THE EFFECT OF ACEBUTOLOL AND PROPRANOLOL ON THE HYPOGLYCAEMIC ACTION OF GLIBENCLAMIDE

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- 1 The effect of acebutolol, a relatively selective β -adrenoceptor blocking drug and propranolol, a non-selective one, on the hypoglycaemic action of glibenclamide after an oral glucose load has been investigated in a group of maturity-onset diabetic patients.
- 2 Glibenclamide significantly reduced the blood glucose levels and both acebutolol and propranolol, at therapeutic doses, were found to modify this action significantly.
- 3 The effect of acebutolol was slightly less than that of propranolol. The difference was not statistically significant.
- 4 The modes of action of sulphonylureas are reviewed and it is suggested that β -adrenoceptor blockers may modify their effect on insulin release. This appears to be a drug interaction rather than an effect of β -adrenoceptor blockade on glucose tolerance.

Introduction

β -adrenoceptor blocking drugs are used extensively and, although they are relatively well tolerated by most patients, there are certain groups who are at particular risk of suffering from the non-cardiac effects of β -adrenoceptor blockade. These groups include those with respiratory disorders, peripheral vascular disease and diabetes mellitus (Kendall, 1981). The possible unwanted effects of β -adrenoceptor blockers which may be experienced by the diabetic include a further deterioration in glucose tolerance, and an impaired glucose production and modified haemodynamic response to hypoglycaemia. Whilst there is now good evidence to suggest that a β_2 -receptor is involved in the latter two and that a relatively β_1 selective β -adrenoceptor blocker causes less disturbance in gluconeogenesis and blood pressure responses to hypoglycaemia (Kendall, 1981), the possible unwanted effects of β -adrenoceptor blockers on glucose tolerance are less clearly defined.

When it became possible to assay insulin levels in the blood, it was shown that β -adrenoceptor agonists enhance insulin secretion (Samols & Weir, 1979). It was also shown that a non-selective β -adrenoceptor blocker would impair insulin secretion whereas a β_1 -selective agent would not (Loubatières *et al.*, 1977).

This suggested that insulin release was enhanced via a β_2 -receptor, a concept which was supported by the observation that the β_2 selective agonists also provoke insulin release (Loubatières *et al.*, 1977; William-Olsson, *et al.*, 1979). However, though it was possible to demonstrate a deterioration of glucose tolerance on a β -adrenoceptor blocker the differences were not great, and in a study of the routine blood sugar control of insulin-treated diabetics the differences between the effects of selective and a non-selective β -adrenoceptor blocker were marginal and not significant (Wright *et al.*, 1979). Furthermore, glucose tolerance tests on two dosage levels of propranolol and two dosage levels of metoprolol produced comparable blood glucose and insulin concentrations (Woods *et al.*, 1980).

Since the sulphonylureas reduce the blood sugar partly by increasing insulin release, the possibility of an interaction between this group of drug and the β -adrenoceptor blocker has to be considered. A comparison has therefore been made of the effects of acebutolol, a relatively selective (Kendall, 1981), and propranolol, a non-selective β -adrenoceptor blocker on the hypoglycaemic action of glibenclamide in a group of maturity onset diabetics.

Methods

Patients

Eight male patients with diet-treated maturity onset diabetes confirmed by random blood sugar concentrations of more than 10 mmol l⁻¹ on at least three occasions were selected for the study. They were aged 42 to 71 (mean $\pm$ s.d. 60.0 $\pm$ 9.6) years and weighed 73 to 89 (mean $\pm$ s.d. 80.6 $\pm$ 6.6) kg. None of them suffered from any of the major contraindications to β -adrenoceptor blocker therapy such as asthma, bradycardia or heart failure and biochemical screening revealed no evidence of hepatic or renal disease.

The study protocol was approved by the Central Birmingham Hospitals Research Ethical Committee. The nature and purpose of the study was explained to the patients and each gave his consent.

Controls

In order to interpret the plasma level data on acebutolol and its metabolite, the results are compared with data obtained from healthy volunteers. This part of the study was performed to demonstrate that the plasma levels of acebutolol and its metabolite attained by the diabetic patients were not 'abnormal'. There were eight volunteers (four females and four males), aged 18 to 27 (mean $\pm$ s.d. 21.6 $\pm$ 2.8) years and weighing 51.5 to 81.5 (mean $\pm$ s.d. 68.4 $\pm$ 10.5) kg. They were given a single dose of 400 mg acebutolol orally. These subjects were younger than the patient groups but there is little evidence to suggest that in healthy individuals age affects plasma levels of mainly metabolised β -adrenoceptor blockers such as propranolol (Schneider *et al.*, 1980), metoprolol (Quarterman *et al.*, 1981) or oxprenolol (Kendall & Quarterman, 1982).

