Beta-adrenoceptor-blocking drugs and blood sugar control in diabetes mellitus

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Summary and conclusions

The effects on diabetic control of the relative cardioselective beta-blocker metoprolol and the non-selective drug propranolol were compared in 20 hypertensive diabetic patients receiving diet alone or diet and oral hypoglycaemic agents. Each drug was given for one month in a double-blind, cross-over study. Fasting, noon, and mid-afternoon blood sugar concentrations rose by 1·0-1·5 mmol/l (18-27 mg/100 ml). The rise with propranolol was not significantly greater than with metoprolol. In a few patients the rise was clinically important.

The small overall change observed in diabetic control should not deter the use of beta-blockers in non-insulin-dependent diabetics, provided control is carefully monitored at the onset of treatment.

Introduction

Catecholamines play a part in the release of insulin[1] and in the clinical reaction to hypoglycaemia[2] and metabolic recovery from it.[3] Adrenoceptor-blocking drugs might therefore be expected to influence the way in which patients, particularly diabetics, respond to fluctuations in blood sugar concentrations. Studies on volunteers[4-6] show that beta-blockers modify the recovery from hypoglycaemia and suggest that selective, $beta_1$-blocking drugs interfere less than non-selective drugs. The possible metabolic effects of beta-blockers in the presence of a high blood sugar concentration, however, have received relatively little attention, though one study[7] showed that glucose tolerance is impaired to a greater extent with non-selective than cardioselective beta-blockers. One explanation for these results is that insulin secretion may be influenced through a $beta_2$-receptor in man as it is in dogs.[8] The relevance of these observations to the routine management of diabetes is unknown.

We decided to see whether long-term treatment with a beta-blocker materially affects blood sugar control in maturity-onset diabetes and if any advantage is gained from choosing a cardioselective agent. With these aims we compared the relatively cardioselective beta-blocker metoprolol[9] with the non-selective agent propranolol in patients with maturity-onset diabetes.

Patients and methods

Twenty hypertensive patients with diabetes mellitus (10 men, 10 women) selected from the diabetic clinic completed the study. Their mean age was 56 ± SE of mean 2 years (range 40-65 years) and mean weight 106% (range 91-122%) of the ideal. Sixteen were taking oral hypoglycaemic agents, nine hypotensive agents, and two diuretics. Selection was based on age (65 years or less), time and method of diagnosis of the diabetes (at least six months before, and from a mid-afternoon blood sugar concentration exceeding 10 mmol/l (180 mg/100 ml)), and degree of diabetic control (stable with diet alone or with diet and oral hypoglycaemic agents). In all cases the hypertension had been noted either before or at their first attendance at the clinic and confirmed by finding a diastolic blood pressure exceeding 95 mm Hg (phase IV) in the sitting position on at least three occasions. Patients with severe renal or hepatic disease, heart failure, obstructive airways disease, gross obesity, or recent myocardial infarction were excluded, as were those taking beta-blocking drugs, monoamine oxidase inhibitors, tricyclic antidepressants, corticosteroids, or beta-agonists. Basic treatment with hypoglycaemic and hypotensive drugs in individual cases was continued unchanged throughout.

Trial design—All patients attended the hospital on four occasions at four-weekly intervals. For the first four weeks a placebo tablet twice daily was prescribed; for the second and third four-week periods they received metoprolol 100 mg twice daily or propranolol 80 mg twice daily, prescribed in random order by means of a double-blind, cross-over technique. Patient compliance was assessed by counting the tablets returned. At each visit a clinical assessment, body weight, electrocardiogram, and changes in pulse and blood pressure with posture and exercise (climbing and descending 53 stairs) were recorded. Fasting (0930-1000), pre-lunch (1200-1230), and mid-afternoon (1530-1600) venous blood samples were taken for measurement of blood sugar, serum insulin, and drug concentrations. Fasting serum cholesterol, triglyceride, and electrolyte concentrations were also measured. On study days drugs were taken at about 1000.

Assays—Blood sugar was measured by Hoffman's ferricyanide method adapted to the AutoAnalyzer. Serum was stored at −20°C and serum insulin measured at the end of the study by a modification of Herbert's method[10] with use of the first international preparation of human insulin as standard and a guinea-pig antihuman insulin antiserum kindly provided by Dr P Sönksen. Serum metoprolol and propranolol concentrations were measured by a modification of the gas-liquid chromatographic technique originally used for oxprenolol.[11]

Statistics—The diabetic, cardiac, and biochemical data were analysed by Grizzle's method[12] to evaluate treatment effects and determine the effect of treatment order. When treatment differences were found the multiple comparison technique of Sheffé[13] was used. The insulin data were logarithmically transformed for the analysis, and the mean and standard errors (see table II) are the de-transformed results.

