Br. J. clin. Pharmac. (1978), **5**, 123–125

THE EFFECTS OF ATENOLOL AND PROPRANOLOL UPON LIPOLYSIS

S.P. DEACON
Pilgrim Hospital, Boston, Lincolnshire

1 The effects of selective and non-selective β-adrenoceptor blockade upon plasma non-esterified fatty acid concentrations in the fasting state and following insulin stress have been studied in normal subjects.

2 Atenolol, propranolol and placebo were compared in a double-blind cross-over trial in eight normal subjects.

3 Atenolol and propranolol significantly lowered plasma non-esterified fatty acid concentrations by a similar degree in the fasting, non-stressed state. This finding suggests that β_1-adrenoceptors are involved in the control of basal lipolysis.

4 Following insulin-induced stress, lower plasma non-esterified fatty acid concentrations were observed with propranolol than with atenolol. This difference may be due to β_2-adrenoceptor involvement in the stress mechanisms controlling lipolysis, or to the differences in the water-lipid solubility properties of these drugs.

Introduction

The classification of the adrenoceptor mediating non-esterified fatty acid (NEFA) mobilisation is a matter of controversy. Although catecholamines produce a rise in plasma NEFA concentrations which is dependent upon the rate of lipolyis in adipose tissue (Gilbert, Kaye & Galton, 1974), the nature of the adrenoceptor mediating lipolysis in man has not been precisely defined. *In vitro* experiments indicated that β-adrenoceptors mediated lipolysis in adipose tissue (Fain, 1973) and Arnold (1972) has shown some similarities between lipolytic and cardiac β-adrenoceptors. He proposed that lipolytic adrenoceptors be classified as β_1. Further work has suggested that both β_1- and β_2-adrenoceptors mediate lipolysis (Ablad, Borjesson, Carlsson & Johnson, 1975). Unfortunately, most of the studies on lipolytic β-adrenoceptor classification have been performed with animal preparations and since there may be species differences, these results are not applicable to man.

Studies in man have shown that β-adrenoceptor blocking drugs may influence many of the metabolic effects of adrenaline and nor-adrenaline (Himms-Hagen, 1967). The non-selective β-adrenoceptor blocking drugs such as propranolol are able to reduce rises in plasma NEFA during stress (Pinter & Pattee, 1967). However, few data on the effects of cardio-selective β-adrenoceptor blocking drugs upon human lipid mobilisation have been published. This study was designed to assess the type of β-adrenoceptor mediating lipolysis in man, by comparing the effects of a cardioselective β-adrenoceptor blocker, atenolol, with those of a non-selective β-adrenoceptor blocker, propranolol, upon plasma NEFA concentrations, both in the fasting state and following insulin-induced stress.

Method

A double-blind cross-over study was performed in eight subjects (seven male) aged 22–29 years. All were healthy, non-obese and taking no other medications. During the trial the subjects took their normal diet and avoided prolonged exercise.

Three episodes of insulin-induced stress were performed in each subject at 7 day intervals. Before each test the subjects took either, (a) atenolol 50 mg twice daily, (b) propranolol 80 mg twice daily or (c) placebo twice daily using identical-looking capsules. These were taken for 48 h with a final dose 1 h before the test.

The subjects were fasted overnight before each test. At the beginning of the test the subjects were rested on couches. Indwelling intravenous cannulae were inserted and kept patent by irrigation with physiological saline. Following a 15 min equilibrium period fasting blood samples were taken. An intravenous bolus of soluble insulin (Actrapid insulin 0.1 u(kg body weight) was then given and further blood samples taken at 30, 60, 90 and 120 min.

Blood glucose levels were estimated using the

GOD-Perid method (Boehringer Pack) to confirm adequate hypoglycaemic stress. The plasma non-esterified fatty acid levels were estimated using a modified Dole titrimetric assay (Trout, 1960).

P values were obtained using a paired Student's *t*-test.

Results

Atenolol and propranolol produced a similar significant depression of fasting NEFA levels (atenolol *v* placebo $P < 0.01$, propranolol *v* placebo $P < 0.05$), equal to a lowering of about 35% of the fasting placebo NEFA concentration (Table 1).

The intensity of the insulin-induced hypoglycaemia was identical in all three groups. Maximum hypoglycaemia occurred at 30 min with a mean blood glucose level of 1.3 mmol/l, and this was followed by blood glucose recovery in all groups.

Following intravenous insulin administration the plasma levels fell in all groups. The fasting placebo NEFA level fell by 49% at 30 min and then recovered with a remaining deficit of 19% at 120 min. Although the fasting NEFA levels were similar for atenolol and propranolol, the NEFA responses after insulin were dissimilar. Their 60 min values were significantly different (atenolol *v* propranolol $P < 0.05$). The fasting atenolol NEFA level fell by 25% at 30 min and recovered to its original value at 120 min. The fasting propranolol NEFA level fell by 47% at 60 min and there remained an 11% deficit at 120 min.

Discussion

All observed plasma NEFA values fell within the normal range 180–840 μmol/l. The doses of atenolol and propranolol were judged to be clinically equipotent, and both the atenolol and propranolol groups showed similar significant depression of plasma NEFA levels in the non-stressed fasting state. Since β_1-adrenoceptor blockade is common to both drugs, this finding suggests that basal lipolysis is mediated via β_1-adrenoceptors.

