Pharmacodynamics and Pharmacokinetics of the HMG-CoA Reductase Inhibitors
Similarities and Differences

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Summary

Hypercholesterolaemia plays a crucial role in the development of atherosclerotic diseases in general and coronary heart disease in particular. The risk of progression of the atherosclerotic process to coronary heart disease increases progressively with increasing levels of total serum cholesterol or low density lipoprotein (LDL) cholesterol at both the individual and the population level.
The statins are reversible inhibitors of the microsomal enzyme HMG-CoA reductase, which converts HMG-CoA to mevalonate. This is an early rate-limiting step in cholesterol biosynthesis. Inhibition of HMG-CoA reductase by statins decreases intracellular cholesterol biosynthesis, which then leads to transcriptionally upregulated production of microsomal HMG-CoA reductase and cell surface LDL receptors. Subsequently, additional cholesterol is provided to the cell by de novo synthesis and by receptor-mediated uptake of LDL-cholesterol from the blood. This resets intracellular cholesterol homeostasis in extrahepatic tissues, but has little effect on the overall cholesterol balance.

There are no simple methods to investigate the concentration-dependent inhibition of HMG-CoA reductase in human pharmacodynamic studies. The main clinical variable is plasma LDL-cholesterol, which takes 4 to 6 weeks to show a reduction after the start of statin treatment. Consequently, a dose-effect rather than a concentration-effect relationship is more appropriate to use in describing the pharmacodynamics. Fluvastatin, lovastatin, pravastatin and simvastatin have similar pharmacodynamic properties; all can reduce LDL-cholesterol by 20 to 35%, a reduction which has been shown to achieve decreases of 30 to 35% in major cardiovascular outcomes. Simvastatin has this effect at doses of about half those of the other 3 statins.

The liver is the target organ for the statins, since it is the major site of cholesterol biosynthesis, lipoprotein production and LDL catabolism. However, cholesterol biosynthesis in extrahepatic tissues is necessary for normal cell function. The adverse effects of HMG-reductase inhibitors during long term treatment may depend in part upon the degree to which they act in extrahepatic tissues. Therefore, pharmacokinetic factors such as hepatic extraction and systemic exposure to active compound(s) may be clinically important when comparing the statins.

Different degrees of liver selectivity have been claimed for the HMG-CoA reductase inhibitors. However, the literature contains confusing data concerning the degree of liver versus tissue selectivity. Human pharmacokinetic data are poor and incomplete, especially for lovastatin and simvastatin, and it is clear that any conclusion on tissue selectivity is dependent upon the choice of experimental model. However, the drugs do differ in some important aspects concerning the degree of metabolism and the number of active and inactive metabolites. The rather extensive metabolism by different cytochrome P450 isoforms also makes it difficult to characterise these drugs regarding tissue selectivity unless all metabolites are well characterised.

The effective elimination half-lives of the hydroxy acid forms of the 4 statins are 0.7 to 3.0 hours. Protein binding is similar (>90%) for fluvastatin, lovastatin and simvastatin, but it is only 50% for pravastatin. The best characterised statins from a clinical pharmacokinetic standpoint are fluvastatin and pravastatin. The major difference between these 2 compounds is the higher liver extraction of fluvastatin during the absorption phase compared with pravastatin (67 versus 45%, respectively, in the same dose range). Estimates of liver extraction in humans for lovastatin and simvastatin are poorly reported, which makes a direct comparison difficult.