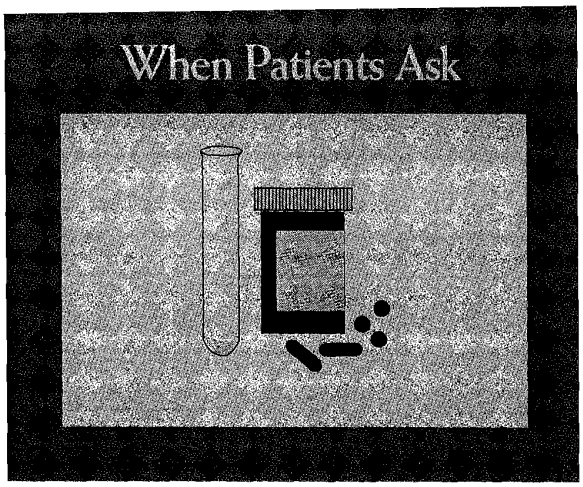

Is My Antihistamine Safe?

by Laurel Ashworth, PharmD

The Food and Drug Administration (FDA) has announced its intention to withdraw the approval of terfenadine (Seldane), terfenadine with pseudoephedrine (Seldane D), and generic versions of terfenadine.[1] Before granting approval for the marketing of fexofenadine (Allegra), terfenadine's active metabolite, the FDA determined terfenadine's benefits outweigh its risks, despite its known potential for serious cardiac effects.

Although its therapeutic benefits are equivalent to those of terfenadine, fexofenadine appears to be free of the potential for adverse cardiac effects.[2] Patients who take terfenadine or have taken it in the past have heard or read about the FDA's intent to withdraw terfenadine from the market and are understandably concerned.

To varying degrees, antihistamines possess sedative, antihistaminic, anticholinergic, and/or antiemetic effects.[3] Diphenhydramine (Benadryl), for example, has pronounced sedative and moderate antihistaminic effects. Thus it is commonly used as a sleeping aid or as treatment for allergic and nonallergic pruritic symptoms. Brompheniramine (Dimetane) and chlorpheniramine (Chlor-Trimetin) have strong antihistaminic activity, minimal sedation, and can provide temporary relief of runny nose and sneezing as a result of the common cold. Promethazine (Phenergan) has potent antiemetic properties. For all their benefits, conventional antihistamines have one overwhelming drawback: many patients cannot take them and function normally in the work-a-day world because antihistamines make them too sleepy.

In 1985, terfenadine was introduced to the American market to relieve the symptoms of allergic rhinitis without causing drowsiness. Astemizole (Hismanal) followed in 1988, loratadine (Claritin) in 1993, and fexofenadine in July 1996. The indications for these four products appear in Table 1. Despite the fact their cost is many-fold higher than older antihistamines, these new agents enjoy widespread use. They are relatively long-acting and effective, have minimal unpleasant (anticholinergic) effects, and cause little or no sedation.[4] In the common vernacular,

Table 1
Comparison of FDA-approved Indications for Nonsedating Antihistamines[8,9,11,12]

	Indication	
	Seasonal allergic rhinitis	Idiopathic chronic urticaria
Astemizole	X	X
Fexofenadine	X	
Loratadine	X	X
Terfenadine	X	

Table 2
Dosing Guidelines for Nonsedating Antihistamines[8,9,11,12]

Parameter	Astemizole	Fexofenadine	Loratadine	Terfenadine
Normal dose: people ≥12 years	10 mg once daily ≥2 hours after meals with no additional food ≥ 1 hour	60 mg BID	10 mg once daily	60 mg BID
Dosage change in hepatic dysfunction	Avoid drug	—	10 mg every other day	Contraindicated
Dosage change in renal dysfunction	Use only with caution	60 mg once daily	10 mg every other day if GFR < 30 mL/min	—

they are known as the "nonsedating" antihistamines. During 1996, 12,834,000 prescriptions were filled for loratadine, ranking it number 16 in the top 200 most commonly dispensed drugs in America.[5] Seldane ranked number 86 with 4,938,000 prescriptions filled in 1996.[5]

