 3% of ideal body weight [2]. The mean ± SEM age of the seven obese non-diabetic volunteers who served as controls for the Type 2 diabetic patients was 43 ± 3 years, and their mean ± SEM weight was 147 ± 8% of ideal body weight.

Experimental design

All patients were consuming a weight-maintaining diet of approximately 22 $Kcal \cdot kg^{-1} \cdot day^{-1}$ (carbohydrate 48%, fat 33%, protein 18%). After an 11-h overnight fast, blood samples were drawn for measurement of plasma glucose, non-esterified fatty acids (NEFA)

and serum C-peptide concentrations at −15 and 0 min before, and every 30 min for 4 h after, consuming a mixed breakfast (11 Kcal/kg; carbohydrate 43%, fat 42%, protein 15%) during a 10-min period [3]. The last chlorpropamide (Diabinese 500–750 mg daily, Pfizer, New York City, USA) doses were given 24 h before the breakfast tests, and insulin (10–200 units daily of NPH and/or regular insulin, Eli Lilly, Indianapolis, Indiana, USA) doses were withheld on the morning of the studies. Immediately after the breakfast studies were completed, insulin and/or chlorpropamide therapy was administered together with oral mebendazole (100–300 mg daily, Vermox, Janssen Pharmaceutica, New Brunswick, New Jersey, USA). Thereafter, patients were discharged from hospital. They were followed every week in the diabetic out-patient clinic, and their weights, fasting plasma glucose concentrations, and insulin and/or chlorpropamide doses were recorded. After treatment for 1 month with mebendazole, all patients were readmitted for repetition of the same studies, while receiving the morning dose of mebendazole.

In order to evaluate the metabolic status after discontinuation of mebendazole, all patients were followed in the out-patient clinic weekly for at least 1 month. Their weights, fasting plasma glucose concentrations and insulin and/or chlorpropamide doses were monitored.

Chemical analyses

Plasma and urine glucose concentrations were determined using a Beckman glucose analyzer (Beckman Instruments, Fullerton, California, USA). Plasma NEFA were extracted by the technique of Dole and Meinertz [4], and concentrations determined by a modification of the colorimetric method of Lorch and Gey [5]. Serum C-peptide concentrations were determined using radioimmunoassay kits (Novo, Copenhagen, Denmark) [6]. The detection limit of C-peptide was 0.01 pmol/ml; the intra-assay and interassay variations were 4% and 6%, respectively.

Statistical methods

Unless otherwise stated, all values are presented as mean ± SEM. Basal values for the breakfast studies were taken as the mean of the −15 min and 0 min values. Statistical differences between different studies were calculated by using Student's t-test for paired or unpaired samples, and analysis of variance was used to determine statistical differences for repeated measurements of substrates and C-peptide concentrations [7].

Results

Plasma glucose concentrations, insulin and chlorpropamide doses and body weights

Fasting plasma glucose concentrations in Type 1 diabetic patients were significantly reduced by 1 month of mebendazole therapy (12.83 ± 1.11 versus 6.56 ± 0.56 mmol/l; $p < 0.05$). These changes occurred despite reduced insulin doses in five out of six Type 1 diabetic patients (83 ± 32 versus 34 ± 8 units/day; NS). In the Type 2 diabetic patients, similar decreases in fasting plasma glucose concentrations were observed (10.22 ± 0.56 versus 7.56 ± 0.67 mmol/l; $p < 0.05$). Insulin doses were also reduced in four out of four Type 2 diabetic patients (69 ± 23 versus 45 ± 12 units/day; NS). Further, chlorpropamide was stopped in one and reduced in two Type 2 diabetic patients. Improvements in fasting plasma glucose concentrations cannot be attributed to weight reduction since four out of six Type 1 diabetic patients gained weight (78 ± 12 versus 82 ± 13 kg; NS) and two out of six Type 2 diabetic patients gained weight (107 ± 9 versus 108 ± 9 kg; NS).

Fasting plasma glucose concentrations in five out of six Type 1 diabetic patients were significantly higher throughout the month after mebendazole was discontinued (6.94 ± 0.56 versus 12.17 ± 2.11 mmol/l; $p < 0.05$). These changes occurred despite increased insulin doses in four out of five of these patients (34 ± 8 versus 52 ± 17 units/day). In one presumed Type 1 diabetic patient, the fasting plasma glucose concentration approached normality, and his insulin doses were gradually and persistently decreased throughout a 5-month period after discontinuation of mebendazole. At that time insulin therapy was withdrawn and chlorpropamide therapy was started.

In all Type 2 diabetic patients throughout the month after discontinuation of mebendazole, fasting plasma glucose concentrations were consistently higher (7.56 ± 0.67 versus 12.11 ± 0.83 mmol/l; $p < 0.001$). Insulin therapy was increased in one Type 2 diabetic patient from 75 to 100 units/day. Chlorpropamide therapy was increased in two Type 2 diabetic patients and restarted in another Type 2 diabetic patient. No significant change in body weight was observed in Type 1 (82 ± 13 versus 82 ± 13 kg; NS) or in Type 2 diabetic (108 ± 9 versus 106 ± 9 kg; NS) patients after discontinuing mebendazole.

