The NEW ENGLAND JOURNAL of MEDICINE

Perspective

MAY 2, 2013

Cardiovascular Risks with Azithromycin and Other Antibacterial Drugs

Andrew D. Mosholder, M.D., M.P.H., Justin Mathew, Pharm.D., John J. Alexander, M.D., M.P.H., Harry Smith, Ph.D., and Sumathi Nambiar, M.D., M.P.H.

Related article, p. 1704

In 2011, approximately 40.3 million people in the United States (roughly one eighth of the population) received an outpatient prescription for the macrolide azithromycin, according to IMS Health.

During that year, we at the Food and Drug Administration (FDA) reviewed the labels of azithromycin and other approved macrolide antibacterials in view of cardiovascular risks that had become evident from published studies and reports emerging through postmarketing surveillance. On the basis of its review, the FDA approved revisions to azithromycin product labels regarding risks of QT-interval prolongation and the associated ventricular arrhythmia torsades de pointes. The revised labels advise against using azithromycin in patients with known risk factors such as QT-interval prolongation, hypokalemia, hypomagnesemia, bradycardia, or use of certain antiarrhythmic agents, including class IA (e.g., quinidine and procainamide) and class III (e.g., dofetilide, amiodarone, and sotalol) — drugs that can prolong the QT interval. In March 2013, the FDA announced that azithromycin labels had been further revised to reflect the results of a clinical study showing that azithromycin can prolong the corrected QT interval.

In a 2012 observational study involving Tennessee Medicaid patients, Ray et al.[1] quantified the risk of death from cardiovascular causes associated with azithromycin as compared with other antibacterial drugs or nonuse. The study showed that the risks of death, both from any cause and from cardiovascular causes, associated with azithromycin were greater than those associated with amoxicillin. For every 21,000 outpatient prescriptions written for azithromycin, one cardiovascular death occurred in excess of those observed with the same number of amoxicillin prescriptions. The excess risk over amoxicillin varied considerably according to cardiovascular risk factors; the researchers estimated that there was one excess cardiovascular death per 4100 prescriptions among patients at high cardiovascular risk but less than one per 100,000 among patients with lower cardiovascular risk.

Agents Associated with Drug-Use Mentions for Chronic Sinusitis and Bronchitis, According to U.S. Office-Based Physician Practices (January 2002–December 2011).*

Medical Condition and Drug	No. of Drug-Use Mentions	Percent of Total Drug-Use Mentions
Chronic sinusitis		
Any drug	206,369,000	100.0
Amoxicillin	50,350,000	24.4
Azithromycin	34,077,000	16.5
Amoxicillin–clavulanate	33,233,000	16.1
Cefdinir	13,124,000	6.4
Clarithromycin	13,027,000	6.3
Moxifloxacin	10,691,000	5.2
Levofloxacin	9,821,000	4.8
Cefuroxime	5,650,000	2.7
Cephalexin	5,454,000	2.6
Trimethoprim–sulfamethoxazole	5,390,000	2.6
All others	25,552,000	12.4
Bronchitis		
Any drug	171,791,000	100.0
Azithromycin	69,790,000	40.6
Amoxicillin	17,934,000	10.4
Clarithromycin	17,413,000	10.1
Levofloxacin	12,167,000	7.1
Moxifloxacin	8,598,000	5.0
Doxycycline	7,693,000	4.5
Amoxicillin–clavulanate	7,361,000	4.3
Cephalexin	5,357,000	3.1
Cefdinir	3,784,000	2.2
Erythromycin	2,965,000	1.7
All others	18,729,000	10.9

* The term "drug-use mentions" refers to the mentioning of a drug by a clinician in association with a diagnosis during an office-based patient visit, as recorded by Encuity Research. It is important to note that a drug-use mention does not necessarily result in the generation of a prescription. Rather, the term indicates that a listed drug was mentioned during an office visit.

The study by Ray et al. has limitations that are intrinsic to observational, nonrandomized clinical studies. In particular, nonrandomized studies cannot exclude the possibility that patients receiving a drug under evaluation differ from control patients in some important but undetected way, causing bias in the results. Such confounding may bias comparisons not only between patients receiving antibacterial drugs and those receiving no antibacterials but also between patients receiving different antibacterials. Although Ray et al. used appropriate analytic methods to address potential confounding, we cannot know for certain whether these methods were fully successful. Replication of the authors' results, through analysis of a distinct data set, would provide more confidence in the finding of increased cardiovascular mortality among patients receiving azithromycin.

