HRVATSKI KONGRES FARMACIJE
S MEĐUNARODNIM SUDJELOVANJEM

CROATIAN CONGRESS ON PHARMACY
WITH INTERNATIONAL PARTICIPATION

Farmaceutska izvrsnost u službi zdravlja
Pharmaceutical Excellence Dedicated to Health

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PHARMACOKINETIC PROFILE OF ATORVASTATIN IN RELATION TO SLCO1B1 C.521T>C AND C.388A> VARIANTS IN HEALTHY VOLUNTEERS
OVISNOST FARMAKOKINETIČKOG PROFILA ATORVASTATINA O SLCO1B1 C.521T>C AND C.388A> VARIJACIJAMA U ZDRAVIH DOBROVOLJACA

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OATP1B1 is an influx transporter known to be implicated as important determinant of the intestinal absorption and hepatobiliary clearance of hydrophilic statins, such as atorvastatin. Several sequence variations have been discovered in the *SLCO1B1* gene encoding OATP1B1, with some of them, such as c.388A>G (p.Asn130Asp) and c.521T>C (Val174Ala) associated with increased and reduced OATP1B1 activity, respectively. The aim of the study was to investigate the effects of these two *SLCO1B1* SNPs on the pharmacokinetics of atorvastatin. Twenty three healthy Macedonian volunteers were genotyped for these two SNPs using TaqMan allelic discrimination assay. After ingestion of a single dose of 80 mg, the plasma concentrations of atorvastatin were mea-sured for 48 h using LC-MS-MS and the C_{max}, T_{max}, $t_{1/2}$, k_{el}, *MRT, Vd, CL,* $AUC_{0\text{-}48h}$ and $AUC_{0\text{-}\infty}$ were determined.

Allele frequencies of the variants were in Hardy-Weinberg Equilibrium, with 39 and 15 % for c.388A>G and c.521T>C, respectively. Low correlation between this SNP pair (R^2 = 0,137; D' = 0,700) was observed. No significant differences in the k_{el}, $t_{1/2}$, C_{max}, T_{max}, $AUC_{0\text{-}48h}$, $AUC_{0\text{-}\infty}$, *MRT, Vd* and *CL* between the carriers of different c.388A>G genotypes were observed. Subject with a c.521CC genotype had markedly higher values for C_{max} and $AUC_{0\text{-}48h}$, 140 and 67 %, respectively, in comparison with the carriers of the c.521TT genotype. These differences lacked statistical significance due to the size of the sample. In addition, the effects of *SLCO1B1* diplotypes on pharmacokinetic parameters were investigated comparing the effects of *15 non-carriers (n = 17) and *15 heterozygotes (n = 6), as *15 homozygotes were not identified in the study. The dominant effect of the c.521T>C SNP was confirmed. Marginal statistical differences were observed in C_{max}, $AUC_{0\text{-}48h}$, $AUC_{0\text{-}\infty}$ and CL, with C_{max} and $AUC_{0\text{-}\infty}$ 45% (p= 0.062) and 38% (n = 0.09) higher, and CL 30% (p = 0.07) lower in *15 heterozygotes/carriers of c.521Callele. Additional studies, with a large sample size are needed to confirm this finding.