TERFENADINE TROUBLES

Several years after terfenadine was marketed, case reports of serious cardiac arrhythmias (torsades de pointes) and deaths associated with terfenadine use began to appear in the medical literature.[6,7] In time, it became clear that cardiotoxicity was promoted by elevated terfenadine levels. The concomitant use of terfenadine with certain macrolide antibiotics and imidazole antifungals delayed the biotransformation of terfenadine to its active metabolite, allowing toxic levels of the parent drug to accumulate. The ingestion of large quantities of terfenadine in excess of the dosage prescribed and/or the presence of significant hepatic impairment likewise contributed to terfenadine-associated cardiotoxicity.[8] The dosage guidelines recommended by the manufacturers appear in Table 2.

Subsequent to these case reports, the FDA required the manufacturer to issue a "Dear Doctor Letter" in August 1990. In July 1992, terfenadine manufacturers were required to add a "black-box warning" to their package insert. The new product labeling alerted users to a possible interaction if terfenadine were taken simultaneously with erythromycin, troleandomycin, ketoconazole, or itraconazole. The warning since has been expanded to include clarithromycin, a newer antibiotic of the erythromycin (macrolide) family.[8] Similar serious cardiovascular adverse events have occurred with the concomitant administration of astemizole and ketoconazole tablets, itraconazole, erythromycin, or quinine. Today, the black-box warning in the astemizole package insert bears a striking resemblance to the terfenadine insert.[9]

Although patient counseling and prominent warnings have reduced the incidence of terfenadine-induced cardiotoxicity secondary to drug-drug interactions, the FDA believes the incidence of these interactions is still unacceptably high and therefore is taking steps to remove terfenadine-containing products from the market. The parent compounds, not the metabolites, for both terfenadine and astemizole are cardiotoxic.[10] Thus far, loratadine and fexofenadine have not been associated with adverse cardiac events.[11,12]

To comprehend why one member of a closely related therapeutic class (the nonsedating antihistamines) can provoke cardiotoxicity while another does not, users need to understand the enzymes that metabolize these drugs. The term *cytochrome P450* refers to a group of enzymes located on the endoplasmic reticulum. Although present in all tissues, the highest concentrations are found in the liver and small intestine, with much smaller quantities in the kidneys, lungs, and brain.[13,14] The primary biologic functions of these enzymes appear to be twofold: metabolism of endogenous compounds and detoxification of exogenous compounds.[15]

CYP CONCERNS

In the literature, the abbreviation CYP is used to denote cytochrome P450. As of 1993, 12 families common to all mammals have been identified. In humans, enzymes of the CYP1, CYP2, and CYP3 families are responsible for most drug metabolism and account for at least 70% of the total CYP content in human liver samples.[13] The CYP isoforms are very specific with regard to their substrates, inhibitors, or inducers. For example, isoform CYP1A2 metabolizes theophylline; CYP2D6 is important in the biotransformation of antidepressants and antipsychotics; CYP2C9 metabolizes phenytoin and the nonsteroidal anti-inflammatory drugs.[10]

Terfenadine undergoes oxidation by CYP3A4 to desalkyl and hydroxy metabolites. The hydroxy metabolite, in turn, is converted to a carboxylic acid derivative (fexofenadine), whose plasma concentrations exceed those of the parent compound by ≥ 100-fold.[16] In the absence of liver disease or drug interactions, terfenadine is barely detectable in

Table 3
Pharmacokinetic Parameters of Nonsedating Antihistamines[3,8,9,11,12]

Parameter	Astemizole	Fexofenadine	Loratadine	Terfenadine
Onset of activity	*	1 hour	1 hour	2 to 4 hours
Half-life	20 to 60 hours	≈ 14 hours	8 hours–parent 28 hours–metabolite	16 to 23 hours
Active metabolite	yes**	no	yes***	yes****
Protein binding	97%	60 to 70%	97 to 99%	97%

