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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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determine the apparent octanol–water partition coefficients ($P_{o/w}$) or distribution coefficients of fluvastatin, atorvastatin, and cerivastatin and compare them with those of pravastatin, lovastatin and simvastatin. One additional objective was to determine $P_{o/w}$ values of pravastatin, lovastatin and simvastatin at physiologically relevant pH 7·4. It is hoped that a comparison of the lipophilicity of all six statins currently in clinical use will provide a physicochemical basis for differentiating some of their pharmacological and clinical effects.

Materials and Method

Materials

All statins were obtained from Bristol-Myers Squibb Co. (Princeton, NJ). For lovastatin and simvastatin, which are marketed as lactone prodrugs, only the active hydroxy acid forms were used. All other chemicals and solvents were of analytical grade or better.

Partition coefficient experiments

The $P_{o/w}$ values of the hydroxy acid forms of various statins were determined by a method similar to that previously reported by Serajuddin et al (1991). Buffer solutions with pH 2 (0·01 M hydrochloric acid), pH 5 (0·1 M sodium acetate/acetic acid), pH 7 (0·035 M sodium phosphate) and pH 7·4 (0·035 M sodium phosphate) were prepared in double-distilled water. The ionic strength of each buffer was adjusted to 0·1 M with sodium chloride. Before use, octanol was saturated with individual buffers, and the aqueous media were saturated with octanol. For each determination, the drug was dissolved in a known volume of octanol in a volumetric flask and an appropriate volume of buffer was then added. The flask was shaken for 30 min at room temperature (~23°C) using a wrist-action shaker, the two layers were then separated and each layer was centrifuged at 6000 rev min^{-1} for 5 min. Samples from both buffer and octanol layers were analysed by HPLC. An octanol solution was diluted 25-fold with methanol before injection onto the HPLC column. The $P_{o/w}$ values were calculated from drug concentrations in octanol and aqueous phases. Each value represents the average of three determinations.

Results and Discussion

The $P_{o/w}$ and log $P_{o/w}$ values of various statins determined in this study, and those previously reported by Serajuddin et al (1991) are summarized in Table 1. The relative lipophilicity of different statins compared with pravastatin is also given. Fluvastatin showed very high partitioning into the octanol phase at pH 2 with a $P_{o/w}$ value of 11 100 and, due to the ionization of the carboxylic acid group present in the molecule (pK_a ~4·5), the $P_{o/w}$ value decreased with an increase in pH. Atorvastatin also had a high $P_{o/w}$ value for the unionized species at pH 2 (15 200), and as expected from the presence of a COOH group, the value decreased with an increase in pH. Despite a high degree of ionization, both fluvastatin and atorvastatin were lipophilic under physiological pH conditions (7 to 7·4), with $P_{o/w}$ values ranging from 47 to 16. Cerivastatin was even more lipophilic at pH 7 and 7·4, with $P_{o/w}$ values of 111 and 46, respectively. Cer-

Table 1. Apparent octanol–water partition coefficients ($P_{o/w}$) of hydroxy acid forms and relative lipophilicity of various HMG–CoA reductase inhibitors as a function of pH.

HMG–CoA reductase inhibitors	pH 2		pH 5		pH 7		pH 7·4	
	$P_{o/w}$ (log $P_{o/w}$)	Relative lipophilicity[a]	$P_{o/w}$ (log $P_{o/w}$)	Relative lipophilicity[a]	$P_{o/w}$ (log $P_{o/w}$)	Relative lipophilicity[a]	$P_{o/w}$ (log $P_{o/w}$)	Relative lipophilicity[a]
Pravastatin	152[b] (2·18)	1	20·9[b] (1·32)	1	0·59[b] (−0·23)	1	0·21 ± 0·01 (−0·67)	1
Lovastatin	11 000[b] (4·04)	72	1560[b] (3·19)	75	50[b] (1·70)	85	15 ± 1 (1·18)	71
Simvastatin	29 500[b] (4·47)	194	4200[b] (3·62)	201	115[b] (2·06)	195	65 ± 5 (1·81)	310
Fluvastatin	11 100 ± 2800 (4·05)	73	3100 ± 100 (3·49)	148	47 ± 4 (1·67)	80	22 ± 2 (1·34)	105
Atorvastatin	15 200 ± 600 (4·18)	100	2400 ± 100 (3·38)	115	41 ± 1 (1·61)	70	16 ± 1 (1·20)	76
Cerivastatin	13 ± 1 (1·11)	0·09	1800 ± 100 (3·26)	86	111 ± 3 (2·05)	188	46 ± 1 (1·66)	219

Values are mean ± s.d. of three determinations. [a]Relative lipophilicity with respect to pravastatin. [b]From Serajuddin et al (1991), with permission.

ivastatin had the highest $P_{o/w}$ value at pH 5, which decreased at pH 2 due to protonation of the pyridine moiety present in the molecule. The experimental log $P_{o/w}$ value of atorvastatin at pH 2 (unionized species) was in good agreement with the calculated log P value (CLOGP) of atorvastatin reported by Roth (1996) (4·18 vs 4·06). There was a difference between the log $P_{o/w}$ value of fluvastatin found in this study and the CLOGP value reported by Roth (1996) (log $P_{o/w}$ 4·05 at pH 2 vs CLOGP of 3·24). Thus, fluvastatin appears to be at least six-times more lipophilic than has been reported in the literature. The experimental log $P_{o/w}$ value of fluvastatin at pH 7, however, does agree with the value reported by Lennernás & Fager (1997) (1·7 vs 1·5) at the same pH.