Trial design

The study was performed using a double-blind cross-over technique in which four identical sets of tablets were given in random order at two weekly intervals.

Each set of tablets was taken at 09.00 h daily for three successive days and on the third day they attended a hospital side room for further investigation.

The four treatments were

- a – 3 placebos
- b – Glibenclamide 5 mg plus 2 placebos
- c – Glibenclamide 5 mg plus 400 mg acebutolol plus 1 placebo
- d – Glibenclamide 5 mg plus 160 mg propranolol plus 1 placebo

On the study days, the patients came to hospital after a 12 h fast and an intravenous cannula was

inserted into a suitable forearm vein. At approximately 09.00 h, time 0 (zero) the third day's tablets were taken with 100 ml cold water. One hour later 50 g glucose was taken in 200 ml water. Blood samples were taken at time 0, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, and 8 h. Part was sent for routine blood sugar measurements performed by the autoanalyser. The results for each individual on each treatment were used to calculate an area under the blood glucose curve (AUC). From these, mean AUC values for each regimen were obtained. The remainder was collected into lithium heparin tubes, the plasma separated and then stored at -20°C until assayed for acebutolol or propranolol as appropriate.

Lunch was given 4 h after the drug had been taken.

Drug assays

Acebutolol and its major metabolite diacetolol were assayed using a high pressure liquid chromatographic technique with UV detection. This involved a modification of an extraction process reported by Emerson *et al.* (1981) and the chromatographic procedure reported by Meffin *et al.* (1977).

Propranolol was assayed by a gas-liquid chromatographic method which is a modification of a published method for oxprenolol (Jack & Riess, 1974).

Statistical analysis

A paired *t*-test was used to evaluate the differences in the blood glucose AUCs and an unpaired *t*-test was used for the plasma acebutolol and diacetolol AUCs. A *P* value of 0.05 or less was considered as being statistically significant.

Results

The mean blood glucose results for each of the four treatment regimens are presented graphically in Figure 1 and the numerical data is given in Table 1 together with the mean AUCs. It is clear that glibenclamide is still exerting an effect at time 0, 24 h after the previous dose and the AUC (time 1–6 h) following a glucose load is certainly significantly less than on placebo (*P* < 0.001). Both β -adrenoceptor blockers significantly increased the blood glucose AUCs, compared to glibenclamide alone, the effect of propranolol being greater than that of acebutolol. However the difference between the effects of the two drugs did not reach statistical significance.

The mean plasma concentration of acebutolol and diacetolol for the diabetic and control subjects are presented in Figure 2. No statistically significant difference was found between the areas under the plasma curves for acebutolol (mean AUC $\pm$ s.d.:

Figure 1 The mean ($n = 8$) blood glucose levels during each of four treatments, a placebo (O), b glibenclamide (■), c glibenclamide and acebutolol (●) and d glibenclamide and propranolol (▲).

Table 1 Blood glucose levels : mean ($n = 8$) $\pm$ s.d. and the areas under the blood glucose curves : mean ($n = 8$) $\pm$ s.d.

Time after dosage (h)	Blood glucose (mmol l ⁻¹)			
	Treatment A all placebos	Treatment B G only	Treatment C G + A	Treatment D G + P
0	8.9 $\pm$ 2.3	7.3 $\pm$ 1.9	7.7 $\pm$ 1.6	7.5 $\pm$ 2.1
1.0	8.2 $\pm$ 2.0	6.8 $\pm$ 1.7	7.4 $\pm$ 1.4	7.3 $\pm$ 2.2
1.5	10.5 $\pm$ 1.5	9.1 $\pm$ 2.7	9.1 $\pm$ 1.5	9.5 $\pm$ 2.2
2.0	13.0 $\pm$ 1.9	10.4 $\pm$ 2.5	11.4 $\pm$ 1.4	10.9 $\pm$ 2.7
2.5	13.6 $\pm$ 2.3	10.9 $\pm$ 3.0	12.2 $\pm$ 1.8	11.6 $\pm$ 3.2
3.0	12.8 $\pm$ 2.6	9.4 $\pm$ 2.9	11.8 $\pm$ 2.1	11.4 $\pm$ 3.0
3.5	11.4 $\pm$ 3.3	7.8 $\pm$ 2.7	10.0 $\pm$ 2.3	10.5 $\pm$ 2.5
4.0	9.8 $\pm$ 3.4	6.6 $\pm$ 2.4	8.8 $\pm$ 2.2	9.0 $\pm$ 2.4
6.0	9.5 $\pm$ 3.8	6.1 $\pm$ 2.2	6.5 $\pm$ 3.1	8.1 $\pm$ 2.8
AUC (mmol h l ⁻¹)	54.4 $\pm$ 13.2	39.4 $\pm$ 11.3	46 $\pm$ 10.1	48.2 $\pm$ 13