Results

Twenty-three patients were admitted to the study, of whom three were excluded from the analysis. One patient failed to attend after the placebo period, one failed to continue with oral hypoglycaemic drugs, and the third died from a myocardial infarction three days after starting placebo tablets.

The two treatment-order groups (placebo to metoprolol to propranolol, and placebo to propranolol to metoprolol) were compared for basic data—for example, age, sex, and race—and changes in clinical symptoms during the study. The propranolol to metoprolol patients had a greater actual body weight initially ($P = 0·031$). There were no other differences between the two groups, and the results are based on the two treatment groups combined.

DIABETIC CONTROL

Diabetic symptoms did not alter appreciably during the active-treatment periods, but two patients noted increased glycosuria while taking metoprolol and propranolol respectively. Fasting, noon, and mid-afternoon blood sugar concentrations rose with both metoprolol

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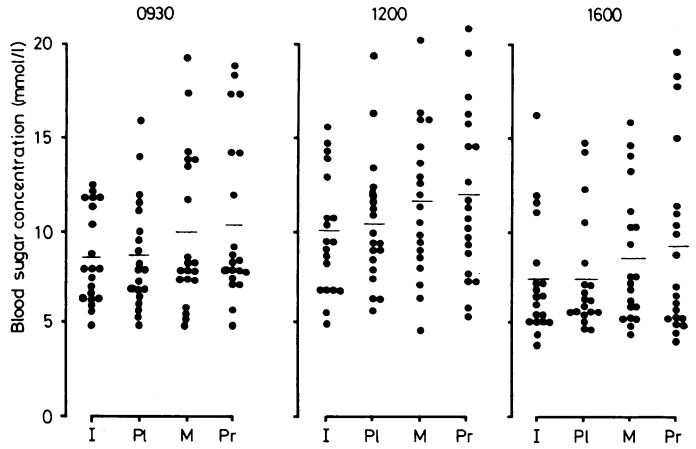

FIG 1—Blood sugar concentrations in all patients at the four assessments. I=Initial. Pl=After placebo for four weeks. M=After metoprolol for four weeks. Pr=After propranolol for four weeks. Bars represent means.
Conversion: SI to traditional units—Blood sugar: 1 mmol/l ≈ 18 mg/100 ml.

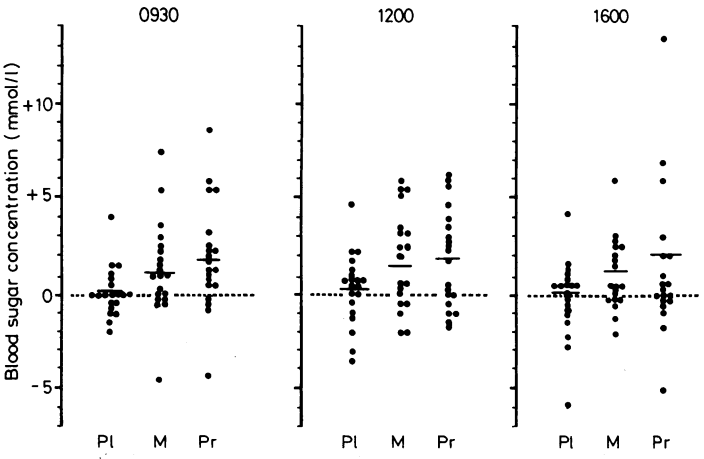

FIG 2—Changes in blood sugar concentrations from initial assessment in all patients. Bars represent mean changes. Pl=After placebo for four weeks. M=After metoprolol for four weeks. Pr=After propranolol for four weeks.
Conversion: SI to traditional units—Blood sugar: 1 mmol/l ≈ 18 mg/100 ml.

TABLE I—*Blood sugar concentrations (mmol/l) in two patients with largest increases*

	Case 1			Case 2		
	Fasting	1200	1600	Fasting	1200	1600
Initial	10·4	8·8	6·6	11·5	14·8	11·3
After placebo	9·7	10·0	10·8	11·5	11·3	8·6
After metoprolol	14·1	14·7	13·5	14·1	12·7	14·3
After propranolol	19·1	14·7	20·0	17·5	21·0	18·4

Conversion: SI to traditional units—Blood sugar: 1 mmol/l ≈ 18 mg/100 ml.

and propranolol (fig 1), the increases being similar at each time point. The overall mean blood sugar concentration after metoprolol (10·1 mmol/l; 182 mg/100 ml) was significantly higher than the overall mean initial and placebo concentration (8·9 mmol/l; 160 mg/100 ml) ($P < 0·01$). Similarly, the overall mean concentration after propranolol (10·7 mmol/l; 193 mg/100 ml) was significantly higher than the mean initial and placebo blood sugar concentrations ($P < 0·01$). The increase in blood sugar after propranolol was greater than after metoprolol but not significantly so ($P > 0·01$). An increase in the concentration of blood sugar during treatment with beta-blockers was found in most patients at all three times measured (fig 2). Table I gives the blood sugar concentrations of the two patients with the greatest increases; neither required insulin subsequently.

