Atenolol, regional myocardial blood flow and S-T segment in canine ischaemic myocardium

A. BERDEAUX, J.R. BOISSIER & J.F. GIUDICELLI

Laboratoire de Pharmacologie II, 15 rue de l'Ecole-de-Médecine 75270—Paris, Cedex 6, France

The effects of atenolol on regional myocardial blood flow (measured by tracer microspheres) and the S-T segment were compared in normal and ischaemic regions on a reproducible model of temporary coronary occlusion in the dog.

The control coronary occlusion did not modify heart rate but induced in the ischaemic area an increase in S-T segment and a decrease in endo- (−71%) and epicardial (−49%) blood flows, resulting in a diminished endo/epi ratio (0.55 ± 0.05 as compared with 1.02 ± 0.05 in the non-ischaemic region).

Atenolol (1 mg/kg, i.v.) decreased heart rate (−28%), lowered S-T segment elevation (−60%) and further reduced endo- and epicardial blood flows without inducing redistribution (endo/epi ratio: 0.61 ± 0.09 in the ischaemic area). In the non-ischaemic area, atenolol also decreased endo- and epicardial blood flows (−40%) without affecting endo/epi ratio (1.08 ± 0.07). Bilateral stellectomy induced similar effects to atenolol administration.

After bilateral stellectomy, atenolol (1 mg/kg, i.v.) induced no additional effects. Finally, under electrosystolic pacing, atenolol (1 mg/kg, i.v.) no longer lowered S-T segment elevation and did not further modify regional blood flows and endo/epi ratio.

It is concluded that atenolol (1) reduces regional myocardial blood flows and S-T segment elevations, these two phenomena being correlated with the decrease in heart rate, (2) does not induce endo-epicardial blood flow redistribution neither in ischaemic nor in non-ischaemic regions.

An indolizine with an amiodarone-like haemodynamic profile

R.H. CHARLIER, J.A. RAUTHIER & J.C. RICHARD

Department of Pharmacological Research, LABAZ Centre Research, 1120—Bruxelles, Belgium

L 9394 or 2-ethyl-3-(4-γ-di-n-butylaminopropoxy-benzoyl)-indolizine hydrochloride (each 10 mg/kg, 5% aqueous solution) produces amiodarone-like haemodynamic effects when injected i.v. (2 min) into the atropinized (1 mg/kg i.v.) and anaesthetized (sodium pentobarbitone, 30 mg/kg i.v.) mongrel dog. Maximal changes in all measured haemodynamic parameters occurred at the end of the injection-time, except for heart rate for which the maximal change was noted after 5 minutes. The average changes were as follows in 11 treated dogs compared to 18 control dogs receiving saline. Heart rate decreased consistently by 31%. Mean blood pressure fell by 48%, diastolic pressure being more reduced than systolic pressure. Myocardial oxygen consumption computed according to the index of Robinson (1967) diminished sharply by 58%. Cardiac output increased by 74%, stroke volume by 160%. L 9394 also enhanced coronary arterial blood flow (as measured electromagnetically in 10 open chest dogs) by 123% on the average. All these changes were very highly significant ($P < 0.001$). Heart rate decrease lasted for at least 3 h without any change, but the other parameters wore off within different times; 1 h in the case of blood pressure and cardiac output, 20 min in the case of coronary blood flow, while myocardial oxygen consumption was still reduced by 30% ($P < 0.05$) after 1 h and stroke volume was still increased by 30% ($P < 0.05$) at the same time. L 9394 is furthermore endowed with non-competitive adrenoceptor-blocking properties since adrenaline and noradranaline-induced hypertension as well as adrenaline- and isoprenaline-induced tachycardia were markedly antagonized but never blocked.

The overall haemodynamic properties of L 9394 are qualitatively similar to those of amiodarone (Charlier, Deltour, Baudine & Chaillet, 1968), which is a very effective medication for the long term treatment of angina pectoris (Charlier, 1971). Furthermore drug-induced bradycardia has been shown to be a highly desirable property for an antianginal drug (Gomoll & Braunwald, 1973; Charlier, 1974), because heart rate is a major determinant of myocardial oxygen consumption (Braunwald, 1971). It is therefore considered that L 9394 is worthy of a clinical trial in patients with angina.

References

BRAUNWALD, E. (1971). Control of myocardial oxygen consumption : physiologic and clinical considerations. *Amer. J. Cardiol.*, **27**, 416–432.

CHARLIER, R. (1971). Antianginal Drugs, *Handb. Exp. Pharmacol.*, Springer Verlag, Berlin-Heidelberg-New York, **31**, 255–288.

