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Effects of single nucleotide polymorphisms and haplotypes of the *SLCO1B1* gene on the pharmacokinetic profile of atorvastatin in healthy Macedonian volunteers

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Abstract:

OATP1B1 is an influx transporter known to mediate the uptake of various endogenous compounds and xenobiotics. Several sequence variations have been discovered in the *SLCO1B1* gene encoding OATP1B1. The aim of this study was to investigate the effects of *SLCO1B1* polymorphisms on the pharmacokinetics of atorvastatin in healthy volunteers of Macedonian origin. Twenty three participants, genotyped for *SLCO1B1* c.388A > G, c.521T > C, c.571T > C, c.597C > T, c.1086C > T, c.1463G > C and c.\*439T > G polymorphisms using TaqMan allelic discrimination assay, ingested a single 80 mg dose of atorvastatin. The plasma concentrations of atorvastatin were measured for 48 h using Tandem Liquid Chromatography-Mass Spectrometry, LC-MS-MS, and the peak plasma concentration (Cmax), time to peak plasma concentration (Tmax), elimination half-life (t1/2), constant rate of elimination (kel), mean residence time (MRT, expo), volume of distribution (Vd/kg), clearance (CL/kg), area under curve AUC0-48h and AUC0-∞ were determined. Our data confirmed that the *SLCO1B1* gene is highly polymorphic, with a frequency of the c.521T > C single-nucleotide polymorphism (SNP) being the lowest (app. 15%) and of all other SNPs alleles above 40%. Exceptions were c.1463G > C and c.1086C > T SNPs for which variant alleles were not identified. The strongest correlation was observed between the c.521T > C and c.571T > C SNPs pair. The haplotype analysis revealed 10 different haplotypes, with *\*1J/\*1K/\*1L* being the dominant, with a frequency of app. 40%. The haplotype *\*15/\*16/\*17*, containing both variant alleles of the functionally most distinguished SNPs, c.388A > G and c.521T > C, occurred with a frequency of 13%. However, *\*15/\*16/\*17* homozygotes were not identified in the study group. In this study, no significant differences in the kel, t1/2, Cmax, Tmax, AUC0-48h, AUC0-∞, MRT expo, Vd and CL between the carriers of different c.388A > G, c.597C > T and c.\*439T > G genotypes were observed. Subject with a variant allele C in the c.521T > C SNP, c.521CC genotype, had markedly higher values for Cmax and AUC0-48h, 140% and 67%, respectively, in comparison with the carriers of the c.521TT genotype. Also, the carriers of the variant allele C at c.571T > C SNP, c.571 CC genotype, had 55% and 43% lower mean Cmax and AUC0-48h in comparison with the carrier of c.571TT. These differences lacked statistical significance due to the size of the sample. In addition, no significant differences in the pharmacokinetic parameters of atorvastatin between the *\*15/\*16/\*17* heterozygotes and *\*15/\*16/\*17* non-carriers were observed. In conclusion, this extensive analysis of the effect of *SLCO1B1* polymorphisms on the pharmacokinetic profile of atorvastatin showed that c.521T > C and c.571T > C SNPs may affect the inter-individual response to atorvastatin. Additional studies, with a large sample size, are needed to confirm this finding.

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