* Without a loading dose, $t_{1/2}$ may be up to 1 week. Biphasic elimination: 20 hours for distribution phase; 7 to 11 days for elimination phase
** Hydroxylated metabolites, primarily desmethylastemizole
*** Descarboethoxyloratadine is active and has a $t_{1/2}$ of 17 to 24 hours
**** The active metabolite is fexofenadine

plasma except when concomitant medications inhibit its metabolism.[17,18] Fexofenadine, rather than terfenadine, is responsible for the antihistaminic activity and apparently has no effect on the heart. On the other hand, terfenadine has no antihistaminic activity but inhibits potassium slow channels in cardiac tissue in a concentration-dependent fashion. This inhibition can prolong the QTc interval of the electrocardiogram and increases the risk of potentially fatal arrhythmias.[19-21] The situation is similar for astemizole in that substantial first-pass metabolism occurs and active metabolites are formed.[10] Table 3 summarizes selected pharmacokinetic parameters of the nonsedating antihistamines.

AN IMPROVED UNDERSTANDING OF THE WAY CYP ENZYMES METABOLIZE DRUGS HAS THE POTENTIAL TO IMPROVE DRUG THERAPY BY ALLOWING CLINICIANS TO BETTER PREDICT WHICH THERAPIES ARE LIKELY TO INTERACT ADVERSELY WITH ONE ANOTHER AND TAKE STEPS TO AVOID SUCH SITUATIONS.

Terfenadine, astemizole, and loratadine are metabolized by CYP3A4.[22] The imidazole antifungal agents ketoconazole and itraconazole are potent and relatively specific inhibitors of CYP3A activity. Of the two, however, only ketoconazole has been associated with terfenadine-induced ventricular arrhythmias.[18,23] Although itraconazole impairs terfenadine metabolism to a lesser degree than ketoconazole, available evidence suggests itraconazole should not be administered with terfenadine or astemizole because of its potential to inhibit CYP3A to the same degree as ketoconazole. At usual therapeutic doses, fluconazole does not detectably impair terfenadine clearance.[23] The new antifungal agent terbinafine does not appear to inhibit CYP to a clinically significant extent.[2]

Studies show that ketoconazole and erythromycin can inhibit the metabolism of loratadine and its metabolite descarboethoxyloratadine (DCL). Fortunately these interactions appear to be of little clinical significance because neither electrocardiographic abnormalities nor other adverse cardiac events have been observed as a result of elevated plasma concentrations of DCL.[24] Loratadine's apparent lack of cardiotoxic effects may be attributable in part to the fact that it does not block the potassium channel involved in repolarization of cardiac cells. Prolonged QTc interval has not been detected clinically with fexofenadine.[2]

The macrolide antibiotics are also inhibitors of CYP3A. Azithromycin does not appear to inhibit terfenadine metabolism to a significant extent, in contrast to erythromycin and clarithromycin.[2] Grapefruit juice, which contains flavonoids that can inhibit CYP3A4, also can increase plasma levels of unmetabolized terfenadine.[25] An improved understanding of the way CYP enzymes metabolize drugs has the potential to improve drug therapy by allowing clinicians to better predict which therapies are likely to interact adversely with one another and take steps to avoid such situations.

LEARNING FROM MISFORTUNE

Life teaches by negative as well as positive examples. Valuable lessons were learned from careful analysis of the unfortunate astemizole- and terfenadine-associated cases of torsades de pointes and the codependency that non-

sedating antihistamines and certain antibiotics/antifungals have for specific isoenzymes. From these cases and the research they generated came an appreciation of the multifaceted, highly specific nature of the CYP family of enzymes. In recent years, we have become aware that a patient's ethnicity, gender, and inherent CYP idiosyncracies influence how he or she metabolizes drugs. Much work remains to be done, but at least the process has begun that will lead to a better understanding of why two similarly matched patients can respond in entirely different ways to a given dose of the same medication. We have so much yet to learn about the clinical nuances of cytochrome P450.

