Potential Drug Interactions in Smokers and Quitters

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Cigarette smoke is known to contain thousands of different compounds. Some of these compounds—including aromatic hydrocarbons, N-nitrosamines, and aromatic amines—have been noted to be carcinogenic.

In addition, cigarette smoking is known to be an enzyme inducer. The induction of CYP1A1, an enzyme that activates procarcinogens in the lung, is thought to be a major mechanism leading to the development of lung cancer.[1] Whereas CYP1A1 is not important for human drug metabolism, cigarettes also induce the activity of CYP1A2, and to a lesser extent CYP2E1 and some of the uridine diphosphate-glucuronosyl transferases—enzymes involved in the glucuronidation of drugs (Table[2]). The effects of cigarettes on other drug-metabolizing enzymes are not well studied.

The most consistently observed effect of cigarettes on drug metabolism is an increase in the clearance of drugs that are substrates of CYP1A2. Selected drugs that interact with smoking are listed in the Table. Other common drugs metabolized by CYP1A2 are duloxetine, erlotinib, frovatriptan, melatonin, mirtazapine, ondansetron, ramelteon, rasagiline, ropinirole, selegiline, tizanidine, triamterene, and warafin.

Table

Drugs Reported to Be Affected by Smoking[2]

Drug	Known Metabolic Pathways	% of Increased Clearance	% of Decreased AUC
Caffeine	1A2	60-70	
Chlorpromazine	2D6		36
Clozapine	1A2, 2C19, 3A4		50
Flecainide	2D6	61	
Fluvoxamine	2D6, 1A2		44
Haloperidol	2D6, 3A4	44	
Mexiletine	1A2, 2D6	25	
Olanzapine	1A2, 2C19, 2D6	98	
Propranolol	2D6, 2C19, glucuronidation	77	
Tacrine	1A2		10-fold
Theophylline	1A2, 3A4	60-100	

AUC = area under the curve.

Secondhand Smoke

It may not be necessary to actually be a smoker to have one's metabolism increased by smoking. A study of children exposed to secondhand smoke found that they had a 50% higher theophylline clearance, compared with matched controls not exposed to smoke.[3]

Similarly, even limited smoking seems to be able to produce a measurable increase in CYP1A2 activity. A recent study compared olanzapine and clozapine dosage in smokers and nonsmokers.[4] Although the mean dose of the 2 drugs was similar for smokers and nonsmokers, the nonsmokers had serum concentrations that were 67% and 50% higher than smokers for olanzapine and clozapine, respectively.

Smoking as few as 7 to 12 cigarettes daily produced the same magnitude of induction on drug metabolism as smoking more than 20 cigarettes daily. Thus, nonsmokers were more likely to have higher blood levels of the drugs and to be at a higher risk of toxicity, compared with smokers.

Effects on Metabolism

This column has previously noted the sensitivity of tizanidine to CYP1A2 inhibitors.[5] Indeed, the CYP1A2 inhibitor ciprofloxacin (Cipro) recently was noted to interact with tizanidine.[6] One would expect the metabolism of tizanidine (and the metabolism of other CYP1A2 substrates) to be increased by smoking.

As smoking-cessation therapy becomes more successful, it is important to be aware of patients taking drugs that are likely to have their metabolism induced during cigarette consumption. With the discontinuation of smoking, the metabolism of these agents will be reduced. This change is likely to be gradual, making the onset of toxicity somewhat slow, delayed, and difficult to evaluate.

Pharmacists should be alert for evidence of excess drug effects as the smoking-induced induction dissipates. Patients may require a gradual reduction in the dosage of chronic drugs that are substrates for CYP1A2 to avoid the development of side effects. PT