

PHARMACOKINETICS OF METFORMIN IN 21 HEALTHY PARTICIPANTS AFTER 500 MG SINGLE ORAL DOSE ADMINISTRATION

Authors: Dainis Kalnacs¹, Linda Zaharenko², Ilze Konrade³, Aivars Lejnieks³, Valdis Pirags^{4,5}, Dace Hartmane⁶, Solveiga Grinberga⁶, Osvalds Pugovics⁶, Janis Klovinš²

¹ Faculty of Medicine, Riga Stradins University, Riga

²Latvian Biomedical Research and Study Center, Riga

³*Riga East Clinical University Hospital "Gailezers", Riga*

⁴Department of Endocrinology, Pauls Stradins Clinical University Hospital, Riga

⁵Faculty of Medicine, University of Latvia, Riga

⁶Latvian Institute of Organic Synthesis, Riga

Key words: Metformin, Pharmacokinetics, LC-MS/MS

Introduction. Metformin is widely used drug to treat patients with type 2 diabetes mellitus (T2DM). To get the most beneficial results from therapy with metformin, it must have individualized prescription.

Aims. The aim of our study is to identify variability between individuals according to pharmacokinetic (PK) parameters of metformin in plasma, erythrocytes and urine, and use obtained data to individualize selection of antidiabetic therapy.

Methods. 21 healthy volunteers (6 men and 15 women, age range 22-49) were investigated after a single oral dose of 500mg of metformin (Metforal Berlin Chemie). For analysis of PK parameters venous blood and urine samples were taken in 7 time points up to 24 h after drug administration according to the study protocol (Ethical review Nr.201212-10L). All plasma,

urine and erythrocyte samples were stored at -20 C until determination of metformin by using liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay.

Results. Especially for our study liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay was developed and used to determine quantity of metformin in plasma, erythrocytes and urine. C_{max} (maximum observed concentration) and t_{max} (time point of observed C_{max}) and AUC_{0-24} (area under curve) were both obtained directly from the measured data. $C_{max/plasma}=395,55-1294,13$ ng/mL ($704,075\pm395,55$), $t_{max/plasma}=1-3$ h ($2,15\pm0,91$), $AUC_{0-24/plasma}=2631,9-9396,8$ ng*h/mL ($5157,9\pm1478$). $C_{max/erytr.}=84,32-290,70$ ng/mL ($158,5\pm61,2$), $t_{max/erytr.}=6-10$ h ($9,6\pm1,2$). $C_{max/urine}=66,42-1025,42$ μ g/mL ($373,685\pm270,398$), $t_{max/urine}=3-10$ h ($5,65\pm2,8$). Serum creatinine = $73,67\pm11,73$ μ mol/L. $AUC_{0-\infty}$, (area under curve from time 0 extrapolated to infinite time), k (elimination rate constant), elimination half-life ($t_{1/2}$), Vd (volume of distribution), Cl (clearance), bioavailability (F) were calculated by using standard equations. Results show great diversity of obtained pharmacokinetic parameters.

Conclusions. As results show variability between individuals according to PK parameters of metformin, the next step will be to combine results with gene variants coding metformin transporters to identify novel markers of metformin individualized therapy.