Clinical Pharmacokinetics of Labetalol

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Summary

Labetalol was the first of a new class of antihypertensive drugs with both α- and β-adrenoceptor blocking properties present in the same molecule. Its efficacy has been confirmed by double-blind studies in the treatment of all grades of hypertension and in angina pectoris. The drug's major dose-related side effect is postural hypotension.

The clinical formulation of labetalol consists of equal proportions of 4 optical isomers. One of these (the RR isomer) is probably responsible for the drug's β-adrenoceptor blockade and another (the SR isomer) produces most of the α-blockade. Most of the presently available pharmacokinetic information concerning labetalol is from studies utilising a fluorimetric assay but this has recently been superceded by more specific high-pressure liquid chromatographic (HPLC) procedures.

Labetalol is absorbed rapidly after oral administration with peak plasma concentrations generally being achieved within 2 hours. The bioavailability varies from 10% to over 80% in different subjects. Average bioavailability has been reported to correlate with age, with values of approximately 30% in the 30- to 40-year age group and approximately 65% at 80 years. There is also evidence that the bioavailability increases moderately when the drug is taken with food. About 50% of the drug is bound to protein in the plasma.

The apparent volume of distribution at equilibrium varies from approximately 200 to over 800L, suggesting that concentration of labetalol occurs in extravascular sites. Radiochemical analysis in animals has shown high levels of accumulation in the lung, liver and kidney with little present in brain tissue. This is in keeping with the relatively low lipid solubility of labetalol.

The half-life of labetalol in plasma is 3 to 3.5 hours. The drug is eliminated mainly by hepatic metabolism with the production of several biologically inactive glucuronides which in turn are excreted in the urine and bile. Approximately 85% of labetalol in the blood is removed during a single passage through the liver; thus, like propranolol, labetalol's clearance is probably flow dependent (i.e. it is sensitive to alterations in hepatic blood flow). Small doses of the drug (i.e. 300mg daily) have been shown to reduce antipyrine clearance by approximately 15%, and further studies are necessary to determine whether high doses produce a greater, possibly clinically significant, inhibition of mixed-function oxidase activity.

After both single doses and during long term treatment the plasma concentration-time profile of labetalol shows marked variation between different individuals. A broad relationship exists between the plasma concentration and the fall in blood pressure, particularly in the upright position. However, individual sensitivity to the drug's hypotensive action also plays a major role in determining the response.
Labetalol [AH5158; 5-(1-hydroxy-2-[1-methyl-(3-phenylpropyl)amino]-ethyl) salicylamide; fig. 1] was the first of a new class of antihypertensive agents with both α- and β-adrenoceptor blocking properties (Farmer et al., 1972). The rationale for the development of this agent was the knowledge that a blockade of 1 adrenoceptor subtype causes a reflex stimulation of the other, i.e. vasoconstriction after β-blockade and tachycardia after α-blockade. Since both of these compensatory responses act to prevent a fall in blood pressure, a relatively weak blockade of both receptor types should act synergistically to produce a lowering of blood pressure with minimal physiological disturbance.

The pharmacological properties of labetalol are relatively complex. The drug is almost equipotent in blocking β1- and β2-adrenoceptors, but like prazosin is highly selective for post-synaptic α1-adrenoceptors (Jarrott et al., 1982) and exerts little or no blockade at the presynaptic α2-adrenoceptors, which are believed to modulate neurotransmitter release (Blakeley and Summers, 1977; Rand et al., 1975). Labetalol is considerably weaker than propranolol as a β-adrenoceptor blocking drug and prazosin as a selective α1-blocking agent. The ratio of its α- to β-blocking potency in man was estimated at between 1 : 3 and 1 : 7 (Richards, 1976; Richards et al., 1977). Dollery (1976) has suggested that this ratio may change with increasing plasma drug concentrations because while the upper plateau of the dose-response curve for β-blockade may be reached at moderate plasma concentrations, maximal α-blockade might only be achieved at higher plasma levels.

Haemodynamic studies in hypertensive patients have confirmed that labetalol's additional α-blocking property produces a pattern of haemodynamic changes unlike that of propranolol and other conventional β-adrenoceptor blocking agents. Single-dose administration of the drug lowers peripheral vascular resistance and causes an immediate dose-related drop in blood pressure (Joekes and Thomson, 1976; Koch, 1976). There is little effect on the resting cardiac output but the increase in cardiac output with exercise is inhibited (Edwards and Raftery, 1976; Mehta and Cohn, 1977). By contrast, the initial effect of propranolol is a decreased cardiac output and an increased peripheral vascular resistance with little immediate reduction in blood pressure (Epstein et al., 1965; Tarazi and Dunstan, 1972).

The antihypertensive efficacy of labetalol has been confirmed in several studies. When administered by intravenous bolus injection (Rosei et al., 1975), intravenous infusion (Brown et al., 1977) or given orally (Ghose et al., 1979), it has been shown to be effective in the management of hypertensive emergencies. It has also been shown to be useful in the long term management of severe hypertensives, allowing a reduction in the number of tablets required for adequate blood pressure control (Louis et al., 1978b). Under double-blind conditions, labetalol has been compared with other antihypertensive agents including methyldopa (Sanders et al., 1979), β-adrenoceptor blocking drugs (McNeil and Louis, 1979) and a combination of β-adrenoceptor blocking agents and vasodilators (Barnett et al., 1978). These studies have also shown that the drug is an effective antihypertensive agent.

Clinical experience has also confirmed the early