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Metformin Reduces Post-Prandial Insulin Needs in Type I (Insulin-Dependent) Diabetic Patients: Assessment by the Artificial Pancreas

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Summary. It has been suggested that biguanides should be used in Type 1 (insulin-dependent) diabetic patients in order to diminish insulin requirements and reduce the chances of insulin reactions. The efficacy of these compounds in such patients has been controversial. We have studied the effect of metformin (850 mg) given at 08.00 h in diminishing insulin needs after a 60 g carbohydrate mixed meal taken at 12.00 h, using an artificial pancreas and a sequential analysis of the results. The morning test dose of metformin or placebo was preceded by 48 h treatment with metformin (850 mg twice daily) or placebo. After the eighth patient a 26% saving of insulin need was demonstrated in the metformin-treated group ($p < 0.01$). Metformin is thus effective in reducing post-prandial insulin needs in Type 1 diabetic patients, although its use in such circumstances requires consideration of several other issues.

Key words: Type 1 diabetes, insulin, artificial pancreas, metformin.

The hypoglycaemic effect of biguanides in Type 2 (non-insulin-dependent) diabetes has been largely proved [1, 2]. Some authors have also tested these drugs in Type 1 (insulin-dependent) diabetic patients in attempts to reduce the daily insulin needs [3–5], the risks of hypoglycaemic reactions in obese patients on hypocaloric diets [6, 7] or to avoid large blood glucose swings in brittle diabetes [8, 10]. Nevertheless the efficacy of biguanides in Type 1 diabetic patients remains controversial [11].

The artificial pancreas has provided a reliable and reproducible method for assessing insulin needs in Type 1 diabetes [12, 13]. The validity of the method has been confirmed recently in studies using pectin [14], guar-gum [15] and mixed meals [16]. We have tested the efficacy of a normal therapeutic dose of metformin in diminishing insulin delivery by the artificial pancreas in Type 1 diabetic subjects after a mixed meal.

Patients and Methods

The eight subjects (age: 26 ± 3 years; weight: 60 ± 3 kg; height: 171 ± 3 cm; duration of diabetes: 8 ± 2 years; daily dose of SC insulin: 75 ± 4 U/day; mean ± SEM) were fully informed diabetic volunteers without ketosis, renal failure or acute illness, whose insulin dependence was assessed according to age of onset, history and the lack of significant post-glucagon C-peptide response. Each patient, serving as his own control, received on two different occasions in the same week a standardized test meal (630 Kcal; carbohydrate 60 g, fat 30 g, protein 30 g) eaten in 10 min between 12.00 and 12.30 h. Each test meal was preceded by 48 h treatment with metformin (850 mg, twice daily) or placebo (in a random double-blind order), the last tablet being taken at 08.00 h on the day of the experiment. To avoid any residual effect of SC insulin, injections were discontinued 24 h before the experiment and the patients were placed on continuous IV insulin infusion until connection to the artificial pancreas between 07.00 and 08.00 h on the day of the experiment. Blood glucose levels and insulin infusion rates were recorded every 2 min for 180 min after the beginning of the meal. The procedure received the approval of the Ethical Commitee of the Hospital.

Statistical Analysis

Insulin delivery by the artificial pancreas was tested using a sequential analysis one-sided test-open plan as described by Armitage [17]. With this method, as soon as the tested parameters reach predetermined boundaries with chosen statistical risks of error, the study may be considered conclusive and ended. In our study, the main parameter tested was the difference in post-prandial insulin delivery by the artificial pancreas with and without metformin. We chose to consider as significant a decrease of three units of insulin for a meal, with a α risk of 0.01 and β risk of 0.10. Blood glucose levels were compared using Student's t-test for paired data.