The increase in blood sugar was not related to tablet compliance or to plasma concentrations of metoprolol and propranolol. There was no significant change in serum insulin concentrations (table II). Fasting serum triglyceride concentrations tended to rise with both metoprolol and propranolol, although the rises were not significant (table II). Five patients were hypertriglyceridaemic in the placebo period; four of these had a further increase and one a decrease in triglyceride concentrations while taking beta-blocking drugs, one during both active-treatment periods, one only when taking metoprolol, and one only when taking propranolol. Changes in serum triglyceride concentrations did not correlate with changes in blood sugar in either the metoprolol ($P = 0·30$) or propranolol ($P = 0·89$) period, nor were they related to initial body weight. Serum cholesterol concentrations were unchanged.

DRUG CONCENTRATIONS

Serum concentrations of metoprolol and propranolol (table II) were similar to those reported in multiple-dose studies on healthy volunteers and non-diabetic hypertensive patients in all but one patient, whose propranolol concentrations were below the sensitivity of the assay. There was no relation between the plasma concentrations of metoprolol and propranolol in individual patients. Only two patients complied less than 75% with the trial medication, and in neither case did this fall below 50%.

CARDIORENAL EFFECTS

Metoprolol and propranolol produced similar and significant effects on resting and standing blood pressure and on pulse rate and blood pressure after exercise (table III). The degree of beta-blockade with

TABLE III—*Results of clinical assessments (means ± SE of mean)*

	Initial	Placebo	Metoprolol	Propranolol
Pulse rate (beats/min):				
Resting	75±2	77±3	62±2	63±2
Standing	82±2	85±4	65±2	64±2
Exercise	92±5	90±5	72±4	73±3
Blood pressure (mm Hg)				
Resting Systolic	165±4	166±5	153±5	152±5
Resting Diastolic	98±2	102±3	94±3	94±3
Standing Systolic	166±4	160±6	149±4	151±6
Standing Diastolic	103±3	100±3	95±3	96±3
Exercise Systolic	182±7	185±6	167±5	166±6
Exercise Diastolic	102±3	105±3	97±3	94±3
Weight (kg)	74·0±2·4	74·4±2·4	74·8±2·4	74·6±2·4

TABLE II—*Metabolic changes and drug concentrations (means ± SE of mean)*

	Initial			Placebo			Metoprolol			Propranolol		
	0930	1200	1600	0930	1200	1600	0930	1200	1600	0930	1200	1600
Serum insulin (mU/l)	9·4±1·3	28·0±1·1	22·0±1·2	7·9±1·4	26·4±1·2	19·1±1·3	10·7±1·3	25·8±1·1	26·3±1·2	8·0±1·4	18·8±1·3	23·0±1·2
Serum triglyceride (mmol/l) (0·80-1·57*)	2·13±0·55			2·04±0·41			2·31±0·51			2·39±0·61		
Serum cholesterol (mmol/l) (3·10-6·00*)	6·42±0·27			6·44±0·30			6·50±0·25			6·34±0·28		
Serum urea (mmol/l) (2·5-7·5*)	4·93±0·37			5·16±0·30			5·41±0·29			5·62±0·33†		
Serum metoprolol (μg/l)							48±10	181±29	115±17			
Serum propranolol (μg/l)										43±8	138±22	87±16

*Reference range. †Significantly different from initial value ($P < 0·05$).
Conversion: SI to traditional units—Serum triglyceride: 1 mmol/l ≈ 88·5 mg/100 ml. Serum cholesterol: 1 mmol/l ≈ 38·6 mg/100 ml. Serum urea: 1 mmol/l ≈ 6 mg/100 ml.

the two active-treatment regimens was therefore comparable. There was a small increase in serum urea with both beta-blocking drugs, but the rise was significant ($P < 0.05$) only with propranolol (table II).

UNWANTED EFFECTS

Few unwanted effects occurred during the study, and no serious eye or skin reactions were noted. The most common complaint was tiredness, which occurred in the placebo and both active-treatment periods, and to a less extent headache, which was most common in the placebo period.

