






VA Center for Medication Safety

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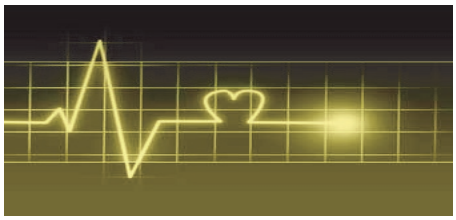
# Medication safety in seconds


A MONTHLY PUBLICATION FROM VA MEDSAFE:
VA'S COMPREHENSIVE PHARMACOVIGILANCE CENTER


## Helping to achieve safe medication use



### *AZITHROMYCIN AND THE RISK OF CARDIOVASCULAR DEATH*

Macrolide antibiotics have well-known proarrhythmic properties. There is now growing evidence in the published literature as well as from cases reported to FDA's Adverse Event Reporting System (AERS) that azithromycin, a broad-spectrum macrolide antibiotic, increases the risk of QT-interval prolongation, torsades de pointes, polymorphic ventricular tachycardia, as well as sudden cardiac death.

The increase in reports of azithromycin-induced ventricular arrhythmias and abrupt fatal effects was recently reported in the New England Journal of Medicine. The investigators conducted a retrospective review of cardiac deaths related to the use of a five day course of azithromycin. The cohort included Medicaid patients receiving a prescription for azithromycin during any time between 1992 and 2006, of which approximately 80% consisted of women with a mean age of 49 years. Subjects who received azithromycin (347,795 prescriptions) were propensity-score-matched to a control group receiving no antibiotics (1,391,180 matched treatment periods) to take into account comorbid and cardiovascular conditions in addition to behavioral risk factors that may influence cardiovascular disease (i.e., smoking, diet, weight, sedentary lifestyle). Furthermore, the study included a second control group of patients with prescriptions for either amoxicillin (1,348,672 prescriptions), ciprofloxacin (264,626 prescriptions), or levofloxacin (193,906 prescriptions) in order to reduce any confounding by the types of infections being treated due to similar indications for use. The study analyzed cumulative incidence, or risk, of cardiovascular death, as well as death from any cause, during a course of antibiotic therapy, defined as a 5-day treatment duration generally recommended with azithromycin use and a 10-day treatment schedule routinely prescribed with the comparator antibiotics.

Results showed a significant increase in the risk of cardiovascular death with a 5-day course of azithromycin when compared to the first 5 days of a 10-day course of either amoxicillin (hazard ratio, 2.49; 95% confidence interval, 1.38 to 4.50; p=0.002) or ciprofloxacin (hazard ratio, 3.49; 95% confidence interval, 1.32 to 9.26; p=0.01), but no significant difference from that with levofloxacin (hazard ratio, 1.27; 95% confidence interval, 0.66 to 2.47; p=0.48). Azithromycin was associated with 29 cardiovascular deaths during the 5-day treatment period (85.2 per 1 million courses), of which 22 (64.6 per 1 million courses)


*(continued on page 2)*



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# NEWS YOU CAN USE

### *FROM THE FOOD AND DRUG ADMINISTRATION (FDA)*

#### *CARDIOLOGY*

FDA recommends against use of Revatio in children with pulmonary hypertension

8/30/2012

Sildenafil (Revatio®) received FDA approval for improving exercise ability and delaying clinical progression of pulmonary arterial hypertension in adults classified as WHO Group I. Off-label use has occurred in the pediatric population. However, results from a recent long-term, randomized, double-blind, multi-center, placebo-controlled, parallel group, dose-ranging clinical trial in 234 pediatric patients (aged 1-17 years) showed:

- Higher risk of death in children associated with high doses compared to low doses; and
- No improvement in exercise ability in children with lower doses.

Therefore, FDA does not recommend use of sildenafil (Revatio®) in children, and new product labeling will reflect this warning. FDA believes that the direct dose-related effect on mortality does not apply to sildenafil marketed as Viagra® used to treat erectile dysfunction due to differences in population and dosing.