Despite such caveats, the results presented by Ray et al. warrant serious attention. A chief strength of the results is the time-limited pattern of the risk: the azithromycin-associated increase in the rates of death from any cause and from cardiovascular causes spanned days 1 through 5, reflecting the typical 5-day duration of azithromycin administration (e.g., Zithromax Z-Pak). On days 6 through 10, an elevated risk of death from cardiovascular causes was no longer detected. This pattern is consistent with the timing of peak plasma azithromycin concentrations and the concomitant risk of QT-interval prolongation. The elevated risk was statistically significant, regardless of whether azithromycin treatment was compared with amoxicillin or with nonuse of an antibacterial drug. Furthermore, the observed excess mortality was attributable solely to cardiovascular deaths and, in particular, to sudden cardiac death; although sudden cardiac death can result from causes other than arrhythmias, an increase in deaths in this category would be the pattern expected from an arrhythmogenic, QT-interval–prolonging drug. Also, the azithromycin-associated risk was higher among patients with cardiovascular disorders, which is consistent with a drug-related arrhythmia.

A new study by Svanström and colleagues (pages 1704–1712), using Danish national health care data, found no difference between

azithromycin and penicillin V in the 5-day risk of cardiovascular death (relative risk, 0.93; 95% confidence interval [CI], 0.56 to 1.55). However, the upper bound of the 95% confidence interval does not exclude an increased risk of as much as 55%. As Svanström et al. point out, the population they studied differed from that studied by Ray et al. with respect to the baseline risk of death and cardiovascular risk factors. Overall, the Danish patients had better cardiovascular health than the Tennessee Medicaid patients. In a subgroup analysis of patients with a history of cardiovascular disease, the risk ratio for azithromycin versus penicillin V was greater than 1, though the difference was not statistically significant (relative risk, 1.35; 95% CI, 0.69 to 2.64). Svanström et al. conclude that their results do not conflict with those of Ray et al. Rather, the effect on cardiovascular mortality may be limited to patients with cardiovascular disease.

One must, of course, weigh any observed drug-associated risk against clinical benefits, so it's appropriate to consider the possibility that certain offsetting benefits of azithromycin may not have been reflected in the risk data analyzed by Ray et al. For example, other studies have suggested that macrolides have an advantage over other antibacterial agents in terms of overall survival from community-acquired pneumonia. In a recent Canadian observational study, researchers followed 2973 outpatients with community-acquired pneumonia and found significantly lower 30-day mortality among patients receiving macrolides than among those receiving fluoroquinolones (adjusted odds ratio, 0.28; 95% CI, 0.09 to 0.86).[2] A recent meta-analysis of observational studies showed a statistically significant 25% difference in mortality among hospitalized patients with community-acquired pneumonia favoring macrolides over non-macrolide antibacterials.[3] Such findings, which must be considered with due regard for the limits of observational studies, do not necessarily contradict the results of Ray et al. Past the 5-day period of risk of azithromycin-associated cardiovascular death, the drug might reduce the longer-term (e.g., more-than-30-day) rate of death due to pneumonia. Pneumonia was an uncommon indication among the Tennessee Medicaid patients treated with azithromycin.

Clinicians must consider the arrhythmogenic potential not only of azithromycin but also of potential alternative antibacterial drugs. An earlier study showed an association between the use of erythromycin and sudden cardiac death, augmented by concomitant use of inhibitors of the cytochrome P-450 3A isozymes that metabolize erythromycin.[4] Labels for erythromycin and clarithromycin include warnings regarding QT-interval prolongation and arrhythmias. All labels for fluoroquinolone products similarly have warnings regarding QT-interval prolongation, and grepafloxacin was withdrawn from the market because of that risk. A recent observational study of elderly residents of Quebec, Canada, showed an association between outpatient fluoroquinolone use and serious arrhythmias (as defined by hospital discharge diagnoses of ventricular arrhythmia or sudden or unattended death).[5] And although Ray et al. found the risk of cardiovascular death to be greater with azithromycin than with ciprofloxacin, they found the risk with levofloxacin similar to that with azithromycin. The authors interpreted this similarity as evidence that levofloxacin may be proarrhythmic; however, levofloxacin was not implicated as proarrhythmic in the Canadian study.

We investigated the most common ambulatory indications for azithromycin by analyzing data from a survey conducted by Encuity Research of approximately 3200 office-based physicians for the decade from 2002 through 2011. Across all age groups of patients, the two most common indications for azithromycin were chronic sinusitis and bronchitis. The table shows the antibacterial drugs that were used most commonly in the United States for these indications. Azithromycin was the leading antibacterial drug for outpatient treatment of bronchitis during this period (even if amoxicillin is combined with amoxicillin–clavulanate). For chronic sinusitis, azithromycin ranked second after amoxicillin. Because the indications are reported by the prescribing physicians, these data don't allow us to assess the diagnostic certainty regarding the infections being treated.