Discussion

These patients showed a significant increase in blood sugar concentrations during both active-treatment periods, though the effects of propranolol were slightly greater. The clinical relevance of these observations is difficult to determine since the actual increase was relatively small and not detectable clinically in most patients. In the long term the potential benefits of controlling hypertension with a group of drugs that are both effective and well tolerated must be weighed against the potential risk of raising the mean blood sugar concentration by 1·0-1·5 mmol/l (18-27 mg/100 ml). Our data, however, suggest that in a few patients both fasting and postprandial blood sugar concentrations will be significantly increased by beta-blockers, and diabetic control should be monitored when such drugs are introduced. Although the increase was marginally less with the selective agent, the differences were not enough to suggest recommending a relatively cardioselective drug when treating diabetics. We used small but standard doses of both drugs to facilitate comparisons in relatively few patients. We do not know whether higher doses would have greater effect.

The mode of action of beta-blockers in raising the blood sugar concentration in diabetics is uncertain. But since beta$_2$-blockade reduces insulin secretion in response to glucose[14] and isoprenaline, this seems to be the most reasonable explanation. Waal-Manning[7] reported improved glucose tolerance and insulin secretion in patients with mild diabetes changed from a non-selective beta-blocker to metoprolol. Our data, however, showed no significant change in the postprandial serum insulin concentrations or increments above fasting values and therefore do not support this hypothesis. We also found a significant increase in fasting blood sugar concentrations, whereas most reports show no effect of beta-blockers on fasting insulin values.[14] We suggest that the increase in blood sugar is probably due to increased glucose output from the liver, either because of insufficient insulin secretion or because of relative preponderance of alpha-receptor-mediated glycogenolysis during treatment with beta-blockers.

Our patients also showed a slight rise in blood urea and serum triglyceride concentrations while taking the beta-blockers. This is interesting, since diabetic patients are apt to suffer from renal disease and atherosclerosis. The changes were very small, however, and the blood urea values remained well within the normal range. The mean increase in serum triglyceride concentration was marginal and has been noted before,[7 15] although when the effects of metoprolol on plasma triglycerides were studied under carefully controlled conditions no change was noted.[16] This observation therefore needs further investigation, and its relevance in terms of its possible contribution to atheroma formation cannot be predicted. Certainly there appears to be no case for undue anxiety, since in clinical studies beta-blockers tended to reduce the incidence of myocardial infarcts in a hypertensive population.[17]

Our study was designed to assess the effects of propranolol and metoprolol on diabetic control under normal conditions over a reasonable length of time. Possibly further changes in diabetic control might occur after longer treatment with beta-blockers, as shown with thiazide diuretics.[18] The overall change in diabetic control in our series was small and should not preclude the use of beta-blockers in non-insulin-dependent diabetics, provided diabetic control is monitored to detect the occasional patient with appreciable deterioration.

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Results of the study were presented to a meeting of the Medical and Scientific Section of the British Diabetic Association.

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ONE HUNDRED YEARS AGO The official notices suggesting abstention from the use of the water supplied by the Caterham Company have now been withdrawn, without, so far as we can gather, any untoward results. We regret to learn that seven deaths have occurred from the epidemic of typhoid fever, out of a total of two hundred and twenty-eight cases which have been reported. The disease has assumed an exceptionally mild character throughout; and the incidence of the attacks has mainly fallen upon children, thus affording an additional argument, if any were needed, in favour of the explanation that the poison was disseminated by water. The warning notices against the use of the water were withdrawn on the receipt by the Mayor of Reigate of a letter from Dr Thorne Thorne, in which he said that though, in the absence of any test capable of showing the safety of the water, it was difficult to speak with authority, he thought the time had come when it might be distributed without danger to the public health. It was, to say the least, unfortunate that, two days after the second notices had been issued and the water was again being used, the Company should have taken occasion to flush their mains for the purpose of getting rid of the sediment of chalk and clay deposited in them through the borings of the Diamond Boring Company. The result of course was that thick and turbid water was distributed; and this, coupled with some cases of relapse, caused a reawakening of the alarm of the inhabitants. The prejudice which is already felt against the Company was thus materially strengthened; and, in fact, an indignation meeting was held at Redhill on the 21st ult to demand a public explanation from the Company as to the cause of the evil. The usual amount of nonsense was talked; but there was certainly something in the contentions of the speakers that the Company should have made as public as possible the explanations which have been offered for the causation of the epidemic and the remedial measures which have been adopted. We are afraid that local confidence in the water has not yet been restored; but there seems no doubt that the Company have done all in their power to prevent any further mischief. Now that the precautions which we have previously detailed have been taken, and the turbidity caused by the recent borings has ceased, we see no reason why the water should not continue to be as great a boon to the neighbourhood as it was before the recent lamentable accident occurred. (*British Medical Journal*, 1879.)