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Differentiation of 3-Hydroxy-3-methylglutaryl-coenzyme A Reductase Inhibitors by Their Relative Lipophilicity

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Abstract

Certain pharmacological and clinical effects of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, commonly known as statins, can be differentiated on the basis of their lipophilicity. Unlike lipophilic statins, a hydrophilic statin has been reported to be selective for the liver due to lower uptake and lower inhibition of cholesterol synthesis in non-hepatic cells.

We compared the lipophilicity of three newer statins, fluvastatin, atorvastatin and cerivastatin, with those of pravastatin, lovastatin and simvastatin, by determining their apparent octanol–water partition coefficients at pH 2, 5, 7 and 7·4.

Under physiological pH conditions of 7–7·4, the relative lipophilicity of various statins currently in clinical use was: simvastatin $\approx$ cerivastatin > lovastatin $\approx$ fluvastatin $\approx$ atorvastatin $\gg$ pravastatin, where pravastatin is 70- to 300-times more hydrophilic than the other statins.

During the past decade, 3-hydroxy-3-methylglutaryl-coenzyme A (HMG–CoA) reductase inhibitors, commonly known as statins, have been established as highly effective therapeutic agents for atherosclerotic diseases in general and coronary heart disease in particular. Although certain structural similarities exist between various statins, Roth et al (1991) and Serajuddin et al (1991) reported that they could be differentiated by their relative lipophilicity. Based on the determination of relative lipophilicity of pravastatin, lovastatin and simvastatin, it was concluded that the greater hydrophilicity of pravastatin accounts for its reduced uptake and inhibition of cholesterol synthesis in non-hepatic cells (Serajuddin et al 1991). Hamelin & Turgeon (1998) recently reviewed the relevance of hydrophilicity and lipophilicity to pharmacological and clinical effects of statins. Several authors indicated that lipophilic statins can be associated with CNS side-effects, such as sleep disturbances, by penetrating the blood–brain barrier (Roth et al 1992; Guillot et al 1993; Saheki et al 1994). The penetration of lipophilic statins into lens was associated with ocular problems in rats due to reduced cholesterol biosynthesis (Mosley et al 1989; de Vries and Cohen 1993; Reijneveld et al 1996). Such compounds might also induce myositis by its effect on muscle cells (Gadbut et al 1995). The hydrophilic pravastatin has lower uptake into non-hepatic cells (van Vliet et al 1995). This, together with its carrier-mediated active transport into hepatocytes (Yamazaki et al 1993; Yamazaki et al 1996), makes pravastatin selective for the liver (Sirtori 1993; Roth 1996; Hamelin & Turgeon 1998).

Since the publication of the relative lipophilicity data on pravastatin, lovastatin and simvastatin by Serajuddin et al (1991), three new statins, namely, fluvastatin, atorvastatin and cerivastatin, have been introduced to clinical use. However, no systematic study on the lipophilicity of these statins has been reported. Some investigators (Malinowski 1998; Otto & Schwandt 1998) classified these statins as lipophilic or hydrophilic without any supporting data. Moreover, the published reports are often contradictory. For example, Otto & Schwandt (1998) classified atorvastatin as lipophilic while Malinowski (1998) reported it to be insoluble in lipid, and despite the high partition coefficient reported for fluvastatin (Roth 1996) some authors (Otto & Schwandt 1998) have classified it as hydrophilic. The purpose of this study was to

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