Betaxolol and glucose-insulin relationships: studies in normal subjects taking glibenclamide or metformin

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1 The potential interaction between selective β₁-adrenoceptor blockers and sulphonylureas or biguanides was studied by comparing the β₁-adrenoceptor antagonist betaxolol with placebo in 12 normal subjects taking glibenclamide or metformin in a single-blind crossover group study.

2 After a 4 day run-in period on no treatment, six subjects took glibenclamide 2.5 mg twice daily, and six subjects took metformin 850 mg twice daily from day 5 to day 19. All subjects took betaxolol 20 mg daily from day 10 to day 13, and placebo from day 5 to day 10 and from day 13 to day 19.

3 Plasma glucose and insulin concentrations were measured fasting and 60 min after a standard breakfast for 3 successive days during each study treatment; plasma potassium, sodium and betaxolol concentrations were also measured.

4 Fasting glucose, insulin and potassium concentrations did not differ significantly between betaxolol and placebo treatment periods in either glibenclamide- or metformin-treated groups. Post-prandial glucose and insulin concentrations were lower and higher, respectively, relative to fasting concentrations but there was no significant difference between any of the treatment periods. Glibenclamide produced significant increases in insulin concentrations compared with drug-free periods (P < 0.01). Plasma potassium and sodium concentrations were not affected by any of the treatments.

5 Plasma betaxolol concentrations were adequate for β₁-adrenoceptor blockade.

6 This study suggests that selective β₁-adrenoceptor blockade with betaxolol does not change fasting or post-prandial glucose-insulin relationships during simultaneous treatment with either the sulphonylurea glibenclamide or the biguanide metformin.

Keywords betaxolol glucose insulin glibenclamide metformin

Introduction

β-adrenoceptor antagonists have been associated with several abnormalities of glucose metabolism: masking of certain symptoms of hypoglycaemia (Lloyd-Mostyn & Oram, 1975), impaired glucose tolerance (Holm et al., 1980), impairment of blood glucose recovery following hypoglycaemia (Deacon & Barnett, 1976), and hypertensive episodes during hypoglycaemia (van Herwaarden et al., 1977). β₁-(cardioselective) adrenoceptor antagonists, which have less effect on recovery from hypoglycaemia (Lager et al., 1979) and are less likely to be associated
with unwanted haemodynamic effects (Saunders et al., 1981), may be preferable when β-adrenoceptor blockade is required in diabetics (Zaman et al., 1982).

Interaction between β-adrenoceptor blockers and oral hypoglycaemic agents has been little studied although propranolol has been shown to impair endogenous insulin secretory response to tolbutamide in man (Massara et al., 1971), and to glibenclamide in dogs (Sirek et al., 1975).

There are no detailed studies of interaction between β-adrenoceptor blockers and metformin. Since diabetics with hypertension or ischaemic heart disease may receive both classes of drugs together for many years, it is clinically important to exclude any significant adverse drug-interaction. In order to explore this area further we studied glucose-insulin relationships in subjects treated with betaxolol, a long-acting highly selective β1-adrenoceptor antagonist (Warrington et al., 1980) and either glibenclamide (a sulphonylurea) or metformin (a biguanide).

Methods

Twelve healthy volunteers gave informed written consent to participate in a single blind, consecutive treatment study (see study design: Figure 1). Six subjects (3F, aged 20–25 years, weight 43–69 kg) took glibenclamide 2.5 mg twice daily, and six subjects (2F, aged 20–25 years, 57–80 kg) took metformin 850 mg twice daily. All subjects took betaxolol, 20 mg daily, during period 3, and placebo during periods 2 and 4. For safety reasons, each subject was informed that they would receive an oral hypoglycaemic drug but they did not know when the additional drug was betaxolol or when it was placebo.

All drugs were taken by mouth with 100 ml water 15 min before a main meal. Each subject claimed to be taking a well-balanced diet for the entire period of the study. Breakfast provided a glucose challenge for pancreatic beta cell insulin secretion and was standardised to approximately 600 calories (60 g carbohydrate): two fried eggs, one piece of toast, 20 g jam, 100 ml sweetened tea, 20 ml milk and 100 ml fruit juice. Alcohol consumption was limited to less than 5 units per week throughout the study.

On each study morning, following a 10 h overnight fast in which no food, alcohol or smoking was permitted, subjects rested for 20 min and a 10 ml venous blood sample was taken for measurement of glucose, insulin, sodium and potassium concentrations. An additional blood sample was taken 60 min after breakfast. Samples were taken on days 0, 3, 4; 5, 6, 7; 10, 11, 12, 13; 14, 17, 18, 19, 20 and 21. Betaxolol was also assayed on days 10–14 and 17. All samples were collected in heparinized tubes, centrifuged at 2000 rev min$^{-1}$ for 20 min and stored at $-20^\circ$C until analysis.

Glucose was determined by a glucose oxidase method (Technicon autoanalyser) and insulin by a radioimmunoassay method. Betaxolol concentrations were determined by a gas-liquid chromatographic method (Bianchetti et al., 1979).

The differences between the fasting and post-prandial values ('delta' values) of glucose and insulin were used to compare the effects of each treatment.

Statistical analysis

Results were expressed as mean and s.e. mean and analysed by a three-way analysis of variance and pairwise comparisons.

