Azithromycin and risk of sudden cardiac death: Guilty as charged or falsely accused?

A March 2013 warning by the US Food and Drug Administration that azithromycin (Zithromax, Zmax, Z-pak) may increase the risk of sudden cardiac death does not mean we must abandon using it. We should, however, try to determine if our patients have cardiovascular risk factors for this extreme side effect and take appropriate precautions.

Azithromycin, a broad-spectrum macrolide antibiotic, is used to treat or prevent a range of common bacterial infections, including upper and lower respiratory tract infections and certain sexually transmitted diseases.

In terms of overall toxicity, azithromycin has been considered the safest of the macrolides, as it neither undergoes CYP3A4 metabolism nor inhibits CYP3A4 to any clinically meaningful degree, and therefore does not interfere with the array of commonly used medications that undergo CYP3A4 metabolism.

Also, in vitro, azithromycin shows only limited blockade of the potassium channel hERG. This channel is critically involved in cardiomyocyte repolarization, and if it is blocked or otherwise malfunctioning, the result can be a prolonged QT interval, ventricular arrhythmias, and even sudden cardiac death. Therefore, lack of blockade, as reflected by a high inhibitory concentration (Table 1), boded well for the safety of azithromycin in terms of QT liability. However, we should be cautious in interpreting in vitro data.

With its broad antibiotic spectrum and perceived favorable safety profile, azithromycin has become one of the top 15 most prescribed drugs and the best-selling antibiotic in the United States, accounting for 55.4 million prescriptions in 2012, according to the IMS Institute for Healthcare Informatics.

The FDA receives 203 reports of adverse events in 8 years

However, beginning with a report of azithromycin-triggered torsades de pointes in 2001, a growing body of evidence, derived from postmarketing surveillance, has linked azithromycin to cardiac arrhythmias such as pronounced QT interval prolongation and associated torsades de pointes (which can progress to life-threatening ventricular fibrillation). Other, closely related macrolides such as clarithromycin and erythromycin are also linked to these effects.

Furthermore, in the 8-year period from 2004 to 2011, the US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) received a total of 203 reports of azithromycin-associated QT prolongation, torsades de pointes, ventricular ar-
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All physicians should consider risk factors for QT prolongation and torsades de pointes when prescribing azithromycin.

Despite these inherent flaws, initial postmarketing surveillance reports cast enough doubt on the long-standing notion that azithromycin is the safest macrolide antibiotic to prompt Ray et al10 to assess its safety in an observational, nonrandomized study of people enrolled in the Tennessee Medicaid program.

They found that, over the typical 5 days of therapy, people taking azithromycin had a rate of cardiovascular death 2.88 times higher than in people taking no antibiotic, and 2.49 times higher than in people taking amoxicillin (TABLE 2).

However, the absolute excess risk compared with amoxicillin varied considerably according to baseline risk score for cardiovascular disease, with 1 excess cardiovascular death per 4,100 in the highest-risk decile compared with 1 excess cardiovascular death per 100,000 in the lowest-risk decile.10,11

Moreover, the increase in deaths did not persist after the 5 days of therapy. This time-limited pattern directly correlated with expected peak azithromycin plasma levels during a standard 5-day course.

Ray et al used appropriate analytic methods to attempt to correct for any confounding bias intrinsic to the observational, nonrandomized study design. Nevertheless, the patients were Medicaid beneficiaries, who have a higher prevalence of comorbid conditions and higher mortality rates than the general population. Therefore, legitimate questions were raised about whether the results of the study could be generalized to populations with substantially lower baseline risk of cardiovascular disease and if differences in the baseline characteristics of the treatment groups were adequately controlled.12,13

The striking observations by Ray et al,10 coupled with the concerns raised by postmarketing surveillance reports, compelled the FDA

<table>
<thead>
<tr>
<th>Macrolide antibiotic</th>
<th>hERG IC₅₀ (µM)ᵃ</th>
<th>CYP3A4 substrate</th>
<th>CYP3A4 inhibitor</th>
<th>Adverse events in FAERSᵇ</th>
<th>Fatal events in FAERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azithromycin³⁻⁵</td>
<td>1,091</td>
<td>No</td>
<td>No</td>
<td>203</td>
<td>65</td>
</tr>
<tr>
<td>Clarithromycin⁴⁻⁵</td>
<td>45.7</td>
<td>Yes</td>
<td>Yes</td>
<td>246</td>
<td>66</td>
</tr>
<tr>
<td>Erythromycin⁴⁻⁵</td>
<td>38.9</td>
<td>Yes</td>
<td>Yes</td>
<td>50</td>
<td>17</td>
</tr>
<tr>
<td>Telithromycin⁴⁻⁵</td>
<td>42.5</td>
<td>Yes</td>
<td>Yes</td>
<td>107</td>
<td>29</td>
</tr>
</tbody>
</table>

ᵃThese represent experimental values obtained under dissimilar experimental conditions. As such, use of these values to directly compare the propensity of each drug to prolong the QT interval and cause torsades de pointes should be avoided.

