Terfenadine therapy: Can we justify the risks?

Editorial

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Résumé

DEPUIS LA MISE EN VENTE DE LA TERFÉNADINE, antihistaminique non sédatif, il y a plus de 20 ans, des rapports sur des cas d'arythmie cardiaque et de mort subite associée à son utilisation ont entraîné son retrait du marché dans certains pays. Néanmoins, la terfénadine est toujours en vente au Canada. Les avantages qu'offre ce médicament pour contrôler les symptômes de la fièvre des foins ne l'emportent sûrement pas sur les risques d'effets indésirables qui peuvent être mortels. De plus, la disponibilité continue de ce médicament est injustifiée compte tenu des solutions de rechange sans danger qui existent.

Concern about the safety of the nonsedating antihistamine terfenadine peaked in January 1997 when the US Food and Drug Administration (FDA) proposed to remove all preparations that contained this drug from the US market.[1] This action was prompted by an unacceptable number of reported cases of fatal and potentially fatal cardiac arryhthmias associated with terfenadine therapy. FDA officials would not reveal to me the most recent numbers in advance of formal publication, but one editorialist has cited about 125 deaths in the US.[2] Some cases were related to intentional overdose, but most were linked to other factors. In addition, a larger number of near-fatal events have been reported.[2] In the UK, 33 cases of serious cardiac arrythmias, 14 of which were fatal, have been linked to terfenadine.[3] In Canada, only 1 death associated with terfenadine has been reported; this low figure no doubt reflects a suboptimal reporting system. I would suspect that many adverse reactions to terfenadine go unrecognized: because both cardiac arrest and the use of antihistamines are common, chances are high that an association between the two in a given case will not be noticed. Mounting evidence of the risks of terfenadine has led to the suspension of this drug from the market in France, Greece and Luxembourg.[3] In the UK it is available by prescription only. Meanwhile, in Canada, terfenadine-containing preparations are strongly promoted as over-the-counter drugs.

Woosley[4] provides a succinct review of how the cardiotoxic effects of terfenadine and of astemizole, another nonsedating antihistamine, came to be recognized. In 1986, 10 years after terfenadine was introduced, the first reports emerged of torsade de pointes after overdose with terfenadine or astemizole. By 1990 the FDA had received reports of 20 cases of torsade de pointes, most of which were not related to overdose, but rather to factors that potentiate the cardiotoxicity of the drug when taken in therapeutic doses. Terfenadine is normally completely converted to its active metabolite, fexofenadine, on its first pass through the liver. It is fexofenadine, not terfenadine, that exerts the drug's beneficial effect. Fexofenadine is not believed to be cardiotoxic. However, if terfenadine reaches the systemic circulation without being metabolized it prolongs the QT interval and thus predisposes the patient to ventricular arrythmias, ventricular fibrillation and death. The following factors are now known to promote this effect:

- Drugs and foods that inhibit the enzyme CYP3A4, which converts terfenadine to fexofenadine, e.g., clarithromycin, erythromycin, fluconazole, ketoconazole, troleandomycin and grapefruit juice.[5]

- The concomitant use of proarrythmic drugs, e.g., quinidine, sotalol.
- Patient factors, i.e., liver or heart disease, congenital prolongation of QT interval, hypokalemia, hypomagnesemia.

The FDA responded by changing the drug labelling to caution users and by making terfenadine available by prescription only. In Canada, the Health Protection Branch put terfenadine-containing products behind the counter so that patients requesting them could be counselled by a pharmacist. However, a CBC *Marketplace* report showed that roughly 50% of patients who requested the drug at a pharmacy were not so counselled.[6]

Is any antihistamine safe? Even rare fatal events are a high price to pay for the symptomatic relief of hayfever. What about older, less costly drugs, or the newer nonsedating antihistamines? Woosley[4] has classified these alternatives as follows:

- cardiotoxic drugs, i.e., terfenadine, astemizole, diphenhydramine, dimenhydrinate. These prolong the QT interval and have been fatal.
- potentially cardiotoxic drugs, i.e., hydroxyzine. This prolongs the QT interval but has not been associated with any deaths.
- safe drugs, i.e., chlorpheniramine, cetirizine, loratadine, fexofenadine. These drugs do not prolong the QT interval and have not been linked to any deaths. (Fexofenadine is available only in the US.)

We should not abandon tried-and-true drugs even at the risk of being called "Jurassic Docs" by our colleagues. Generic products containing chlorpheniramine have an excellent track record with respect to safety, a long duration of action (1–2 days)[7,8] and greater effectiveness as an antipruritic in comparison with nonsedating antihistamines.[8] Chlorpheniramine causes mild sedation, especially when taken as recommended on the package (4 mg every 4–6 hours). However, recent research on the action of this drug has shown that a much lower dosage (up to 8 mg at bedtime)[8] minimizes the problem of sedation (and of tolerance to sedation) while achieving near-maximum histamine receptor blockade. In view of this data, neither the use of repeated doses nor of timed-release formulations is justified. An additional bonus of single-dose chlorpheniramine is its low cost: roughly 3 cents per 4-mg generic tablet, versus about $1.00 per tablet for nonsedating antihistamines. If a trial of chorpheniramine of up to 8 mg at bedtime is ineffective or still causes problematic sedation, then the use of a safe nonsedating antihistamine such as cetirizine is justified.

Afterword

Having dealt with the evidence-based therapeutics of antihistamines, I will report the results of an emotion-based experiment. Among the members of my family who are allergic to pollen and animal dander I was able to recruit a captive series of volunteers (n = 1, i.e., myself) to test the hypothesis that low-dose chlorpheniramine is as effective as standard therapy in controlling the symptoms of allergic rhinitis. Because I was to be the sole granting agency, I used a cost-effective design that involved the purchase of 1000 4-mg chlorpheniramine tablets (wholesale, of course). A 4-mg dose at bedtime was associated with a marked reduction in sneeze count and tissue use in the study group. Occasional failure to remember to take the pill constituted the basis for control observations. The only important limitation of the study was possible underreporting of drug-induced drowsiness, since no-one in my family was likely to notice any divergence from my normal state. I have since recommended this approach to allergy relief to a large number of grateful, mentally alert patients who have reported satisfaction with both symptom and wallet control.

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