The effect of metoprolol on plasma lipids

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Summary

Fifteen hypertensive patients entered a single-blind study to examine the effects of metoprolol (100 mg twice daily) on fasting plasma lipids. In 12 patients who completed the study, non-esterified fatty acid concentrations fell, but cholesterol and triglyceride levels were unchanged after 12 weeks' treatment. These results conflict with earlier reports of the effect of metoprolol on plasma triglyceride concentrations.

Introduction

β -adrenoreceptor blocking drugs have been reported as having various effects on basal plasma lipid levels. For example, the non-selective drug propranolol has been reported (Tanaka *et al.*, 1976) as reducing plasma non-esterified fatty acids initially, and subsequently, after 7 weeks' treatment, as increasing their concentration. There is conflicting evidence (Waal-Manning, 1976; Nilsson, Hansson and Hökfelt, 1978) on the effect of the cardioselective β -adrenoreceptor blocking drug metoprolol on fasting plasma triglyceride concentrations. The present study was designed to observe the effects on fasting plasma lipid levels in hypertensive patients treated with metoprolol for a period of 12 weeks and subsequently to observe the changes over 4 weeks after the withdrawal of treatment.

Patients and methods

Fifteen out-patients (8 male) with uncomplicated essential hypertension were selected for the study. Their ages ranged from 31 to 67 (mean 47) years, and their average blood pressure at the start of the study before treatment with metoprolol was 159/104 mmHg. Eight patients were newly diagnosed and had not received any treatment for hypertension before the study. Of the remaining 7, 4 had previously been treated with a combination of propranolol and bendrofluazide, 2 with hydralazine and one had

been treated with methyl dopa. No patient had a history of angina, myocardial infarction, heart failure, stroke or asthma. All patients had grade I or II hypertensive fundal changes and a plasma urea of less than 10 mmol/l. The study was approved by the hospital's ethics committee and informed consent recorded for each patient.

Design of the study

The study was of single-blind design with 3 treatment periods. Before the study proper there was a run-in period of 4 weeks when no medication was given. In the first treatment period patients received a placebo for 4 weeks. The treatment in the second period was metoprolol 100 mg twice daily and this was continued for 12 weeks. In the third and final period, placebo was again administered for 4 weeks. The placebo and active drugs were identical in appearance and the times of administration were the same.

Patients were seen at 2-weekly intervals. At each visit blood pressure was measured with a Hawksley (random-zero) sphygmomanometer after resting for 3 min in the supine position. Diastolic blood pressure was recorded at the point of muffling of sound (Korotkoff IV). Blood pressure was measured by the same individual throughout the study. Pulse rate was measured after blood pressure had been recorded at each visit. The patient's weight and fundal appearance were noted.

Patients were told that blood chemistry would be examined at each visit but the fact that plasma lipids were to be studied was not revealed until after the study, in case patients chose to alter their diet and hence possibly influence the result of the study. For the same reason patients were not given advice on weight reduction or cigarette consumption until after completion of the study. At each visit, at a time 30 min after taking their morning medication, a small intravenous cannula (Abbot 21) was inserted into a forearm vein under local anaesthetic (1%

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lignocaine) in each patient. After a further 30 min blood was drawn without cuff pressure for measurement of serum albumin (Northam and Widdowson, 1967) and globulin (Autoanalyser Methods), plasma cholesterol (Robertson and Cramp, 1970), triglyceride (Cramp and Robertson, 1968) and non-esterified fatty acid (Carruthers and Young, 1973) concentrations. At the end of each treatment period blood was also taken for haematological and biochemical tests (haemoglobin, white cell count; serum bilirubin, aspartate transaminase and alkaline phosphatase; plasma sodium, potassium and urea). Patients were instructed to take only water from 11.00 pm on the evening before attending the clinic. They were asked not to smoke any tobacco or consume any alcohol on the evening before their attendance in the clinic. Tablet containers were collected at each visit, their contents discreetly counted and new tablets issued. A symptom enquiry was performed at each visit.

Criteria for withdrawal from the study were established before it began and were: (1) troublesome symptomatic side effects; (2) unacceptable blood pressures – defined as lying diastolic blood pressure above 120 mmHg on 2 successive visits; (3) deterioration of cardiac, renal, respiratory or hepatic function; (4) development of angina, myocardial infarction or stroke; (5) failure to adhere to the regime.

Statistical analysis

The Scheffe (1953) test was used to compare the average values obtained in the metoprolol treatment period with the average values obtained during the placebo periods. A 2-tailed *t* test was used to compare data at particular times in the treatment period with the corresponding values obtained at the end of the first placebo period. A *P* value of <0.05 was accepted to refute the null hypothesis.

Results

Twelve patients completed the study. One was withdrawn because of persistent bradycardia while receiving metoprolol and 2 patients failed to adhere to the protocol. All data from the remaining patients were available for analysis.

