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Novel delivery systems of atorvastatin should be evaluated for pharmacodynamics instead of pharmacokinetics

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Sir,

This letter is written in response to the recent investigation entitled 'Preparation and evaluation of self-microemulsifying drug delivery systems (SMEDDS) containing atorvastatin' authored by Shen & Zhong published in September 2006 issue. The letter tries to highlight the importance of assessment of novel delivery systems of atorvastatin, such as SMEDDS, for their pharmacodynamic effect instead of pharmacokinetics.

Atorvastatin, like all other statins, is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, which catalyses the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in sterol biosynthesis (Malhotra & Goa 2001). The low oral bioavailability (~14%) of atorvastatin is mainly due to presystemic clearance by CYP3A4 in gastrointestinal mucosa and hepatic first-pass metabolism and, to some extent, P-glycoprotein-mediated efflux (Lennernas 2003). These problems necessitate design of novel delivery strategies, such as self-microemulsifying drug delivery systems (SMEDDS), to improve the oral bioavailability of atorvastatin.

The SMEDDS described by Shen & Zhong resulted in a 1.4- to 1.5-fold improvement in the various pharmacokinetic parameters, such as C_{max}, AUC and bioavailability, as compared to the conventional tablets. It is important to understand the potential mechanism for the improvement in the pharmacokinetic parameters of atorvastatin observed with SMEDDS although these reasons are not discussed in detail by the authors. The improvement in bioavailability of the therapeutic agent observed with SMEDDS is considered to be an interplay of several factors, such as inhibition of CYP3A4 or P-glycoprotein efflux, improvement in the lymphatic transport, increasing membrane fluidity to facilitate transcellular absorption and opening of tight junctions to increase paracellular transport (Porter & Charman 1997; O'Driscoll 2002; Holm et al 2003). As atorvastatin is completely absorbed after oral administration (Lennernas 2003), the main factors that would have been responsible for the increase in its bioavailability by SMEDDS are inhibition of CYP3A4 and improvement in the lymphatic transport.

The SMEDDS described by Shen & Zhong include Cremophore RH 40 (polyethoxylated castor oil derivative), Labrafil 1944 CS, Labrafac (medium chain triglycerides) and propylene glycol. Cremophores (polyethoxylated castor oil derivatives) are known to inhibit the metabolism of CYP3A4 susbtrates like midazolam (Gonzalez et al 2004). Cremophore RH 60-based microemulsions (analogue of Cremophore RH 40) are known to improve the oral bioavailability of CYP3A4 substrates like nitrendipine (Kawakami et al 2002). Recently, Labrafil 1944 CS-based SMEDDS have been shown to improve the oral bioavailability of carvedilol, a CYP2D6 and CYP3A4 substrate (Wei et al 2005). Medium-chain triglycerides are known to improve the lymphatic transport of therapeutic agents (Porter & Charman 1997; O'Driscoll 2002; Holm et al 2003). Hence, we believe that the improvement in the pharmacokinetic parameters of atorvastatin SMEDDS could be a combined effect of inhibition of CYP3A4-induced presystemic metabolism and improved lymphatic transport.

However, it should be noted that atorvastatin, like all the other statins, acts in the liver to demonstrate its lipid-lowering action (Stancu & Sima 2001). It is also noteworthy that plasma concentrations of atorvastatin acid and its metabolites do not correlate with the reduction in LDL cholesterol, indicating that there is a poor pharmacokinetic–pharmacodynamic relationship. This issue has adequately been discussed by Lennernas (2003). Therefore, to improve the therapeutic efficacy of atorvastatin, it is imperative that the effective concentration of atorvastatin be increased in the liver instead of the plasma. Thus, in the case of atorvastatin, increase in the

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bioavailability does not guarantee improved pharmacodynamics or therapeutic efficacy. In view of this, novel oral delivery systems such as SMEDDS should be evaluated for their ability to improve the pharmacodynamics of atorvastatin in a suitable animal model such as hypercholesterolaemic rats.

Nonetheless, the assessment of pharmacokinetic parameters of atorvastatin from SMEDDS is important, as the increased plasma concentration of atorvastatin may be associated with the increased risk of myopathy and rhabdomyolysis (Tomlinson et al 2001). In such cases, dose adjustment (or reduction) may be required. Finally, the ideal delivery strategy for atorvastatin would be one that would decrease its intestinal and hepatic metabolism and improve its targeting to liver. These features are very difficult to meet with existing novel oral delivery systems. Conjugation of atorvastatin to ligands that have high affinity to asialoglycoproteins may be a novel approach to improve liver targeting and ultimately therapeutic efficacy of atorvastatin, but it has not been reported to date.

Sincerely,

Abhijit A. Date and Mangal S. Nagarsenker

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