The administration of insulin lowers plasma NEFA (Steinberg, 1963; Butcher, Baird & Sutherland, 1968) by stimulating glucose uptake and favouring the re-esterification of non-esterified fatty acids into triglyceride. However, the resulting hypoglycaemia promotes the secretion of adrenaline and noradrenaline (Goldfien, 1961) and this increase in circulating catecholamines raises the plasma NEFA concentration (Mueller & Horwitz, 1962). Pilkington, Lowe, Robinson & Titterington (1962) and Pilkington, Lowe, Foster, Robinson & Antonis (1966) have shown that this rise in plasma NEFA concentration is antagonised by β-adrenoceptor blockade using propranolol, but not by α-adrenoceptor blockade.

The plasma NEFA responses for atenolol and propranolol were dissimilar following the administration of intravenous insulin. The greater fall and impaired recovery of plasma NEFA levels seen with propranolol suggests that β_2-adrenoceptors are involved in the lipolytic response to insulin-induced stress. Similar findings have been obtained by Ablad, Borjesson, Carlsson & Johnson (1975), who compared the metabolic effects of the cardioselective drug, metoprolol, with propranolol in the anaesthetised dog. Therefore, it is probable that the lipolytic response to insulin-induced stress is mediated by both β_1- and β_2-adrenoceptors.

However, this difference in lipolytic response to insulin-induced stress might be related to the water-lipid solubility properties of these drugs. Propranolol is relatively more lipid soluble than atenolol, and is able to cross the blood brain barrier (*Br. med. J.*, 1976a & b) whereas atenolol does not (Barrett, 1973). Cordon, Weiss & Mueller (1974) have suggested that the rapid rise in plasma NEFA following stress is not due to increased plasma catecholamine concentrations but is mediated via increased sympathetic nervous activity. Hence the difference in lipolytic response may be due to the central blockade or propranolol impairing sympathetic nervous activity.

Also, since propranolol is relatively more lipid soluble than atenolol, it might be expected to show a higher affinity for adipose tissues. The resulting higher concentration of propranolol in adipose tissues would produce a greater blocking effect upon local lipolysis. This effect may not be obvious in the non-stressed state.

The clinical implications of this study are that the cardioselective β-adrenoceptors may prove less effective in suppressing stress-induced rises in plasma NEFA.

Table 1 Mean plasma NEFA levels ± standard errors (μ mols/l)

Drug	*0 min*	*30 min*	*60 min*	*90 min*	*120 min*
Placebo	670 ± 83	343 ± 41	373 ± 35	379 ± 52	545 ± 62
Atenolol	433 ± 83	325 ± 69	332 ± 28	357 ± 43	431 ± 65
Propranolol	436 ± 63	284 ± 37	231 ± 45	284 ± 33	386 ± 36

References

ABLAD, B., BORJESSON, I., CARLSSON, E. & JOHNSON, G. (1975). The effects of metoprolol and propranolol on some metabolic responses to catecholamines in the anaesthetised dog. *Acta Pharmac. Tox.*, **36**, suppl. V, 85–95.

ARNOLD, A. (1972). Differentiation of receptors activated by catecholamines. *Il Farmaco Ed. Sci.*, **27**, 79–100.

BARRETT, A.M. (1973). A new type of cardioselective adrenoreceptive blocking drug. *Br. J. Pharmac.*, **48**, 340P.

British Medical Journal (1976a). β-blockers in stress and anxiety. *Br. med. J.*, **1**, 415.

British Medical Journal (1976b). Clinical aspects of the blood brain barrier. *Br. med. J.*, **2**, 133.

BUTCHER, R.W., BAIRD, C.E. & SUTHERLAND, E.W. (1968). The effects of lipolytic and antilipolytic substances on 3′5′-monophosphate levels in isolated fat cells. *J. biol. Chem.*, **243**, 1705–1712.

CORDON, P.V., WEISS, J.L. & MUELLER, P.S. (1974). The effects of small intravenous doses of epinephrine on serum insulin, glucose tolerance and serum fatty acid levels. *Diabetes*, **23**, 743–747.

FAIN, J.N. (1973). Biochemical aspects of drug and hormone action on adipose tissue. *Pharmac. Rev.*, **25**, 67–118.

GILBERT, C.H., KAYE, J. & GALTON, D.J. (1974). Does lipolysis in adipose tissue determine the levels of plasma fatty acids in man? *Clin. Sci. Mol. Med.*, **47**, 1P.

GOLDFIEN, A. (1961). Plasma epinephrine and norepinephrine levels during insulin induced hypoglycaemia in man. *J. clin. Endocrinol.*, **21**, 296–304.

HIMMS-HAGEN, J. (1967). Sympathetic regulation of metabolism. *Pharmac. Rev.*, **19**, 367–461.

MUELLER, P.S. & HORWITZ, D. (1962). Plasma free fatty acids and blood glucose responses to analogues of norepinephrine in man. *J. Lipid Res.*, **3**, w51–255.

PILKINGTON, T.R.E., LOWE, R.D., ROBINSON, B.F. & TITTERINGTON, E. (1962). Effect of adrenergic blockade on glucose and fatty acid mobilisation in man. *Lancet*, **ii**, 316–317.

PILKINGTON, T.R.E., LOWE, R.D., FOSTER, R., ROBINSON, B.F. & ANTONIS, A. (1966). Effect of sympathomimetic compounds with beta-adrenergic effects on plasma-free fatty acids in man. *J. Lipid Res.*, **7**, 73–76.

PINTER, E.J. & PATTEE, C. (1967). The effect of β-adrenergic blockade on resting and stimulated fat mobilisation. *J. clin. Endocrinol.*, **27**, 1441–1450.

STEINBERG, D. (1963). In: *The control of lipid metabolism.* pp. 111–138.

TROUT, D.L. (1960). Titration of free fatty acids of plasma. A study of current methods and a new modification. *J. Lipid Res.*, **1**, 199–202.

(Received March 18, 1977)