REFERENCES

1. Cruzan SM. FDA talk paper [cited 13 January 1997]. Available at *http://www.fda.gov/bbs/topics/ANSWERS/ANS00780.html*
2. Fexofenadine. Med Lett Drug Ther 1996;38(986):95-6.
3. Hebel SK, publisher. Facts and comparisons. St. Louis (MO): Facts and Comparisons; 1993: p. 188.
4. Masheter HC. Terfenadine: the first nonsedating antihistamine. Clin Rev Allergy Immunol 1993;11:5-34.
5. The top 200 drugs. American Druggist 1997;214(2):30-7.
6. Mathews DR, McNutt B, Okerholm R, Flicker M, McBride G. Torsades de pointes occurring in association with terfenadine use. JAMA 1991;266:2375-6.
7. Crane JK, Shih H-T. Syncope and cardiac arrhythmia due to an interaction between itraconazole and terfenadine. Am J Med 1993;95:45-6.
8. Product information. Seldane brand of terfenadine. Hoechst Marion Roussel, Kansas City (MO); 1995.
9. Product information. Hismanal brand of astemizole. Janssen Pharmaceutica, Titusville (NJ); 1993.
10. Cupp MJ, Tracy TS. Role of the cytochrome P450 3A subfamily in drug interactions. US Pharmacist 1997;22:HS9-21.
11. Product information. Claritin brand of loratadine. Schering Corp., Kenilworth (NJ); September 1995.
12. Product information. Allegra brand of fexofenadine. Hoechst Marion Roussel, Kansas City (MO); August 1996.
13. Slaughter RI, Edwards DJ. Recent advances: the cytochrome P450 enzymes. Ann Pharmacother 1995;29:619-24.
14. Murray M, Reidy GF. Selectivity in the inhibition of mammalian cytochromes P450 by chemical agents. Pharmacol Rev 1990;42:85-101.
15. Krishna D, Klotz U. Extrahepatic metabolism of drugs in humans. Clin Pharmacokinet 1994;26:144-60.
16. Yun C, Okerholm RA, Guengerich FP. Oxidation of the antihistaminic drug terfenadine in the human liver microsomes: role of cytochrome P450 3A(4) in N-dealkylation and C-hydroxylation. Drug Metab Dispos 1992;21:403-9.
17. Honig PK, Woosley RL, Zamani K, Conner D, Cantilena L. Changes in the pharmacokinetics and electrocardiographic pharmacodynamics of terfenadine with concomitant administration of erythromycin. Clin Pharmacol Ther 1992;52:231-8.
18. Honig PK, Wortham DC, Zamani K, Conner DP, Mullin JC, Cantilena LR. Terfenadine-ketoconazole interaction: pharmacokinetic and electrocardiographic consequences. JAMA 1993;269:1513-8.
19. Woosley RL, Chen Y, Freiman JP, Gillis RA. Mechanism of the cardiotoxic actions of terfenadine. JAMA 1993;269:1532-6.
20. Monahan BP, Ferguson CL, Killeavy ES, Lloyd BK, Troy J, Cantilena LR. Torsades de pointes occurring in association with terfenadine use. JAMA 1990;264:2788-90.
21. Woosley RL, Chen Y, Pinney SP. Terfenadine and cardiac death. J Allergy Clin Immunol 1993;91:262.
22. Ketter TA, Flockhart DA, Post RM. The emerging role of cytochrome P450 3A in psychopharmacology. J Clin Psychopharmacol 1995;15:387-98.
23. Von Moltke LL, Greenblatt DJ, Duan SX, Harmatz JS, Wright CE, Shader RI. Inhibition of terfenadine metabolism in vitro by azole antifungal agents and by selective serotonin reuptake inhibitor antidepressants: relation to pharmacokinetic interactions in vivo. J Clin Psychopharmacol 1996;16:104-12.
24. Haria M, Fitton A, Peters DH. Loratadine: a reappraisal of its pharmacological properties and therapeutic uses in allergic disorders. Drugs 1994;48:617-37.
25. Honig P, Wortham D, Lazarev A, Cantilena LR. Grapefruit juice alters the systemic bioavailability and cardiac repolarization of terfenadine in poor metabolizers of terfenadine. J Clin Pharmacol 1996;36:345-51.

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