Pharmacology of Combined $\alpha$-$\beta$-Blockade II

Haemodynamic Effects of Labetalol

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Summary

The cardinal haemodynamic disturbance in established hypertension is an increased total peripheral resistance and a subnormal blood flow, particularly during exercise. The spontaneously occurring changes in central haemodynamics have been followed in young males with essential hypertension over a 17-year period: a gradual increase in total peripheral resistance and blood pressure, and a gradual fall in cardiac output and stroke volume, have been demonstrated.

Labetalol is a unique antihypertensive agent which induces both $\alpha$- and $\beta$-blockade. Numerous studies have shown that when labetalol is given intravenously to patients with mild to moderate essential hypertension, blood pressure falls within a few minutes - partly due to reduction in cardiac output and heart rate and partly due to reduction in total peripheral resistance. In most series the average reduction in blood pressure was 17 to 22%, the reduction in total peripheral resistance 11 to 14%, and the reduction in cardiac output 2 to 10%. Thus, the reduction in cardiac output with labetalol is less than that seen after single-dose injection of $\beta$-blockers without intrinsic sympathomimetic activity. After intravenous injection, the blood pressure-lowering effect is most marked in the upright position and during muscular exercise when cardiac output is usually significantly reduced.

Labetalol reduces blood pressure in severe hypertension. Intravenous doses of 0.2 to 0.8 mg/kg bodyweight reduce blood pressure by approximately 20%. This hypotensive effect is partly due to a reduction in total peripheral resistance and partly due to a fall in cardiac index. When the reduction in blood pressure is gradual and moderate ($< 20\%$), it is mainly produced by a reduction in total peripheral resistance.

During long term use labetalol induces haemodynamic changes rather similar to those seen after bolus injection. However, during prolonged use there is a tendency to normalisation in cardiac output and stroke volume; the sustained decrease in blood pressure is mainly due to a reduction in total peripheral resistance.

In a recent 6-year follow-up study where 15 patients were studied before treatment and after 1 and 6 years on long term labetalol treatment, a tendency to normalisation of central haemodynamics was found. Over the years total peripheral resistance was gradually reduced by 15 to 20% at rest as well as during exercise. Stroke volume gradually increased and after 6 years of treatment was approximately 10% higher than the pretreatment value. This compensated for the reduced heart rate and no significant reduction in cardiac output was seen either during exercise or at rest.

Studies of the regional circulation have shown that labetalol reduces renal vascular resistance and forearm resistance. Coronary blood flow is slightly decreased but the reduction is less than that seen after conventional $\beta$-blockers. The effect on the pulmonary
circulation is modest, and a significant reduction in pulmonary resistance is usually not seen.

The responses to short and long term administration of labetalol differ from the responses to β-blockers, α-blockers and calcium antagonists. The long term responses resemble the effects of prolonged administration of prazidilol, a combined β-blocker and vasodilator. Prazidilol has been withdrawn from clinical trials and although several new compounds have been developed, labetalol is the only drug generally available for the treatment of hypertension which has both β-blocking and vasodilating or α-blocking properties.

The haemodynamic effects of labetalol are well documented and would seem to make labetalol a particularly useful antihypertensive drug.

Irrespective of what the triggering mechanism might be, increased pressure in the systemic circulation reflects a disturbance in the ratio between cardiac output and total peripheral resistance. In the early stages of essential hypertension the cardiac output at rest is usually normal or might even be higher than in normotensive controls, but during muscular exercise it is subnormal - because of the limited increase in stroke volume. When mild to moderate hypertension is left untreated over several years, the cardiac output and stroke volume fall and total peripheral resistance increases. The blood flow to the kidney, splanchnic organs, skin and later also to skeletal muscles is reduced. Thus, in the majority of hypertensive patients for whom drug treatment is considered necessary, the cardinal haemodynamic disturbances are an increase in total peripheral resistance and a subnormal cardiac output, particularly during exercise (Birkenhager et al., 1982; Bühler, 1982; Lund-Johansen, 1980a,b, 1983a). These functional changes are at least partly caused by a gradual increase in arteriolar wall thickness. This results in increasing peripheral resistance and a gradual restructuring of the left ventricular wall, which lead to decreased compliance and reduced cardiac pump function during exercise (Folkow, 1982).

Against this background it might seem more logical to reduce blood pressure in established hypertension by reducing arteriolar resistance rather than by a reduction in cardiac pump function. The early vasodilators such as phenoxybenzamine were not very successful in long term use (Koch-Weser, 1974). In the last decade, better results have been obtained with prazosin, a postsynaptic α1-receptor blocker. Prazosin produces a sustained reduction in total peripheral resistance without any immediate or long term fall in cardiac output or renal perfusion (de Leeuw et al., 1978; Lund-Johansen, 1974). However, in some patients, prazosin is a weak or ineffective antihypertensive agent.

The use of β-receptor blockers, now widely used as first-choice treatment of established hypertension, is associated with a significant fall in cardiac output at rest and during exercise. Even during prolonged treatment, heart rate and cardiac output remain lowered and the circulatory system is changed from a ‘high-pressure normal blood flow’ pattern towards a ‘normal-pressure low blood flow’ pattern (Lund-Johansen, 1983c; Tarazi and Dus-tan, 1972).

However, when appropriate doses of α- and β-receptor blockers are used in combination, a substantial reduction in the blood pressure at rest and during exercise can be achieved which is partly due to reduced total peripheral resistance and partly due to a decrease in cardiac output. With the combination, the reduction in blood flow is less than when the β-blockers are used alone, and cardiac output during exercise is not reduced (Lund-Johansen, 1977).

Labetalol, which has now been used in the treatment of hypertension for more than 7 years, is a unique antihypertensive agent, inducing both α- and β-blockade (Brogden et al., 1978; Prichard and Richards, 1982). A large number of experimental and