In this study, the relative lipophilicity of various statins over the physiological pH range of 7 to 7·4 was: simvastatin ≈ cerivastatin > lovastatin ≈ fluvastatin ≈ atorvastatin ≫ pravastatin. Pravastatin is 70- to 300-times more hydrophilic than the other statins, which are lipophilic. Roth (1996) reported that lipophilic statins penetrate peripheral tissues, directly inhibit tissue sterol synthesis and produce direct effects on cell proliferation, cholesterol esterification, intimal hyperplasia and atherosclerotic lesion formation. These effects on peripheral tissues were not found with the hydrophilic pravastatin, and thus its activity is targeted to hepatic cells. Among the lipophilic statins, simvastatin and cerivastatin are about 2·5- to 4-times more lipophilic than lovastatin, fluvastatin and atorvastatin. There is no clear evidence in the literature whether such a relatively small difference in lipophilicity has any differentiating effects on their activity.

References

de Vries, A. C. J., Cohen, L. H. (1993) Different effects of hypolipidemic drugs pravastatin and lovastatin on the cholesterol biosynthesis of the human ocular lens in organ culture and on the cholesterol content of the rat lens in vivo. Biochim. Biophys. Acta 1167: 63–69

Gadbut, A. P., Caruso, A. P., Galper, J. B. (1995) Differential sensitivity of C_2–C_{12} striated muscle cells to lovastatin and pravastatin. J. Mol. Cell. Cardiol. 27: 2397–2402

Guillot, F., Misslin, P., Lamaire, M. (1993) Comparison of fluvastatin and lovastatin blood-barrier transfer using in vitro and in vivo methods. J. Cardiovasc. Pharmacol. 21: 339–346

Hamelin, B. A., Turgeon, J. (1998) Hydrophilicity/lipophilicity: relevance for the pharmacology and clinical effects of HMG–CoA reductase inhibitors. Trends Pharmacol. Sci. 19: 26–37

Lennernás, H., Fager, G. (1997) Pharmacodynamics and pharmacokinetics of the HMG–CoA reductase inhibitors: similarities and differences. Clin. Pharmacokinet. 32: 403–425

Malinowski, J. M. (1998) Atorvastatin: a hydroxymethylglutaryl-coenzyme A reductase inhibitor. Am. J. Health Syst. Pharm. 55: 2253–2267

Mosley, S. T., Kalinowski, S. S., Schafer, B. L., Tanaka, R. D. (1989) Tissue-selective acute effects of inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase on cholesterol biosynthesis. J. Lipid Res. 30: 1411–1420

Otto, C., Schwandt, P. (1998) Gibt es Unterschiede zwischen verschiedenen Statinen? Internist 39: 987–993

Reijneveld, J. C., Koot, R. W., Bredman, J. J., Joles, J. A., Bár, P. R. (1996) Differential effects of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors on the development of myopathy in young rats. Pediatr. Res. 39: 1028–1035

Roth, B. D. (1996) The impact of tissue selectivity on the antiatherosclerotic activity of HMG-CoA reductase inhibitors. Curr. Pharm. Des. 2: 139–154

Roth, B. D., Bocan, T. M. A., Blankley, C. J., Chucholowski, A. W., Creger, P. L., Creswell, M. W., Ferguson, E., Newton, R. S., O'Brien, P, Picard, J. A., Roark, W. H., Sekerke, C. S., Sliskovic, D. R., Wilson, M. W. (1991) Relationship between tissue selectivity and lipophilicity for inhibitors of HMG–CoA reductase. J. Med. Chem. 34: 463–466

Roth, T., Richardson, G. R., Sullivan, J. P., Lee, R. M., Merlotti, L., Roehrs, T. (1992) Comparative effects of pravastatin and lovastatin in nighttime sleep and daytime performance. Clin. Cardiol. 15: 426–432

Saheki, A., Terasaki, T., Tamai, I., Tsuji, A. (1994) In vivo and in vitro blood-brain barrier transport of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors. Pharm. Res. 11: 305–311

Serajuddin, A. T. M., Ranadive, S. A., Mahoney, E. M. (1991) Relative lipophilicities, solubilities, and structure-pharmacological considerations of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, pravastatin, lovastatin, mevastatin, and simvastatin. J. Pharm. Sci. 80: 830–834

Sirtori, C. R. (1993) Tissue selectivity of hydroxymethylglutaryl coenzyme A (HMG CoA) reductase inhibitors. Pharmacol. Ther. 60: 431–459

van Vliet, A. K., van Thiel, G. C. F., Huisman, R. H., Moshage, H., Yap, S. H., Cohen, L. H. (1995) Different effects of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors on sterol synthesis in various human cell types. Biochim. Biophys. Acta 1254: 105–111

Yamazaki, Y., Suzuki, H., Hanano, M., Tokui, T., Komai, T., Sugiyama, Y. (1993) Na^+-independent multispecific anion transporter mediates active transport of pravastatin into rat liver. Am. J. Physiol. 246: G36–G44

Yamazaki, Y., Kobayashi, K., Sugiyama, Y. (1996) Primary active transport of pravastatin across the liver canalicular membrane in normal and mutant Eisai hyperbilirubinemic rats. Biopharm. Drug Dispos. 17: 607–62