The mean blood pressure and pulse rate at the end of the first placebo period were 159/104 mmHg and 75/min respectively. At the end of the metoprolol treatment period these readings fell significantly to 127/83 mmHg and 60/min respectively (Table 1). The mean plasma triglyceride concentration was unchanged at 1.3 mmol/l in each of the 3 treatment periods.

The mean plasma non-esterified fatty acid concentration fell significantly at 2 weeks after metoprolol was introduced from 760 to 553 $\mu\text{mol/l}$, and this fall

TABLE 1. Physiological and biochemical effects of metoprolol (12 patients)

Day Treatment	28 Placebo	112 Metoprolol	140 Placebo
Blood pressure (mmHg)	159/104	127*/83*	149/99
Pulse (beats/min)	75	60†	70
Non-esterified fatty acids ($\mu\text{mol/l}$)	760	553†	788
Cholesterol (mmol/l)	5.8	6.3	5.9
Triglycerides (mmol/l)	1.3	1.3	1.3
Albumin (g/l)	41	38*	42
Globulin (g/l)	23	24	22

**P* < 0.05 †*P* < 0.01 compared with first placebo period

was consistent throughout the entire treatment period of 12 weeks. The levels rose to pre-treatment values 2 weeks after stopping metoprolol.

Cholesterol levels were slightly increased in the metoprolol treatment period but this increase did not attain statistical significance. There was a slight but significant fall in serum albumin concentration but globulin concentration was unaffected by metoprolol. Body weight of the patients was unchanged as were all of the other biochemical and haematological variables examined.

Two patients developed tiredness in the metoprolol treatment period which was not apparent in the placebo periods and was therefore thought to be related to metoprolol.

Discussion

There is currently much debate about whether β -adrenoreceptor blocking drugs or diuretics should be used as first-line treatment for moderate hypertension. The incidence of carbohydrate intolerance after diuretic therapy is significant (Breckenridge *et al.*, 1967). Diuretics may be associated with a rise in serum cholesterol concentration (Ames and Hill, 1976). There is evidence that raised triglyceride concentrations increase the risk of cardiovascular death when they exceed 1.7 mmol/l irrespective of the cholesterol concentration (Pelkonen *et al.*, 1977). Earlier studies (Waal-Manning, 1976) using similar doses of metoprolol to those employed in this study had shown that metoprolol increased plasma triglycerides. Clearly if this effect were to be confirmed it would provide a theoretical disadvantage for the use of metoprolol. It is not clear why there should be a discrepancy between the present study and that of Waal-Manning although it has been suggested (Nilsson *et al.*, 1977, 1978) that such discrepancies might arise from different patient selection criteria. In a study in which patients were investigated under metabolic ward conditions (Nilsson *et al.*, 1978), metoprolol was found not to affect fasting triglyceride levels nor those values for triglycerides obtained after food and exercise. Propranolol has

also been reported as producing no change in triglyceride concentrations (Spottl, Holzknecht and Braunsteiner, 1968), but that study did show a reduction in free serum cholesterol at the end of 8 weeks' treatment.

Plasma non-esterified fatty acid concentrations have been shown to increase within 24 hr of a myocardial infarction. In non-diabetic patients with myocardial infarction it was found (Spottl *et al.*, 1968) that the plasma concentration of non-esterified fatty acids are significantly higher in those who subsequently develop ventricular fibrillation. Thus, a raised level of non-esterified fatty acids might be potentially harmful in hypertensive patients. Propranolol has been reported (Tanaka *et al.*, 1976) as initially reducing and subsequently increasing non-esterified fatty acid concentrations, atenolol (Deacon, 1978) as reducing them, practolol (Ghosh, Cochrane and de Bono, 1975) as having no effect, while pindolol (Schlierf, Papenberg and Raetzer, 1973) as causing an increase. Metoprolol has previously been reported (Nilsson *et al.*, 1978; Newman, 1977) as having no effect on plasma non-esterified fatty acid levels under basal conditions. The reason for the disparity between the findings in the present study and earlier reports is not clear.

Metoprolol caused a small but significant fall in the serum albumin concentration. It is unlikely that this was due to a dilutional effect since the serum globulin concentration was not affected. A similar effect has been observed in a study on oxprenolol (Pearson *et al.*, 1976). Non-esterified fatty acids are avidly bound to albumin (Goodman, 1958) but the relationship is a stoichiometric one. Thus, the reduction in serum albumin (7%) would not account for the much larger (27%) reduction in non-esterified fatty acids.

Conclusion

Metoprolol in doses which significantly reduce raised arterial blood pressure has no effect on plasma triglyceride or cholesterol concentrations, but causes a significant reduction in plasma non-esterified fatty acids. This may be of advantage in patients with risk factors for myocardial infarction including those with hypertension.

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