CHARLIER, R. (1974). Physiopathologie de l'angor et médication antiangineuse à long terme. Conceptions actuelles. *Nouv. Presse Méd.*, **37**, 2407–2410.

CHARLIER, R., DELTOUR, G., BAUDINE, A. & CHAILLET, F. (1968). Pharmacology of amiodarone, an anti-anginal drug with a new biological profile. *Arzn. Forsch.*, **18**, 1408–1417.

GOMOLL, A.W. & BRAUNWALD, E. (1973). Comparative effects of sotalol and propranolol on myocardial contractility. *Arch. int. Pharmacodyn.*, **205**, 338–354.

ROBINSON, B.F. (1967). Relation of heart rate and systolic blood pressure to the onset of pain in angina pectoris. *Circulation*, **35**, 1073–1083.

Oxprenolol in angina pectoris

S.H. TAYLOR & U. THADANI

University Departments of Cardiovascular Studies and Medicine, The General Infirmary, Leeds

Symptomatic, ECG and circulatory effects of the β-adrenoceptor antagonist oxprenolol were evaluated during treadmill walking in a placebo controlled double-blind study in 35 male patients with stable, uncomplicated angiographically-defined angina pectoris. After a single oral dose of oxprenolol (160 mg), plasma concentration, increase in treadmill walking time, reduction in ECG ST depression and attenuation of exercise tachycardia and systolic pressure increase peaked at 1–2 h and thereafter slowly declined over 8 hours.

Plasma concentration at 1 h was linearly related to the oral dose of oxprenolol. Dose-response measurements demonstrated a significant correlation between reduction in anginal pain, ECG ST depression, exercise tachycardia and systolic pressor response and the logarithm of the dose of drug.

In eight patients there was no increase in exercise tolerance, despite similar plasma concentrations and similar ECG and circulatory changes to those in patients with significant extension of angina time.

Oxprenolol, 160 mg twice daily, affords a rapid and effective treatment in the majority of patients with exercise-induced angina pectoris.

Some complementary data on AH 5158, an inhibitor of both α- and β-adrenoceptors

P. HARICHAUX & L. HARY

Laboratoire de Physiologie, Faculté de Médecine, 12, rue Frédéric Petit, 80036 Amiens, Cedex, France

Inhibitory properties of AH 5158 (5[1-hydroxy-2-[(1-methyl-3-phenylpropyl)amino]ethyl]salicylamide) upon both α- and β-adrenoceptors, mainly in heart (β_1 receptors) and blood vessels (α receptors) have been reported (Farmer, Kennedy & Levy, 1971; Farmer, Kennedy, Levy & Marshall, 1972; Kennedy & Levy, 1975).

Our own results show that: (a) in guinea-pigs (anaesthetized with urethane), AH 5158 (1–3 mg/kg) inhibits the protective β_2 effects of isoprenaline (20 µg/kg) and salbutamol (30 µg/kg) against the broncho-constrictive effects of 5-hydroxytryptamine, acetylcholine and histamine; (b) in the isolated rabbit duodenum (Tyrode solution), AH 5158 (5×10^{-6}–10^{-5} g/ml) inhibits the relaxing effect of $0.5–1 \times 10^{-6}$ isoprenaline (β_2), $0.5–1 \times 10^{-6}$ adrenaline (α–β_1) and 10^{-7}–10^{-6} noradrenaline (α); (c) whilst looking for possible metabolic effects, we established a slight intrinsic effect of AH 5158 (5 and 10 mg/kg) on plasma K^+ level in the rat (anaesthetized with urethane- and an inhibitory effect (for the same doses and species) on sympathomimetically-induced hyperglycaemia.

These results bring additional data to the pharmacological properties of AH 5158, which might have therapeutic applications.

References

FARMER, J.B., KENNEDY, I. & LEVY, G.P. (1971). Some characteristics of AH 5158, a drug which blocks both α- and β-adrenoceptors. *J. Pharmac.*, **2**, 192–194.

FARMER, J.B., KENNEDY, I., LEVY, G.P. & MARSHALL, R.J. (1972). Pharmacology of AH 5158; a drug which blocks both α- and β-adrenoceptors. *Br. J. Pharmac.*, **45**, 660–675.

KENNEDY, I. & LEVY, G.P. (1975). Combined α- and β-adrenoceptor blocking drug AH 5158: further studies on α-adrenoceptor blockade in anaesthetized animals. *Br. J. Pharmac.*, **53**, 585–592.