Abstract

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Title of rigorous thesis: Interaction of selected anti-HCV drugs with placental OCTN2 transport protein.

The aim of this rigorous work was to test the interaction of paritaprevir and daclatasvir with the placental OCTN2 transporter, which ensures the transport of L-carnitine as a cofactor of the fatty acid oxidation process to obtain sufficient energy for correct intra-arterial fusion growth. No drugs in this group have been approved for the treatment of chronic hepatitis C in pregnancy, therefore examining their effect on the transport of L-carnitine via OCTN2 can create certain image concerning to the fetal and maternal safety.

In the first part of my thesis the transport and accumulation of radioactively labeled L-carnitine via monolayers of BeWo b30 cells in the presence of paritaprevir and daclatasvir was assayed and the concentration of radiolabeled L-carnitine inside the cell layer.

In the second part of my thesis we focused on the evaluation of the presence of paritaprevir and daclatasvir on its gene expression of the OCTN1 and OCTN2 carnitine transporters (or their coding genes *SLC22A4* and *SLC22A5*) by qRT-PCR.

The results of the transport studies only suggested potential effects of both substances on the transport of carnitine by OCTN2, we did not see a more convincing statistically significant effect on the transfer of L-carnitine across the placenta and accumulation in the trophoblast layer, indicating the relative safety of these substances from the point of view effects of carnitine homeostasis in pregnancy. Expression studies of the carnitine transporters then revealed an indirect interaction of paritaprevir with *SLC22A4* and *SLC22A5* at 72-hour exposure, which temporarily upregulated gene expression on both genes. Based on data available, the safety of daclatasvir and paritaprevir during pregnancy with regard to L-carnitine in the placenta can be estimated as they do not reduce the amount of this cofactor for

the fatty acid oxidation that is essential for healthy fetal development and prevention of maternal complications during pregnancy.

Keywords

Hepatitis C; paritaprevir; daclatasvir; L-carnitine; OCTN2 transporter; BeWo b30 cells