

Consultation-Liaison Psychiatry Drug-Drug Interactions Update

SCOTT C. ARMSTRONG, M.D.

KELLY L. COZZA, M.D.

This edition of the drug-drug update could be subtitled, "Breakfast mainstays can cause drug-level variations." We are featuring articles about grapefruit juice, caffeine, and smoking. Some, if not most, of our patients partake in at least one of these on a regular basis, often in the morning. Although technically not prescribed drugs, these three have potential consequences for the drugs you and your colleagues prescribe.

Grapefruit juice inhibits primarily gut-wall cytochrome P (CYP)450III A4, and possibly CYP450IA2 in the liver. Caffeine and smoking can have problems associated with CYP450IA2, a cytochrome that is exclusively found in the liver and accounts for about 10% of all liver cytochrome activity.

CYP450IA2 can be inhibited by some compounds (activity reduced), thus raising some drug levels, or it can be induced (activity gradually increases when exposed to some compounds), thus lowering some drug levels. After reading this column, we hope you'll never think of breakfast the same way again.

1. Fuhr U: Drug interactions with grapefruit juice: extent, probable mechanism, and clinical relevance.

Drug Safety 1998;18(4):251-272

Many case summaries and studies have been published over the last 10 years about grapefruit juice and its potential for raising drug levels. This, in my opinion, is the definitive review on the topic.

Grapefruit juice effectively inhibits a gut-wall cytochrome isoenzyme, CYP450III A4. Actually, it is not the juice itself; but the author indicates that

the exact chemical is unclear. It appears to be a psoralen compound, most likely 6',7'-dihydroxybergamottin. Whatever the compound(s), it seems that it(they) are not present in other citrus fruits.

What does the clinician need to know about the perils of drinking grapefruit juice? By inhibiting the isoenzyme in the small intestine, any drug metabolized by a first-pass mechanism via III A4 could show enhanced levels. The next question, of course, is what are the drugs metabolized by first pass by III A4? This review gives drugs that have actually been studied with grapefruit juice, but also emphasizes that other drugs not studied should be used with caution with grapefruit juice. Drugs extensively studied that have had clinically enhanced effects (or side effects) with grapefruit juice include most calcium channel blockers (felodipine, nifedipine, and verapamil in particular), the triazolobenzodiazepines (midazolam and triazolam), cyclosporin, the nonsedating antihistamines (although the two mentioned, terfenadine and astemizole, are now both off the market in the United States), steroid hormones (estradiol derivatives), and the protease inhibitor saquinavir.

The author points out astutely, however, that other drugs should be expected to have enhanced levels but have not been specifically studied. These include (my list): tertiary tricyclic antidepressants, clozapine, pimo- zide, buspirone, alprazolam, zolpidem, other protease inhibitors, cisapride, sildenafil, ondansetron, cortisol, and some anti-neoplastic agents. That is a lot of medications!

Also, grapefruit juice appears to mildly inhibit CYP450IA2 (in the liver)

and has been shown in some studies to modestly raise tricyclic, caffeine, and theophylline levels. This effect may be due to inhibition caused by a different psoralen compound than the one mentioned above.

Does this mean grapefruit juice is contraindicated with all these drugs? Not necessarily, but being very cautious is warranted. One might believe that since this is only a temporary gut-wall effect, the timing of ingestion of the grapefruit juice and medication can eliminate the problem. The author indicates that the effect may be sustained and that relying on patients to time their grapefruit juice ingestion with their medications may be unrealistic. Also, others have pointed out that grapefruit juice could be used as a "sparing" agent for expensive drugs. It has been done with cyclosporin, but, again, there are problems with fluctuating juice concentration and timing.

Should this information change your practice? At my hospital, our pharmacy and therapeutics committee looked at this information and decided to exclude grapefruit juice from the menu. We just felt we did not need the added problem of the rare patient using grapefruit juice regularly and having untoward effects from enhanced levels of a drug like alprazolam (sedation) or worse, pimo- zide (cardiac conduction problems).

Overall, this review is well written and comprehensive. My knowledge on the topic before reading this review was good, but this article certainly improved it. I would suggest it as a reference for anyone wanting more detailed information on drug-grapefruit juice interactions. — SCA

2. Miners JO, Birkett DJ: The use of caffeine as a metabolic probe for human drug-metabolizing enzymes. *Gen Pharmacol* 1996; 27(2):245–249

Caffeine is a drug. We often forget this because it exists in so many things we consume on a daily basis (an average greater than 200 mg/day in North America). Hence, we should expect that caffeine will occasionally have altered drug levels depending on what- ever else is consumed.