Results

Table 1 summarises the results of this study. There were no significant differences in fasting

![Figure 1](https://example.com/f1.png)  
**Figure 1** Study design: a partial single-blind, consecutive treatment study. Betaxolol was given on days 10, 11 and 12.
Betaxolol and glucose-insulin relationships

Table 1: Effects of betaxolol with glibenclamide (GB, n = 6) or metformin (MF, n = 6) on plasma insulin and glucose concentrations during different treatment periods. Results are expressed as mean (s.e. mean).

<table>
<thead>
<tr>
<th>Period/Treatment</th>
<th>Fasting glucose (mmol)</th>
<th>Post-prandial glucose (mmol)</th>
<th>Fat.-insulin (Δ β U ml⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GB</td>
<td>MF</td>
<td>MF</td>
</tr>
<tr>
<td></td>
<td>4.2(0.1)</td>
<td>4.2(0.1)</td>
<td>4.2(0.1)</td>
</tr>
<tr>
<td>1 No drugs</td>
<td>0.3(0.5)</td>
<td>-0.8(0.2)</td>
<td>-1.2(0.3)</td>
</tr>
<tr>
<td>2 P+GB/MF</td>
<td>4.2(0.1)</td>
<td>4.2(0.1)</td>
<td>4.2(0.1)</td>
</tr>
<tr>
<td>3 BTX+GB/MF</td>
<td>4.5(0.1)</td>
<td>4.5(0.1)</td>
<td>4.5(0.1)</td>
</tr>
<tr>
<td>4 P+GB/MF</td>
<td>4.8(0.1)</td>
<td>4.8(0.1)</td>
<td>4.8(0.1)</td>
</tr>
<tr>
<td>5 No drugs</td>
<td>4.7(0.1)</td>
<td>4.7(0.1)</td>
<td>4.7(0.1)</td>
</tr>
</tbody>
</table>

P = placebo; BTX = betaxolol; * P < 0.05; ** P < 0.01, compared with periods 1 and 5; Δ = ‘delta’ values: differences between fasting and post-prandial glucose and insulin concentrations.

and post-prandial glucose concentrations between any of the study periods. Post-prandial glucose values were lower than those in the fasting state but these decreases were similar during drug-free and oral hypoglycaemic treatment periods. Concentrations of insulin, sodium and potassium during fasting did not differ significantly between study periods.

Mean post-prandial insulin concentrations were higher than in the fasting state during all study periods, with glibenclamide producing a significantly greater increase in insulin compared with the drug-free periods (P < 0.01). Fasting betaxolol concentrations during period 3 (days 10–14) ranged from 11.7–32.5 ng ml⁻¹ (glibenclamide group) and 9.3–26.1 ng ml⁻¹ (metformin group). These concentrations are adequate for β-adrenoceptor antagonism (Warrington et al., 1983).

Betaxolol did not differ significantly from placebo in respect of post-prandial insulin concentrations and did not impair the hyperinsulinaemia induced by glibenclamide. Betaxolol was undetectable in blood by day 17.

Discussion

We designed this study to determine the effect of β₁-adrenoceptor antagonism on glucose metabolism during treatment with oral hypoglycaemics; we used as a model the β₁-adrenoceptor antagonist betaxolol in healthy volunteers treated with glibenclamide or metformin. A single-blind (rather than a double-blind) design for the study was chosen since all study measures were objective and consisted of fully-independent laboratory-based tests; in addition, a double-blind design would have increased considerably the burden on the volunteers.

We found no significant evidence of a disturbance in the glucose-insulin relationship during any of the treatment periods indicating no clinically important interaction between betaxolol and glibenclamide or metformin.

Control of plasma glucose is complex: β-adrenoceptor blockade could theoretically interfere at several distinct sites via antagonism predominantly at the β₂-adrenoceptor. In our study, the failure of betaxolol to alter glucose and insulin concentrations significantly probably is a reflection of its high selectivity for the β₁-adrenoceptor and is in agreement with previous studies comparing metabolic effects of selective and non-selective β-adrenoceptor blockade (Davidson et al., 1977; Saunders et al., 1981). In particular, our findings complement those of
Saunders et al. (1981) who showed that betaxolol, in contrast to propranolol, had no effect on recovery from insulin-induced hypoglycaemia in normal subjects.

Interactions between β-adrenoceptor blockers and sulphonylureas have been reported (Massara et al., 1971; Zaman et al., 1982) and probably result from inhibition of sulphonylurea-induced insulin release, although other mechanisms such as inhibition of glucose uptake and tissue utilization (by stimulating growth hormone release) have been suggested (Dornhorst et al., 1985). In one study (Zaman et al., 1982), therapeutic doses of the β1-selective drug, acebutolol, and propranolol were both found to modify the hypoglycaemic action of glibenclamide. However, in the present study, betaxolol did not blunt the hyperinsulinaemic response to glibenclamide.

The lack of interaction between betaxolol and metformin is entirely expected since metformin’s therapeutic action on glucose metabolism does not involve an increase in insulin concentrations; moreover, its glucose-lowering effect is difficult to demonstrate in non-diabetic subjects unless glucose concentrations are artificially raised (Hermann, 1979).

Results of short-term studies on healthy volunteers may not necessarily be extrapolated to long-term treatment of patients, but this study, which failed to demonstrate any significant interaction between betaxolol and either glibenclamide or metformin, supports the view that β1-adrenoceptor selective agents are preferable when concurrent treatment with a β-adrenoceptor blocker and an oral hypoglycaemic drug is required.

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References


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