#### *PAIN MANAGEMENT*

Codeine use in certain children after tonsillectomy and/or adenoidectomy may lead to rare, but life-threatening adverse events or death

8/15/2012

Genetic variations in DNA result in different cytochrome P450 2D6 enzyme activity that may lead to quicker metabolism of codeine into morphine leading to life-threatening levels in the body and the potential for toxicity, including respiratory depression or death. Certain racial/ethnic populations express this "ultra-high metabolizer" genotype more than others, with ranges from as low as 1% in people of Northern European decent to up to almost 30% in those with African/Ethiopian backgrounds. Three pediatric deaths and one case of severe respiratory depression occurred in children found to have the "ultra-high metabolizer" genotype. These children, ranging from ages 2-5 years, received usual doses of codeine products for analgesia after undergoing tonsillectomy and/or adenoidectomy for obstructive sleep apnea. FDA recommends to:

- Consider alternative analgesic agents for children post-tonsillectomy and/or adenoidectomy for obstructive sleep apnea syndrome due to already compromised breathing status; and
- If codeine-containing products are clinically indicated, use the lowest dose in the shortest time on an "as needed" basis (not scheduled or administered more than 6 times a day).

# Helping to achieve safe medication use

### *AZITHROMYCIN AND RISK OF CARDIOVASCULAR DEATH*

*(continued from page 1)*

comprised sudden cardiac deaths. An estimated 47 additional cardiovascular deaths per 1-million 5-day courses with azithromycin in comparison to amoxicillin were derived from study data. Moreover, a 5-day course of azithromycin maintained a significant increase in the risk of death from any cause compared to the first 5 days of a course of amoxicillin (hazard ratio, 2.02; 95% confidence interval 1.24 to 3.30; p=0.005), but not with ciprofloxacin (hazard ratio, 1.75; 95% confidence interval, 0.91 to 3.37; p=0.09) or levofloxacin (hazard ratio, 1.07; 95% confidence interval, 0.61 to 1.85; p=0.82). When compared to a matched period of no antibiotic treatment, 5-days of azithromycin therapy increased the risk of cardiovascular death (hazard ratio, 2.88; 95% confidence interval, 1.79 to 4.63; p<0.001) and death from any cause (hazard ratio, 1.85; 95% confidence interval 1.25 to 2.75; p=0.002).

Since azithromycin is commonly used in VA, awareness of this safety concern can help providers to recognize veteran patients potentially at risk for developing an adverse cardiac event with azithromycin and to weigh the risks versus benefits when considering antibiotic therapy. Although the Medicaid cohort mostly consisted of young, female patients, one cannot preclude similar adverse events from occurring in an elderly and mainly male population with multiple co-morbidities. High-risk patients with a predisposition to cardiac adverse events may warrant use of alterative antimicrobial agents or class of agents. Providers should continue to report any adverse reactions with the use of azithromycin by entering the information into CPRS' Allergies/ Adverse Reactions field and/or via local reporting mechanisms. Adverse events should also be reported, as appropriate, to the VA ADERS program and FDA MedWatch (1-800-FDA-1088, fax 1-800-FDA 0178, online at *https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm*, or by mail).

**REFERENCE**:
Ray WA, Murray KT, Hall K, Arbogast PG, Stein CM. Azithromycin and the Risk of Cardiovascular Death. *N Eng J Med* 2012; 366:1881-90.

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# Getting the most from our safety surveillance

## *IDENTIFYING POTENTIALLY PREVENTABLE ADVERSE DRUG REACTIONS IN THE VA ADVERSE DRUG EVENT REPORTING SYSTEM (VA ADERS)*

Adverse drug events (ADEs) entered into the VA Adverse Drug Event Reporting System (VA ADERS) may be evaluated for elements that signal potential preventability. VA ADERS poses preventability questions with each adverse drug reaction entered to focus on factors involved with the ADE as well as potential steps that may have circumvented the event (Table 1). While individual assessment of each question can denote potential preventability, the overall determination of preventability for the event should derive from the collective answers to the series of questions as well as from any changes in pharmacotherapy based on the patient's clinical presentation that could have prevented the event. For example, Questions 1-4 suggests potential preventability when answered "NO". A "NO" answer to Question 1 indicates an inappropriate drug choice and that a therapeutic alternative may less likely lead to an adverse outcome if selected. Furthermore, Questions 5-9 imply potential preventability when answered "YES". A "YES" answer to Question 5 would necessitate a critical comparison to all questions to ascertain the appropriateness of this agent given the history of allergy or previous adverse reaction.

