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 methyldopa. 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) sphygmanometer 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 (Abbott 21) was inserted into a forearm vein under local anaesthetic (1%
lignocaine) in each patient. After a further 30 min
blood was drawn without cuff pressure for measure-
ment of serum albumin (Northam and Widdowson, 1967) and globulin (Autoanalyser Methods), plasma
cholesterol (Robertson and Cramp, 1970), triglyc-
eride (Cramp and Robertson, 1968) and non-esterified fatty acid (Carruthers and Young, 1973) concentra-
tions. At the end of each treatment period blood
was also taken for haematological and biochemical
tests (haemoglobin, white cell count; serum bili-
rubin, aspartate transaminase and alkaline phos-
phatase; 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 con-
sume any alcohol on the evening before their attend-
ance 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) deterio-
ration 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 com-
pare 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 unch-
changed at 1.3 mmol/l in each of the 3 treatment
periods.

The mean plasma non-esterified fatty acid concen-
tration fell significantly at 2 weeks after metoprolol
was introduced from 760 to 553 μmol/l, and this fall

<table>
<thead>
<tr>
<th>Day</th>
<th>Treatment</th>
<th>Placebo</th>
<th>Metoprolol</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
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<td>28</td>
<td>Blood pressure (mmHg)</td>
<td>159/104</td>
<td>127*</td>
<td>83*</td>
</tr>
<tr>
<td>112</td>
<td>Pulse (beats/min)</td>
<td>75</td>
<td>60†</td>
<td>70</td>
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<td>140</td>
<td>Non-esterified fatty acids (μmol/l)</td>
<td>760</td>
<td>553†</td>
<td>788</td>
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<td></td>
<td>Cholesterol (mmol/l)</td>
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<td>6.3</td>
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<td></td>
<td>Triglycerides (mmol/l)</td>
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<td>1.3</td>
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<td></td>
<td>Albumin (g/l)</td>
<td>41</td>
<td>38*</td>
<td>42</td>
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<td></td>
<td>Globulin (g/l)</td>
<td>23</td>
<td>24</td>
<td>22</td>
</tr>
</tbody>
</table>

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

Table 1. Physiological and biochemical effects of meto-
prolol (12 patients)

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 meto-
prolol. Body weight of the patients was unchanged
as were all of the other biochemical and haemato-
logical variables examined.

Two patients developed tiredness in the meto-
prolol 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 hyper-
tension. 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 tri-
glycerides. 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 triglyc-
eride levels nor those values for triglycerides
obtained after food and exercise. Propranolol has
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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 Boho, 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.

References


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doi: 10.1136/pgmj.55.648.709

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