Glucose, NEFA, and C-peptide concentration responses to breakfast tests

In Type 1 diabetic patients plasma glucose concentrations before mebendazole were abnormally high prior to and throughout the 4-h breakfast tests (Fig. 1). After one month of therapy, fasting and post-cibal glucose concentrations were lower than pretreatment values ($p < 0.05$) but were consistently higher than those of lean control subjects ($p < 0.05$).

Before mebendazole administration basal C-peptide concentration in Type 1 diabetic patients was comparable to that of lean controls (0.23 ± 0.07 versus 0.38 ± 0.04 pmol/ml; Fig. 1). In contrast, post-cibal C-peptide concentrations were remarkably lower in Type 1 diabetic patients than in lean controls. Further, no significant post-cibal rise was observed in the patients. These results are similar to those reported by others [8]. Following one month of mebendazole administration, C-peptide concentrations in response to breakfast rose from a basal value of 0.48 ± 0.19 pmol/ml to a peak value of 1.00 ± 0.28 pmol/ml at 60 min post-cibal ($p < 0.05$) and declined slowly thereafter. It is remarkable that after mebendazole administration the C-peptide responses of Type 1 diabetic patients were similar to those observed in the lean control subjects.

Basal NEFA concentration in Type 1 diabetic patients before taking mebendazole was not significantly

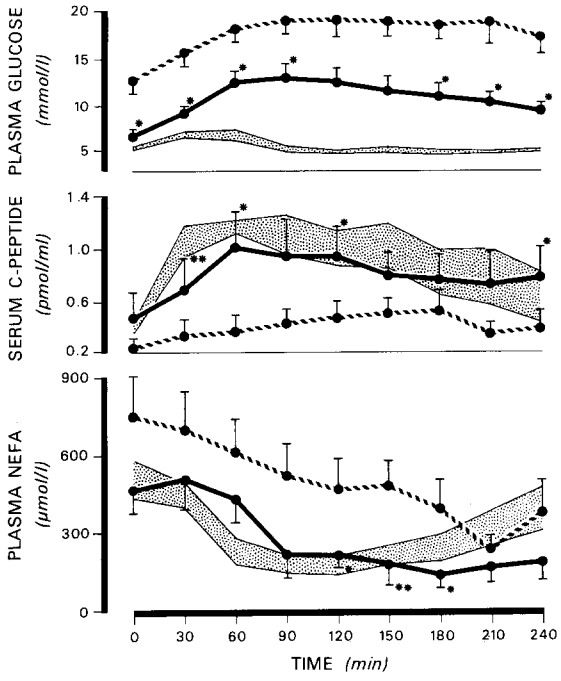

Fig. 1. Circulating concentrations of glucose, C-peptide and NEFA in response to breakfast in lean controls and Type 1 diabetic patients before (---) and after (___) 1 month of mebendazole therapy. The shaded area represents one standard error above and below the mean observations in normal control subjects. Results for Type 1 diabetic patients are expressed as mean ± SEM. *$p < 0.05$; **$p < 0.025$

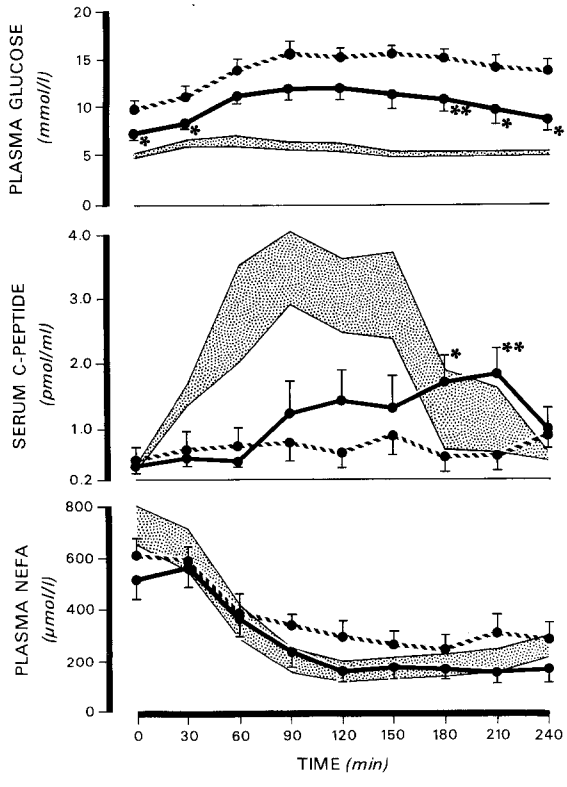

Fig. 2. Circulating concentrations of glucose, C-peptide and NEFA in response to breakfast in obese control subjects and Type 2 diabetic patients before (---) and after (___) 1 month of mebendazole therapy. The shaded area represents one standard error above and below the mean observations in obese control subjects. Results for the Type 2 diabetic patients are expressed as mean ± SEM. *$p < 0.05$; **$p < 0.025$

higher than the lean control value, and post-cibal plasma NEFA concentrations decreased in a manner similar to lean controls but were significantly higher than lean values at 60 and 90 min post-cibal ($p < 0.05$). After one month of taking mebendazole, basal plasma NEFA concentration and post-cibal values were significantly lower than before therapy at 120, 150 and 180 min ($p < 0.05$; all values).