Results

Insulin Delivery by Artificial Pancreas

The results of the sequential analysis are shown in Figure 1. After patient 8, it was possible to conclude that the assigned limit of 3 U insulin per patient per meal had

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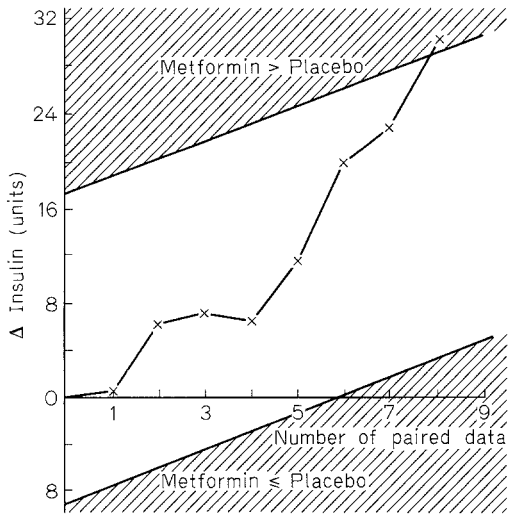

Fig. 1. Results of sequential analysis. Δ *insulin* = [total insulin delivery during 180 min after meal with placebo] – [total insulin delivery after meal during same period with metformin]. *Number of paired data* = number of patients receiving the two meals. Upper limit: Metformin superior to placebo; lower limit: Metformin inferior or equivalent to placebo

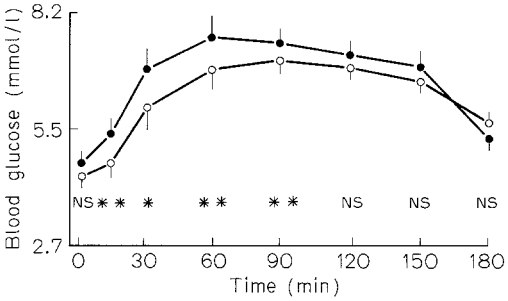

Fig. 2. Blood glucose changes during two test meals when preceded by placebo (●——●) or metformin (○——○). Mean ± SEM of eight observations. * $p < 0.05$, ** $p < 0.01$. *NS:* not significant

been reached, demonstrating a significant saving effect of metformin compared with placebo. The mean amount of insulin delivered by the artificial pancreas in 180 min was 19.2 ± 3.5 U with placebo and 15.3 ± 2.0 U with metformin ($p < 0.01$). The decrease in insulin delivery after metformin was 4.0 ± 1.4 U (mean ± SEM), corresponding to a 26% reduction of the initial requirements.

Blood glucose

Figure 2 shows the mean blood glucose variations during 180 min following the two test meals. Blood glucose values were significantly lower in the metformin group at 15, 30, 60 and 90 min.

Discussion

The use of biguanides in Type 1 diabetes has been controversial. Some studies have shown that insulin requirements were significantly decreased during the administration of biguanides [3, 11], an effect which seems to be maximal shortly after commencing the drug [4, 5]. Some authors have also claimed that biguanides 'smooth out' blood glucose profiles in brittle diabetic patients [7, 10] but this has been denied by others [3, 5, 11].

The artificial pancreas may be a good method for testing the efficacy of drugs or other treatments modifying blood glucose control in Type 1 diabetes, and perhaps easier than conventional clinical trials. In a previous study [16], we showed that the total amount of insulin delivered by artificial pancreas to restore basal blood glucose values after a meal was closely correlated with the total amount of carbohydrate in the meal, the results being reproducible in lean subjects. We have also used this method to assess the efficacy of pectin in Type 1 diabetes [14]. Similar results have been obtained for guar gum by other workers using an artificial pancreas [15].

This study therefore suggests that metformin is effective in reducing post-prandial blood glucose levels and insulin requirements in Type 1 diabetic subjects. The effect may be more pronounced in patients with high insulin requirements, but the number of such patients was too small to draw clear conclusions on this point. It should be noted, however, that the mean insulin delivery by the artificial pancreas after the test meal is higher in this small group of patients than in our previous work [16].

A decrease in insulin requirements may be of interest in diminishing peripheral hyperinsulinism and its possible consequences [18]. However, this study was not designed to show that the risk of insulin reaction was diminished or that metformin was effective in stabilizing brittle diabetes. It is indeed questionable whether the addition of metformin in the long term is to be recommended in Type 1 diabetic patients. Though the drug appears to be effective and generally well-tolerated, it has occasional troublesome side-effects and could potentially be dangerous in these patients who may develop renal and vascular complications of their diabetes [19].

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