Answering these preventability questions can help minimize the recurrence of harm by uncovering areas of the medication use process that need additional regulation or system improvements to enhance the procedures involved in drug selection, monitoring, administration, or adherence. Sharing data from preventability analyses via provider and staff education can increase awareness of potential weaknesses in the medication process locally as well as nationally for targeted intervention. An example of consequent process improvements includes the development of prescribing alerts based on dose, drug-drug interactions, and previous ADEs that provide a "flag" associating potential risk with a particular order. Process improvements like this may have national applications depending on patterns of care across the VA system. However, not all risk can be eliminated, and in the case of a non-preventable adverse drug reaction, unwanted adverse effects may still occur. Nevertheless, having a system in place to detect potentially preventable ADEs can help optimize safe and appropriate medication use while reducing the morbidity and mortality associated with adverse events.


**REFERENCES**

1. Winterstein AG, Hatton RC, Gonzalez-Rothi R, et al. Identifying clinically significant preventable adverse drug events through a hosptial's database of adverse drug reaction reports. Am J Health-Syst Pharm. 2002; 59:1742-9.


**Table 1. Questions assessing potential preventability included with each VA ADERS report.**

| | Preventability Questions |
|---|---|
| 1 | Was the drug involved considered appropriate for the patient's clinical condition? |
| 2 | Was the dose, route, or frequency of administration appropriate for the patient's age, weight or disease state? |
| 3 | Was required therapeutic drug monitoring or other necessary laboratory test(s) performed? |
| 4 | Were adjustments in therapy made based on drug monitoring or available lab results? |
| 5 | Was there a history of allergy or previous reactions to the drug or drug class? |
| 6 | Was there a drug interaction involved in the reaction? |
| 7 | Was a critical serum drug level (or laboratory monitoring test) documented? |
| 8 | Was poor compliance involved in the reaction (missing dose, late doses)? |
| 9 | Was hypercompliance involved in the reaction (taking more than prescribed)? |

Adapted from Winterstein et al. [1]

**Table 2. Preventability Questions and Answers to Example Case**

| | *Preventability Questions* | |
|---|---|---|
| *1* | *Was the drug involved considered appropriate for the patient's clinical condition?* | *Y* |
| *2* | *Was the dose, route, or frequency of administration appropriate for the patient's age, weight or disease state?* | *Y* |
| *3* | *Was required therapeutic drug monitoring or other necessary laboratory test(s) performed?* | *Y* |
| *4* | *Were adjustments in therapy made based on drug monitoring or available lab results?* | *NA* |
| *5* | *Was there a history of allergy or previous reactions to the drug or drug class?* | *Y* |
| *6* | *Was there a drug interaction involved in the reaction?* | *Y* |
| *7* | *Was a critical serum drug level (or laboratory monitoring test) documented?* | *N* |
| *8* | *Was poor compliance involved in the reaction (missing dose, late doses)?* | *N* |
| *9* | *Was hypercompliance involved in the reaction (taking more than prescribed)?* | *N* |

## EXAMPLE OF POTENTIALLY PREVENTABLE ADR REPORTED TO VA ADERS

***Patient presents to the emergency room with confusion, difficulty ambulating, and falling. Active medications include simvastatin 10mg at bedtime (reported as the primary suspect medication) and gemfibrozil 600mg twice daily (reported as the secondary suspect medication), in addition to niacin (Slo-Niacin) 500mg twice daily, morphine sulfate (MS Contin) 15 mg twice daily, and acetaminophen/hydrocodone 5/500 mg every 6 hours as needed. Labs consist of BUN 70, SCr 4.9, SGOT 384, SGPT 95, and CPK 12,840. Patient was admitted for intravenous hydration in addition to discontinuation of simvastatin, gemfibrozil, and niacin due to diagnosis of rhabdomyolysis. Symptoms resolved and the patient was discharged. Subsequent medical record review revealed a previous hospital admission for the patient in 2010 for rhabdomyolysis, confusion, and weakness with primary suspect medication simvastatin 20 mg at bedtime and secondary suspect medication gemfibrozil 600 mg twice daily.***

***Preventability questions were answered as follows in Table 2. Answers that signify potential preventability include: #5 = YES, #6 = YES. The assessment revealed that use of alternative agents may have helped to avoid this adverse event due to the drug-drug interaction between concomitant use of simvastatin and gemfibrozil that may have led to the rhabdomyolysis.***


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