G Glibenclamide; A Acebutolol; P Propranolol

Figure 2 The mean ($n = 8$) plasma concentrations of acebutolol (a) and diacetolol, (b) in diabetic (●) and control (○) subjects. The bars indicate s.e. of the mean.

diabetics $4160 \pm 902 \text{ ng h ml}^{-1}$; controls $4066 \pm 911 \text{ ng h ml}^{-1}$, $P > 0.05$) or diacetolol (diabetics $7261 \pm 1864 \text{ ng h ml}^{-1}$; controls $5526 \pm 1239 \text{ ng h ml}^{-1}$, $P > 0.05$). The mean plasma concentrations of propranolol are presented in Table 2 and are discussed in relation to published data.

There was no correlation between plasma levels of either drug and the corresponding blood sugar value.

Discussion

The results presented demonstrate that glibenclamide significantly reduces the blood glucose levels after a glucose load and that a single dose will reduce the fasting glucose 24 h post dosing, as has been shown before (Sönksen *et al.* 1981). We have also shown that β -adrenoceptor blocking drugs significantly modify this action. These effects were achieved using therapeutic doses and we have demonstrated that the plasma levels attained for acebutolol, on the third day of the regimen were similar to those for healthy controls after a single dose of the same size. The levels of propranolol on the third day of the regimen are also comparable to those of healthy controls given a single dose of 160 mg standard propranolol (McAinsh *et al.*, 1978), bearing in mind that accumulation is known to occur during repeated oral administration (Wood *et al.*, 1978).

Table 2 Mean plasma propranolol levels $\pm$ s.d. of eight diabetic subjects

Time after Dosage (h)	Concentration (ng ml ⁻¹)
0	30 $\pm$ 54
1.0	206 $\pm$ 122
1.5	198 $\pm$ 67
2.0	223 $\pm$ 88
2.5	224 $\pm$ 78
3.0	181 $\pm$ 79
3.5	147 $\pm$ 80
4.0	127 $\pm$ 45
6.0	116 $\pm$ 60
8.0	97 $\pm$ 43

The reason for the observed effect of the β -adrenoceptor blockers on the action of this sulphonylurea is unclear. The mode of action of sulphonylureas has been extensively investigated and their immediate effect is considered to be achieved by promoting insulin release (Feldman & Lebovitz, 1971), though their long term therapeutic benefits are thought to be mediated by extrapancreatic mechanisms (Feldman & Lebovitz, 1969; Davidson *et*

al., 1970; Feldman & Lebovitz, 1971; Hetcht, *et al.*, 1973; Barnes *et al.*, 1974; Shenfield *et al.*, 1977). Since our observations were made during an acute study, it would seem most likely that the β -adrenoceptor blockers are having an effect on sulphonylurea-induced insulin release. Previous studies have shown that propranolol depresses insulin response to tolbutamide in normal subjects (Massara *et al.*, 1971; De Divitiis *et al.*, 1968) and to glibenclamide in normal dogs (Sirek *et al.*, 1975). Our study has shown that both cardioselective and non-selective β -adrenoceptor blockade modify the action of a sulphonylurea in diabetic patients with the former having a slightly less effect.

The failure to demonstrate a convincing difference between the two β -adrenoceptor blockers might be construed as casting doubts on the selectivity of acebutolol or on the role of predominantly β_2 -adrenoceptors in insulin release. However evidence suggesting that acebutolol is relatively selective is becoming fairly convincing (Wollam *et al.*, 1979; Mue *et al.*, 1979; Decalmer, *et al.*, 1978) as are the data implicating β_2 adrenoceptors in insulin release

discussed earlier. Furthermore previous studies designed to investigate the possible advantages of the selective agent metoprolol in terms of lack of adverse effects on glucose tolerance have not been convincing (Wright *et al.*, 1979; Woods *et al.*, 1980). Thus the possible benefits of relative selectivity on glucose tolerance and response to sulphonylureas appear at best marginal. The reason for this is not clear. Nevertheless, since cardioselective β -adrenoceptor blockers have less effect on recovery from hypoglycaemia (Deacon *et al.*, 1977) and are less likely to be associated with unwanted haemodynamic effects (Lager *et al.*, 1979) these agents may be preferable when β -adrenoceptor blockade is required in diabetics.

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