



PIC QUESTION OF THE WEEK: 9/14/09

Q: What role does p-glycoprotein play in drug-drug interactions?

A: P-glycoprotein (P-gp) is a cell surface protein that actively regulates the transfer of drugs and other substrates from the intracellular to the extracellular environment. It is commonly found in gastrointestinal (GI), renal, hepatic, cardiac, brain, nerve, and reproductive tissue. P-gp serves to remove toxic substances and drugs from these tissues and appears to play a significant role in the ability of tumor cells to develop resistance to chemotherapy. P-gp actively limits drug *absorption* from the GI tract, *excretion* of metabolites into bile and the intestinal lumen, and the *renal clearance* of many compounds. It also restricts drug entry into the CNS, blood cells, placenta, etc. In summary, P-gp activities can result in a decrease in the bioavailability; distribution, disposition, and serum levels of many drugs. Like the CYP-450 enzymes, drugs that inhibit or induce P-gp function can lead to significant drug interactions. Several reports indicate that co-administration of specific drugs or herbal supplements that inhibit or induce P-gp can result in pharmacokinetic interactions resulting in adverse reactions or sub-therapeutic drug levels. For example, induction of P-gp by rifampicin leads to a decrease in plasma concentration of digoxin, whereas inhibition of P-gp by quinidine increases the levels of some cardiac glycosides. It is well established that macrolides are potent inhibitors of both P-gp and CYP3A4. In one study, the co-administration of macrolides led to a significant increase in serum levels of digoxin compared to controls. The study also showed significant inhibition of P-gp-mediated digoxin transport. Digoxin is not metabolized by CYP3A4, thus leading to the conclusion that the significant increase in digoxin levels was due to the inhibition of P-gp. Examples of P-gp *inhibitors* include antiarrhythmics, antineoplastic agents, macrolides, antidepressants, PPIs, cyclosporine, and anti-retroviral agents. Clotrimazole, midazolam, nifedipine, phenobarbital, and phenytoin can *induce* this transmembrane glycoprotein. In cancer chemotherapy, some interactions involving P-gp may be beneficial as they can enhance intracellular drug concentrations resulting in greater cell kill. Our understanding of the physiologic effects of this unique protein is expanding and the significance of its function in drug interactions continues to be evaluated.

References:

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