Pharmacokinetic Interactions Between *Hypericm perforatum* L. and Conventional Drugs

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INTRODUCTION

Hypericum perforatum (HP), more commonly known as St. John's wort, is a popular medicinal herb used for the treatment of depression. Other pharmacological effects attributed to this plant are its hypolipidemic activity [2], attenuation of irritable bowel syndrome [3] and inflammatory bowel diseases [4], antimicrobial activity [5,6], wound healing potential [7], and antinociceptive [8] and nootropic activities [9].HP affects the pharmacokinetics of many drugs by inducing cytochrome P450 (CYP) isozymes, such as CYP3A4, CYP2C19, CYP2C9, and the P-glycoprotein (P-gp) transporter.

OBJECTIVES

To review drugs that are metabolized by CYP3A4, CYP2C19, CYP2C9 and P-gp as their plasma concentrations affected by concomitant use of HP.

RESULTS

Effect of HP and its constituents on CYP isozymes

the effects of HP on various CYP enzymes have been summerized in table 1.

Effect of HP and its constituents on P-glycoprotein (P-gp)

Expression of P-gp increased 4.2 fold from baseline in subjects treated with 600 mg HP three times daily for 16 days. Direct inducing effects of HP on intestinal P-gp/MDR1 was recorded in in rats and humans following 2 weeks administration of HP. Hyperforin is a major constituent of HP in inducing P-gp activity.

Pharmacokinetic interactions of HP with drugs

Many drugs are substrates of CYP isozymes and/or P-gp and thus their pharmacokinetics can be influenced by HP. Some of the drugs that their pharmacokinetics are affected by HP were discussed below and detailed in table 2.

Table 1. Effects of *Hypericum perforatum* on different CYP isozymes

CYP isozyme	Target	HP constituent	Dosage	Duration	Effect
CYP1A2	Rat	Extract	400 mg/kg/day	10 days	Moderate induction
CYP1A2	Human	Extract	300 mg tid	2 weeks	Weak induction
CYP2C19	In vitro CYP enzymes	Extract	-	30 minute	Weak inhibition
CYP2C19	Human	Extract	300 mg tid	2 weeks	Moderate induction
CYP2C6	Rat	Extract	100 mg/kg/day	10 days	weak inhibition
CYP2C9	In vitro cell culture	Hyperforin	-	48 hours	Moderate induction
CYP2C9	In vitro CYP enzymes	Extract	-	30 minute	Weak inhibition
CYP2D2	Rat	Extract	100 mg/kg/day	10 days	weak induction
CYP2D6	In vitro CYP enzymes	Extract	-	30 minute	Weak inhibition
CYP2E1	Mouse	Extract	140 or 280 mg/kg/day	3weeks	Moderate induction
CYP2E1	Human	Extract	300 mg tid	4 weeks	Weak induction
CYP3A	Human	Extract	300 mg tid	2 weeks	Moderate induction
CYP3A2	Rat	Extract	100 mg/kg/day	10 days	Moderate induction
CYP3A4	In vitro cell culture	Extract	-	40 hours	Strong induction
CYP3A4	Human	Extract	300 mg tid	4 weeks	Moderate induction
CYP3A4	In vitro cell culture	Hyperforin	-	48 hours	Strong induction
CYP3A4	Human	Extract	300 mg tid	2 weeks	Moderate induction
CYP3A4	Human	Extract	300 mg tid	2 weeks	Weak induction

Table 2. Effects of *Hypericum perforatum* preparations on metabolism of different drugs

Target drug	HP		Study duration	Effects
	Constituent(s)/dosage form	Dose		
Amitriptyline	Extract/tablet	900 mg daily	2 weeks	↓AUC of amitriptyline
Atorvastatin	Extract/tablet	300 mg bid	12 weeks	↑serum LDL & total cholesterol
Bupropion	Dried plant/tablet	325 mg tid	2 weeks	↓AUC of bupropion
Clopidogrel	Extract/tablet	300 mg tid	2 weeks	↑Inhibition of platelet aggregation
Clozapine	Extract/tablet	300 mg tid	ND	↑Disorganization and tension in patient
Cyclosporine	Extract/tablet	300 mg bid	3 weeks	↓AUC of cyclosporine; organ rejection
Digoxin	Extract/tablet	300 mg tid	10 days	↓AUC of digoxin
Docetaxel	Hyperforin	0.1, 0.5, or 1.5 µmol/L	2 days	↑Docetaxel metabolism
Finasteride	Extract/tablet	300 mg bid	2 weeks	↓AUCof finasteride
Gliclazide	Extract/tablet	300 mg tid	15 days	↓AUC of gliclazide
Midazolam	Extract/dried extract	1000 mg/kg/day	1 week	↓Midazolam concentrations
Omeprazole	Extract/tablet	300 mg tid	2 weeks	↓AUC omeprazole
Oral contraceptives	Extract/capsule	300 mg tid	During 2 menstrual cycles	↑Breakthrough bleeding in the treatment cycles; follicle growth and probable ovulation
Simvastatin	Extract/caplet	300 mg bid	2 weeks	↓Plasma concentration of simvastatin ;↑LDL & total cholesterol
Tacrolimus	Extract/tablet	600 mg daily	2 weeks	↓AUC & Cmax
Warfarin	Extract/tablet	1 g flowering top tid	21 days	↓AUC, t1/2 ↑CL/F of warfarin

CONCLUSION

Chronic administration of HP induces CYP isozymes and P-gp, while acute exposure usually results in inhibition of these agents. Hyperforin is a major constituent of HP in affecting CYP isozymes and P-gp. Chemotherapeutics, cardiovascular drugs, immunosuppresants, statins, benzodiazepines, anticoagulants and oral contraceptives are examples of drugs which their pharmacokinetics is affected by HP. HP does not cause significant influence on pharmacokinetics of some drugs etabolized by CYP enzymes like carbamazepine, ibuprofen and theophylline. Irinotecan toxicity and clopidogrel hyporesponsiveness may be decreased by HP. Because of possible reduction of bioavailability of oral contraceptives administered concurrently with HP, women who use HP preparations with oral contraceptives should use additional preventive methods of unintended pregnancy.

REFERENCES

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