The effect of chronic treatment with asenapine and iloperidone on the expression and activity of cytochrome P450 in the brain and liver

Schizophrenia is a serious mental illness, which is currently afflicted by more than 400,000 people in Poland. This psychosis is characterized by a disorder of perception of the self and the surrounding world, thinking and feeling emotions. Despite many years of research and attempts to develop increasingly effective drugs, there is still no proper pharmacotherapy of this disease. Modern drugs used in people suffering from schizophrenia (atypical neuroleptics), despite their wide profile of action, require administration to patients for a long period of time (many months or even years). Hence, these drugs may have a significant effect on the expression and activity of cytochrome P450 (CYP), which may translate into the metabolism of drugs and physiologically important endogenous compounds, not only in the liver, but also other organs and tissues, including the brain.

Cytochrome P450 is a group of isoenzymes responsible for the metabolism of most drugs and other xenobiotics (pro-mutagens and pro-carcinogens) and endogenous substances such as cholesterol, bile acids, steroids, neurotransmitters and vitamins. The highest concentration of these enzymes is found in the liver, but they have also been identified in other tissues, such as the brain, lungs and kidneys. Changes in cytochrome P450 activity may prove to be important not only for pharmacotherapy, but also for the physiological state of the body.

During therapy of schizophrenia neuroleptics may be combined with other psychotropics or with drugs belonging to other pharmacological groups (eg. with cardiovascular drugs or antibiotics), which patients may take simultaneously. It may lead to pharmacokinetic interaction at the level of cytochrome P450-catalyzed metabolism, which may be dangerous for patients. Due to the different qualitative and quantitative composition of cytochrome P450 isoenzymes in the brain and liver as well as differences in enzyme regulation in individual organs or tissues, it seems advisable to investigate the effect of prolonged administration of new atypical neuroleptics on cytochrome P450 expression not only in the liver, but also in the brain, i.e. the target of their therapeutic action. The brain metabolism of xenobiotics (including drugs) and endogenous compounds with the participation of cytochrome P450 is a new and relatively poorly understood area of research. But it is worth of special interest due to the possibility of explaining the basics of individual variations in response to drugs affecting the central nervous system and the origins of adverse side-effects of these drugs, which can lead to neurodegenerative changes and be the cause of brain pathology.

The aim of these project is to investigate the effect of prolonged administration of the atypical neuroleptics − asenapine and iloperidone on the expression and activity of cytochrome P450 isoenzymes of the CYP1A, CYP2D and CYP3A subfamilies, which are engaged in the metabolism of steroids, neurotransmitters and drugs. After administration of pharmacological doses of asenapine or iloperidone to rats, the activity and expression (protein and mRNA levels) of cytochromes P450 will be measured in the liver and selected brain structures that are responsible for the therapeutic or side-effects of the neuroleptics.

The results of this project should provide valuable data allowing to predict metabolic interactions (at the level of cytochrome P450) between the investigated neuroleptics and other drugs taken simultaneously by schizophrenic patients. In addition, the planned studies may reveal addition pharmacological targets of the two novel neuroleptics in the brain, involving their effects on brain metabolism of endogenous neuroactive substrates.