



ROVINJ

21.-24. svibnja 2015. / May 21-24, 2015
Kongresni centar Cap Aureo / Congress Centre Cap Aureo

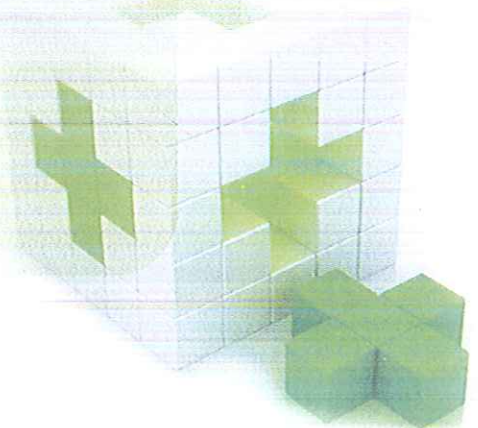
HRVATSKI KONGRES FARMACIJE S MEĐUNARODNIM SUDJELOVANJEM

CROATIAN CONGRESS ON PHARMACY WITH INTERNATIONAL PARTICIPATION

Farmaceutska izvrsnost u službi zdravlja
Pharmaceutical Excellence Dedicated to Health

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FARMACEUTSKO-BIOKEMIJSKIM FAKULTETOM SVEUČILIŠTA U ZAGREBU
FACULTY OF PHARMACY AND BIOCHEMISTRY, UNIVERSITY OF ZAGREB
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AGENCIJOM ZA LIJEKOVE I MEDICINSKE PROIZVODE REPUBLIKE HRVATSKE
CROATIAN AGENCY FOR MEDICINAL PRODUCTS AND MEDICAL DEVICES

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MINISTARSTVA ZDRAVLJA REPUBLIKE HRVATSKE
MINISTRY OF HEALTH OF THE REPUBLIC OF CROATIA

i / and
MINISTARSTVA ZNANOSTI, OBRAZOVANJA I SPORTA REPUBLIKE HRVATSKE
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with International Participation

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Book of Abstracts

21. – 24. svibnja 2015.
Kongresni centar Cap Aureo, Rovinj, Hrvatska

May 21 to 24, 2015
Congress Centre Cap Aureo, Rovinj, Croatia

Nakladnik / Published by
Hrvatsko farmaceutsko društvo
Croatian Pharmaceutical Society

Za nakladnika / For the Publisher
Maja Jakševac Mikša

Urednica knjige sažetaka / Book of Abstracts Editor
Branka Zorc

Urednica programa / Programme Editor
Maja Jakševac Mikša

Dizajn naslovnice / Cover design
Anita Galić

Prijelom i tisak / Layout and print
Dizajn Studio ADI d.o.o.

P/FZ-51

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

A. Daka¹, A. Dimovski¹, A. Kapedanovska¹, M. Vavlukis², A. Eftimov¹,
N. Labachevski³, K. Jakjovski³, N. Matevska Geshkovska¹, D. Nebija⁴,
K. Mladenovska¹

¹ Faculty of Pharmacy, Blv. Mother Theresa 47, Skopje, Republic of Macedonia

² University Clinic of Cardiology, Blv. Mother Theresa 17, Skopje, Republic of Macedonia

³ Faculty of Medicine, St. 50th Division 6, Skopje, Republic of Macedonia

⁴ Faculty of Medicine, Mother Theresa street, Prishtina, Kosovo

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 measured for 48 h using LC-MS-MS and the C_{max} , T_{max} , $t_{1/2}$, k_{el} , MRT , Vd , CL , AUC_{0-48h} and $AUC_{0-\infty}$ 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_{0-48h} , $AUC_{0-\infty}$, 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_{0-48h} , 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_{0-48h} , $AUC_{0-\infty}$ and CL , with C_{max} and $AUC_{0-\infty}$ 45% ($p = 0.062$) and 38% ($n = 0.09$) higher, and CL 30% ($p = 0.07$) lower in *15 heterozygotes/carriers of c.521C allele. Additional studies, with a large sample size are needed to confirm this finding.