

TITLE

PHARMACOKINETIC SIGNIFICANCE OF DIABETES-INDUCED CHANGES IN CYP3A ACTIVITY

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CYP3A is a well characterized isozyme from the CYP family. In humans, it is predominantly expressed in adult liver and small intestine. This enzyme is responsible for the metabolism of approximately 60% of all therapeutic drugs and hence, the prevailing activity of this enzyme is a deciding factor for the bioavailability of orally administered drug, if it is metabolized by this enzyme. Literature indicates that the activity CYP3A is often modulated in several pathological conditions either due to the disease itself or the drugs used in that condition. Incidentally, diabetic subjects exhibit low CYP3 activity; insulin also plays an important role in the expression of CYP; flavonoids that are used as add-on therapy in diabetes are CYP3A inhibitors. The bioavailability of oral antidiabetic agents such as Pioglitazone and Nateglinide is considerably determined by their first pass metabolism taking place in the liver and small intestine wherein microsomal monooxygenases - cytochrome P450 (CYP, EC 1.14.14.1) has profound role to play. In this situation, disease or drug induced alterations in CYP3A activity are likely to alter the bioavailability of these oral antidiabetic agents, taking their levels beyond the therapeutic levels. Hence, the experiments were carried out to understand the influence of hyperglycemia; and flavonoid treatment on CYP3A activity and its pharmacokinetic significance. These studies revealed that diabetic rats as well as flavonoid treated non-diabetic rats exhibited low CYP3 activity and higher blood levels of Pioglitazone and Nateglinide. The findings emphasize the need to assess CYP3A activity for better therapeutic drug monitoring.