Abstract

In recent years, tyrosine kinase inhibitors have been more and more used for the targeted cancer therapy, due to their ability to disrupt intracellular signalling pathways associated with the development of tumours. Cabozantinib is the tyrosine kinase inhibitor which has been approved for the treatment of thyroid cancer and it is also effective against several other types of cancer. However, multiple drugs combination is often used in anticancer therapy, which may result in their cytochrome P450-mediated interactions. Although this may affect the therapeutic effect of the drugs and cause adverse effects on the organism, very little is known about the effect of cabozantinib on biotransformation enzymes. Therefore, the effect of cabozantinib not only alone but also in combination with the known cytostatic ellipticine on the expression and the activity of cytochromes P450 1A1, 1A2 and 1B1 in rat liver and kidney in vivo was studied in this work. The gene expression was determined by quantitative PCR, the amount of protein was studied by Western blotting and consecutive immunodetection. The enzyme activity was studied using specific marker reactions, 7-ethoxyresorufin O-deethylation for CYP1A1, 7-methoxyresorufin O-demethylation for CYP1A2 and 17β-estradiol 4-hydroxylation for CYP1B1.

Our results showed that cabozantinib is a weak inducer of CYP1A1 and 1A2 in the liver that was reflected in increased gene and protein expression as well as increased enzyme activity of these two CYP isoforms. A weak induction potential on CYP1B1 is also not excluded. In this work, the significant induction potential of ellipticine on CYP1A1, 1A2 and 1B1 in rat liver at all monitored levels was further confirmed. Co-treatment of cabozantinib with ellipticine increases the induction potential of ellipticine on CYP1A1 and 1A2 expression. The inducing effect of cabozantinib could result in changes of metabolism of co-administered drugs biotransformed by these enzymes, and could affect their therapeutic effect and cause possible adverse effects on the organism.

Key words: tyrosine kinase inhibitors, cabozantinib, ellipticine, cytochromes P450, expression, activity