The risks and benefits of antibacterial therapy should be considered in prescribing decisions. Pharmacologic and epidemiologic data point to lethal arrhythmias as a potential consequence of QT-interval prolongation with use of azithromycin, other macrolides, and fluoroquinolones. This possibility should give clinicians pause when they're considering prescribing antibacterial drugs, especially for patients with preexisting cardiovascular risk factors or

clinical conditions in which antibacterial drug therapy has limited benefits.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

From the Office of Surveillance and Epidemiology, Division of Epidemiology II (A.D.M., J.M.), the Office of Antimicrobial Products, Division of Anti-Infective Products (J.J.A., S.N.), and the Office of Communications, Division of Health Communications (H.S.), Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD.

1. Ray WA, Murray KT, Hall K, Arbogast PG, Stein CM. Azithromycin and the risk of cardiovascular death. N Engl J Med 2012;366:1881-90.
2. Asadi L, Eurich DT, Gamble JM, Minhas-Sandhu JK, Marrie TJ, Majumdar SR. Guideline adherence and macrolides reduced mortality in outpatients with pneumonia. Respir Med 2012;106:451-8.
3. Asadi L, Sligl WI, Eurich DT, et al. Macrolide-based regimens and mortality in hospitalized patients with community-acquired pneumonia: a systematic review and meta-analysis. Clin Infect Dis 2012;55:371-80.
4. Ray WA, Murray KT, Meredith S, Narasimhulu SS, Hall K, Stein CM. Oral erythromycin use and the risk of sudden cardiac death. N Engl J Med 2004;351:1089-96.
5. Lapi F, Wilchesky M, Kezouh A, Benisty JI, Ernst P, Suissa S. Fluoroquinolones and the risk of serious arrhythmia: a population-based study. Clin Infect Dis 2012;55:1457-65.

DOI: 10.1056/NEJMp1302726

Discrimination at the Doctor's Office

Holly Fernandez Lynch, J.D., M. Bioethics

Doctors dedicate themselves to helping others. But how selective can they be in deciding whom to help? Recent years have seen some highly publicized examples of doctors who reject patients not because of time constraints or limited expertise but on far more questionable grounds, including the patient's sexual orientation, parents' unwillingness to vaccinate (in surveys, as many as 30% of pediatricians say they have asked families to leave their practice for this reason), and most recently, the patient's weight.

Sometimes these refusals are couched in terms of a physician's conscientious beliefs or appear to be attempts to encourage behavior the physician deems desirable. In other cases, the physician seeks to justify such actions using outwardly neutral terms. For example, the Massachusetts doctor who recently decided to reject all new patients weighing more than 200 lb claimed that she needed to protect her staff from injuries.[1] Similarly, 14% of obstetrics–gynecology practices polled by the *South Florida Sun-Sentinel* in 2011 said they have set weight limits for new patients, citing reasons ranging from lack of specialized equipment to fear of malpractice suits over complications caused by obesity.

Despite the varied rationales, patients who are rejected are likely to feel discriminated against. Unlike physicians who refuse to provide a particular service across the board, so that no patient can argue that he or she has been treated differently from others, the physicians in these instances do treat certain patients differently because of their personal characteristics. Of course, physicians ought to tailor their behavior to patients' characteristics when doing so is medically relevant, but differential treatment based on negative moral judgments about patients should not be tolerated. Indeed, the American Medical Association's Ethical Rule 10.05 permits refusal of services that are beyond the physician's competence, not medically indicated, or "incompatible with the physician's personal, religious, or moral beliefs" but emphasizes that physicians "cannot refuse to care for patients based on race, gender, sexual orientation, gender identity, or any other criteria that would constitute invidious discrimination."

Legal standards largely accord with this formulation, with some additional nuance. Although physicians owe substantial duties to their existing patients, including an obligation to avoid abandonment, initiation of a doctor–patient relationship is voluntary for both parties. There is, however, an important exception: physicians may refuse a prospective patient only for a reason that is not prohibited by contract or law. Local, state, and federal laws prohibit certain types of discrimination against patients. For example, many states prohibit places of "public accommodation," including doctors' offices and hospitals, from discriminating on the basis of characteristics such as race, color, national origin, nationality, ancestry, religion, creed, age, marital status, familial status, sex, sexual orientation, gender identity, medical condition, disability, or other personal features — although, beyond the baseline federal protections, the grounds that are included vary by jurisdiction. Title VI of the federal Civil Rights Act of