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Commentary

Potential Role of P-Glycoprotein in Affecting Hepatic Metabolism of Drugs

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P-glycoprotein (P-gp) is a transmembrane efflux transporter that has many important functions in drug therapy, disposition and metabolism (1–6). We recently suggested (7) that P-gp in the liver may be very critical to the metabolism of tacrolimus, a P-gp substrate, in normal mice since its mean hepatic intrinsic clearance was reduced by 10-fold in P-gp knockout mice compared to normal mice (7). This commentary extends our earlier (7) findings by reporting similar trends of the P-gp effect from our extensive review of many excellent studies on kinetics of many extensively metabolized drugs in normal and P-gp knockout mice.

As shown in Table I, in addition to tacrolimus, total clearances of intact vinblastine (8) and paclitaxel (9) were also markedly reduced in knockout mice after intravenous dosing. Total plasma radioactivity levels at certain hours from erythromycin (10), cyclosporine (11) and quinidine (12) were also much higher in knockout mice. The above data (Table I) may suggest that the hepatic metabolic clearances of these drugs may be significantly reduced in mice lacking P-gp. However, one should caution that the fate of metabolites may complicate the above interpretation when total radioactivities were measured (10–12). Our finding on erythromycin appears to be different from results based on the erythromycin breath test indicating an increase in hepatic metabolism of the drug in the P-gp knockout mice (personal communication from Erin G. Schuetz). The reason for this apparent difference remains to be studied. Also, in view of apparent reduced clearance of erythromycin in the P-gp knockout mice, the appropriateness of using erythromycin breath test for CYP3A activity was recently questioned (1).

Similar trends are also observed for five drugs after oral administration (Table II). The pattern of intravenous and oral data for erythromycin appears to be similar to that reported for tacrolimus (3). Although these increased plasma levels might be attributed to enhanced (probably up to six-fold and seven-fold for rifampin and erythromycin, respectively, based on linear kinetics) oral absorption due to absence of P-gp in the intestine (5,10), this is probably not likely to be a major factor since rifampin is rapidly and completely absorbed in fasted humans and at least 70% of erythromycin was absorbed in rats (13). The much higher plasma radioactivities of indinavir, nelfinavir and saquinavir in knockout mice (Table I) were attributed to enhanced drug absorption due to the absence of intestinal P-gp since no increases in plasma level were observed following intravenous administration (14). Because total clearances for these drugs in rodents are known to be near hepatic blood flow, intravenous blood or plasma data may not be sensitive to detect modest changes in hepatic clearance or extraction (e.g., a change from 0.99 to 0.95 of the extraction ratio may result in about 4% decrease in hepatic clearance). On the other hand, oral plasma or bioavailability data may be more sensitive (in the above example, the bioavailability may increase five-fold assuming no effect on absorption) to reflect any change in hepatic intrinsic clearance (15). Thus, intestinal absorption may not be a major factor in their low bioavailability.

Since the absence of P-gp in knockout mice may indirectly result in reduced apparent hepatic intrinsic clearance of drugs due to potential inhibition of metabolism by accumulated metabolites (7), this may then trigger a natural defense mechanism by increasing the production of hepatic enzymes as having been elegantly demonstrated using mice and human cell lines (5). The enhanced enzyme production has also been validated *in vitro* by the increased rate of midazolam hydroxylation (5); in such situation the impact of the P-gp knockout mice on the rate of metabolism may be quite different for some drugs depending on whether one examines the *in vivo* system (reduction in rate) or the *in vitro* system (increase in rate probably due to the lack of inhibition by metabolite in the much diluted medium). Some reduced hepatic clearances in knockout mice apparently were not entirely due to reduced biliary secretion (7; Table I). For tacrolimus, the potential of biliary secretion of metabolite(s) and its build-up in hepatocytes may account for reduced hepatic clearance observed. For cyclosporine (11) there was unexpectedly a trend for increased biliary secretion

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Table I. Effect of Deficiency of P-Glycoprotein in the Knockout Mice on the Total Clearance (CL) or Plasma Level (C_p) and Biliary Secretion of Six Extensively Metabolized Drugs After Intravenous Administration Compared to the Normal Mice

Drug	Effect on CL or C_p	Effect on biliary secretion	Reference
Tacrolimus	65% decrease in CL	No[ca]	7
Vinblastine	34% decrease in CL	No	8,16
Paclitaxel	51% decrease in CL	No	9
Erythromycin	50% increase in C_p[b] at 1 hr	Unknown	10
Cyclosporine	90% increase in C_p[b] at 24 hr	Increase[c]	11
Quinidine	300% increase in C_p[b] at 4 hr	Unknown	12

[a] Significant reduction in knockout mice in terms of relative amount, but insignificance in terms of the total amount, less than 1% in all mice.
[b] Based on the total radioactivity; 3 other drugs in the Table being based on the parent compound.
[c] Only increased significantly at 24 hr.

of total radioactivities at 8 and 24 hr, perhaps due to the induction of an unknown transporter or a shift in metabolic pathway leading to more extensive biliary secretion of metabolite(s). The exact reason for the suggestion (7) that P-gp may be responsible for the rapid appearance of hepatically formed more water-soluble metabolites, such as glucuronides and sulfates, in blood circulation shortly after intravenous administration is not clear since P-gp is well known to be located on biliary canalicular membranes. In this regard, one may argue that P-gp can not serve as an effective pump to rapidly transport more water soluble metabolites formed in hepatocytes into blood circulation as previously suggested (7). It is likely that efflux transporters other than P-gp may be involved and the exact role of P-gp in this process, if any, remains to be investigated. Altered expression of hepatic metabolic enzymes and possible other efflux transporter(s) in the knockout mice (6) may also partly account for the reduced hepatic metabolic clearances of drugs.

Interestingly, the deficiency of P-gp in knockout mice had no significant effect on the disposition of ketoconazole (1), morphine (11) and dexamethasone (11). Therefore, the importance of P-gp in affecting hepatic metabolic clearance may vary greatly with drugs in the P-gp knockout mouse model. This may represent a challenging area for future research. The above potential interplays between P-gp and hepatic enzymes may also be applied to other transporters and organs such as intestine (17). Whether or not the present findings in mice can also be applied to humans remains to be seen. It is possible that P-gp may also indirectly play an important role in some drug-drug and drug-food interactions involving enhanced or reduced metabolism of drugs and metabolites; further studies on this are needed.

Table II. Effect of Deficiency of P-Glycoprotein in the Knockout Mice on the Plasma Radioactivity of Five Extensively Metabolized Drugs After Oral Administration Compared to the Normal Mice

Drug	% Increase in blood or plasma radioactivity	Reference
Rifampin[a]	600% at 24 hr	5
Erythromycin[b]	700% at 4 hr	1
	250% at 4 hr	9
Indinavir	100% at 4 hr	14
Nelfinavir	400% at 4 hr	14
Saquinavir	300% at 4 hr	14

[a] Intact drug analyzed.
[b] Blood samples analyzed.

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