Clinical Pharmacokinetics of 3-Hydroxy-3-Methylglutaryl-Coenzyme A Reductase Inhibitors

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Summary

3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase is the key enzyme of cholesterol synthesis. HMG-CoA reductase inhibitors are potent reversible inhibitors of this enzyme, which act by competing for the substrate HMG-CoA.

This review is mainly devoted to the 4 main HMG-CoA reductase inhibitors used today: lovastatin, simvastatin, pravastatin and fluvastatin. Depending upon the dosage, these drugs are able to reduce plasma cholesterol levels by more than 40%. After absorption, each undergoes extensive hepatic first-pass metabolism.
Up to 5 primary metabolites are formed, some of which are active inhibitors. The elimination half-lives vary from 0.5 to 3.5 hours and excretion is mainly via the faeces. A limited number of drug interactions has been reported. Increases in liver enzymes and muscle creatine kinase activity are among the most severe adverse effects.

These powerful drugs should be reserved for patients with high plasma cholesterol levels and/or those with cardiovascular disease.

New therapeutic approaches to atherosclerosis are currently under investigation. HMG-CoA reductase inhibitors are the cornerstone of this research.

Drugs capable of lowering circulating blood lipid levels first appeared in the early 1950s, even though epidemiological studies showing a direct correlation between cholesterol blood levels and coronary risk were not yet available. But before 1970, lipid-lowering therapy was not considered satisfactory because of its adverse effects, toxicity and, very often, modest efficacy. In the interim, a better knowledge of cholesterol biosynthesis and catabolism provided an opportunity for researchers to design and synthesise new drugs.

With the advent of second-generation fibrates (e.g. fenofibrate), which act mainly by breaking down cholesterol (or cholesterol-containing particles), a new era was opened. At the same time, Endo began an intense period of research into therapeutic inhibition of cholesterol biosynthesis.

Sterols are used in the synthesis of plasma membranes in all cells. The rate-limiting enzyme in cholesterol synthesis is 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzymatic activity takes place during the early steps that lead from acetate to the cholesterol skeleton (fig. 1).

The idea was to find some HMG-CoA reductase inhibitors of microbial origin that were able to prevent the development of the membranes of other microbes. Mevastatin, the first representative of this new class of compounds, was obtained from a strain of *Penicillium citrinum* (fig. 2). Japanese investigators prepared 23 mg of crystalline mevastatin from 600 L of culture filtrate. Three years later, the same compound was isolated by American researchers from *Penicillium brevicompactum*.

The major difference between the open form of the substituent R₃ and HMG-CoA is the presence of a methyl group on R₃ (figs 1 and 2). The inhibitors with a lactone substituent R₃ must tautomerise to the open form *in vivo* to become active.

This review concerns the 4 HMG-CoA reductase inhibitors used today: lovastatin, simvastatin, pravastatin and fluvastatin. Clinical development of mevastatin was discontinued for safety reasons;