In Type 2 diabetic patients before mebendazole administration, fasting plasma glucose concentration was 10.22 ± 0.56 mmol/l, peaked at 90 min post-cibal (15.89 ± 1.39 mmol/l) and declined slowly thereafter (Fig. 2). One month after mebendazole, fasting plasma glucose concentration (7.56 ± 0.67 mmol/l) was significantly lower than before mebendazole as were 30, 180, 210 and 240 min post-cibal values ($p < 0.05$).

Before mebendazole, fasting serum C-peptide concentration (0.52 ± 0.23 pmol/ml) in Type 2 diabetic patients was comparable to that (0.38 ± 0.04 pmol/l) of obese control subjects (Fig. 2). Conversely, post-cibal values were lower at 30, 60, 90, 120 and 150 min than obese control subjects ($p < 0.005$). Futher, the peak value of 0.92 ± 0.31 pmol/l reached at 150 min post-cibal was not statistically different than the basal value in these patients. These results are comparable to those reported by others [8]. After 1 month of mebendazole, post-cibal serum C-peptide concentrations were significantly higher than pretreatment values at 180 and 210 min ($p < 0.05$), with a peak value (1.84 ± 0.41 pmol/l) reached at 210 min. Thus, after mebendazole the amount of C-peptide released was increased, but the pancreatic β cell secretory response to nutrients was diminished and delayed.

Basal and post-cibal plasma NEFA concentrations in the group of Type 2 diabetic patients were not significantly different from the obese control values (Fig. 2). After one month of mebendazole, basal and post-cibal NEFA concentrations were slightly lower than before, but these changes were not statistically significant.

Discussion

In these preliminary studies, we investigated the effect of oral mebendazole on metabolic control in 12 diabetic patients. Eight of these patients were chronically resistant to conventional treatment and, therefore, were not representative of most diabetic populations. We have shown that the addition of mebendazole to the therapy of these patients for 1 month lowered fasting and post-cibal plasma glucose and NEFA concentrations and increased C-peptide concentrations. This is due to enhanced β-cell secretion induced by a direct secretagogue effect of mebendazole.

We observed that after 1 month of mebendazole, C-peptide secretion in Type 1 diabetic patients was comparable to that observed in lean controls. This is surpris-

ing because these patients did not normalize their plasma glucose concentrations (Fig. 1).

Two Type 1 diabetic patients had acquired insulin immunoresistant states and developed severe ketoacidosis while taking 160–200 units of insulin daily. In both of these patients the administration of mebendazole (100 mg/day for 1 month) achieved excellent glycaemic control necessitating gross reductions in their insulin doses.

Four of the Type 1 diabetic patients were of recent onset; therefore, it could be argued that the improvement in β-cell function was due to the clinical remission ('honeymoon period or Brush effect') [9, 10] and not to the effects of mebendazole administration. However, it is unlikely that all four patients would go into partial spontaneous remission simultaneously, as the frequency of this phenomenon in Type 1 diabetes is only approximately 20% [11]. This is in keeping with the fact that one patient did improve to the degree that he did not require exogenous insulin therapy 5 months after initiating mebendazole administration. Whether his recovery was natural or drug-induced is unknown.

Before initiating mebendazole, all Type 2 diabetic patients were treatment failures to intensive conventional therapy. Nonetheless, all responded favourably to one month of mebendazole administration (Fig. 2).

It is possible that the effect of mebendazole on metabolic control in Type 1 and Type 2 diabetes may be transient. In more protracted studies (not shown), we have evidence revealing the evanescent effect of mebendazole as an insulin secretagogue in some diabetic patients. This study was also limited because we may not have used the best therapeutic dose or imidazole compound. Mebendazole is poorly absorbed from the gut [12], and bioavailability to stimulate β-cell secretion may have limited its secretagogue effect.

In conclusion, this preliminary study was designed to gain evidence that mebendazole improves metabolic conditions in diabetic patients. The study contains the uncertainties present in any clinical experiment which lacks a control patient group. However, it was impractical to attempt a full scale, randomized clinical trial until the preliminary data were available [13]. Although it is possible that factors other than mebendazole therapy contributed to the observed results, it is highly unlikely. Twelve out of 12 patients initially had favourable responses to mebendazole administration. Further, the follow-up results of each patient, subsequent to the discontinuation of mebendazole, revealed rapid deterioration in metabolic status of all but one Type 1 diabetic patient and in all six Type 2 diabetic patients and add support to the contention that mebendazole is an insulin secretagogue.

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