This article, albeit a bit old for drug interaction literature, is a nice review of caffeine's metabolism. The title of the article is a misnomer, because the use of caffeine as a probe is only one point of many made in this review.

Caffeine (CA) has a very complicated metabolism. However, the dominant initial metabolite is paraxanthine (PX); 80% of CA is metabolized to PX. Besides PX, there are 16 other known metabolites, but they are rather "minor players" and are really of some interest only to research pharmacologists, and not to bedside clinicians.

CA is metabolized to PX, through demethylation, by CyP450IA2. The authors discuss using CA as a probe. This implies that measuring its diminishment is a good measure of IA2 activity. This can be useful to determine phenotypes of IA2, but, more importantly, in drug development, to determine if drugs either induce or inhibit IA2.

On a practical level, knowledge of CA's primary metabolic route, is important. The authors point out that smoking induces IA2 (see next review). Hence, CA levels are lower in smokers than nonsmokers (given equal doses of CA). I have often wondered if this is one reason why smokers need that cup of Java with their cigarette—because they don't get the kick from the CA as much as a nonsmoker would.

But there are other things that can induce IA2 not mentioned in the article, such as charbroiled foods, brussels sprouts, cabbage, rifampin, and omeprazole: Quite a varied list.

CyP450IA2 activity can also be inhibited. The authors point out an old drug, furafylline, is a strong inhibitor of IA2, and CA clearance is markedly reduced by this drug. Fluvoxamine, a commonly used SSRI, also potently inhibits this liver enzyme and could certainly cause problems when started in a coffee drinker, as has been reported.¹² Ciprofloxacin is also a potent inhibitor, although one study suggests there would be a major problem with this drug and CA,³ I can find no case reports in the literature showing CA toxicity with ciprofloxacin. I wonder if some have interpreted anxiety or agitated delirium as a direct side effect of ciprofloxacin (a known side effect), and not from an interaction with CA?

In summary, a caffeine intake history would help tremendously in clinically sorting any problems associated with caffeine and smoking or the medications/foods noted above. — SCA

References

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3. Parker AC, Preston T, Heaf D, et al: Inhibition of caffeine metabolism by ciprofloxacin in children with cystic fibrosis as measured by the caffeine breath test. *Br J Clin Pharmacol* 1994; 38(6):573–576

3. Schrenk D, Brockmeier D, Morike K, et al: A distribution of CYP1A2 phenotypes among smokers and nonsmokers in a cohort of healthy volunteers. *Eur J Clin Pharmacol* 1998; 53(5):361–367

This article is a bit esoteric, but overall it gives several good insights into the consequences that cigarette smoke can have with drug levels.

Essentially, this group has found that cigarette smoke induces CyP450IA2. They used caffeine as a probe (see above review) and compared smokers' and nonsmokers' clearance of caffeine. The results were dramatic, and there was a five–six-fold difference in clearance of caffeine.

After reading this article, I asked myself, "With this basic knowledge, what should the clinician look for?" Since most people start smoking at a young age, before they develop medical problems, I believe the main issue is to watch out for those patients who stop smoking. They may be at risk for drug levels escalating over several weeks as the induced enzyme corrects itself.

We want our patients to stop smoking, but I doubt that clinicians have drug lists identified that could be problematic once smoking cessation has been achieved. Drugs partly metabolized by IA2 include clozapine, olanzapine, tertiary TCAs (demethylation), mirtazepine, and fluvoxamine. Phenacetin, theophylline, and pentoxifylline rely heavily on IA2 for clearance. All these drugs could have enhanced drug levels with serious side effects once smoking has ceased. — SCA

Dr. Armstrong is Medical Director, Willmar Regional Treatment Center, Willmar, Minnesota; and Dr. Cozza is HIV Psychiatrist at the Department of Medicine, Walter Reed Army Medical Center, Washington, DC. email Dr. Armstrong at scott.armstrong@state.mn.us. Address correspondence to Dr. Armstrong, Willmar Regional Treatment Center, 1550 Hwy 71 N, Willmar, MN 56201.