ᵇAdverse event reporting from postmarketing surveillance does not account for prescription volume and is often subjected to significant bias from confounding variables, quality of reported data, duplication, and underreporting of events.

RAY ET AL FIND A HIGHER RISK OF CARDIOVASCULAR DEATH

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THE FDA REVISES AZITHROMYCIN’S WARNINGS AND PRECAUTIONS

The striking observations by Ray et al,10 coupled with the concerns raised by postmarketing surveillance reports, compelled the FDA
Although azithromycin may increase the relative risk of a cardiovascular event, for most otherwise-healthy patients the absolute risk is miniscule.
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ventricular arrhythmias and sudden death and to subsequently improve how these patients are monitored when the use of QT-prolonging and torsadogenic drugs is medically necessary.\textsuperscript{15}

\section*{AN ELECTRONIC MEDICAL RECORD FLAGS QTc $\geq$ 500 MS}

On the heels of these AHA/ACC suggestions, our hospital has adopted an institution-wide QT alert system. Here, the electronic medical record system (Centricity EMR; GE Healthcare) uses a proprietary algorithm to detect and electronically alert ordering physicians when a patient has a prolonged QT interval, and gives information about the potential clinical significance of this electrocardiographic finding.\textsuperscript{16} Physicians also receive a warning when ordering QT-prolonging drugs in patients at risk.

This system is still in its infancy, but it has already confirmed that a prolonged QT interval (QTc $\geq$ 500 ms) is a powerful predictor of death from any cause and has demonstrated that mortality rates in those with prolonged QT intervals increase in a dose-dependent fashion with the patient's number of modifiable risk factors (eg, electrolyte disturbances or QT-prolonging medications) and nonmodifiable risk factors (eg, genetic disposition, female sex, structural heart disease, diabetes mellitus).\textsuperscript{16} We have also found evidence that modifiable risk factors may have a more pronounced effect on mortality risk than nonmodifiable risk factors.\textsuperscript{16}

These findings suggest that information technology-based QT alert systems may one day provide physicians with an important tool to efficiently identify and possibly even modify the risk of cardiovascular death in patients at high risk, for example, by correcting electrolyte abnormalities or reducing the burden of QT-prolonging medications.

\section*{CONSIDER RISK OF QT PROLONGATION WHEN PRESCRIBING AZITHROMYCIN}

For most institutions and clinical practices, such electronic QT alert systems are still years if not decades away. However, in light of the information summarized above, all physicians should begin considering risk factors for QT prolongation and torsades de pointes (summarized in \textbf{TABLE 3}) and weighing the risks and benefits of prescribing azithromycin vs alternative antibiotics with minimal QT liability. This should be relatively simple to do. Things to keep in mind:

\begin{itemize}
  \item Although azithromycin may increase the relative risk of a cardiovascular event, for most otherwise-healthy patients, the absolute risk is miniscule.
\end{itemize}

\begin{table}[h]
\centering
\caption{Risk factors for QT prolongation and torsades de pointes}
\begin{tabular}{|l|}
\hline
\textbf{Modifiable risk factors} \\
Electrolyte disturbances \\
  Hypocalcemia (calcium < 4.65 mg/dL) \\
  Hypokalemia (potassium < 3.4 mmol/L) \\
  Hypomagnesemia (magnesium < 1.7 mg/dL) \\
QT-prolonging medication polypharmacy \\
  Concurrent use of $\geq$ 1 QT-prolonging medication (see www.azcert.org) \\
\textbf{Nonmodifiable risk factors} \\
Common diagnoses \\
  Acute coronary syndrome \\
  Anorexia nervosa or starvation \\
  Bradycardia (< 45 bpm) \\
Cardiac heart failure (ejection fraction < 40%; uncompensated) \\
Congenital long QT syndrome or other genetic susceptibility \\
Congenital QT prolongation (eg, long QT syndrome) \\
Diabetes mellitus (type 1 and 2) \\
Hypertrophic cardiomyopathy \\
Hypoglycemia (documented and in absence of diabetes) \\
Pheochromocytoma \\
Status post cardiac arrest (within 24 hours) \\
Status post syncope or seizure (within 24 hours) \\
Stroke, subarachnoid hemorrhage, or other head trauma (within 7 days) \\
Personal or family history of QT interval prolongation or sudden unexplained death in the absence of a clinical or genetic diagnosis \\
Elderly (> 65 years of age) \\
Female \\
\hline
\end{tabular}

While no formal risk scorecard for drug-induced QT-prolongation exists, a “pro-QTc” score $\geq$ 4 based on risk factors similar to those listed above was an independent predictor of mortality in patients with QT interval prolongation.\textsuperscript{14} Unfortunately, the predictive value of these risk factors in patients with normal or borderline QT intervals has not been assessed.
\end{table}
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- In a patient at risk (eg, with baseline QT prolongation or multiple risk factors for it), if azithromycin or another QT-prolonging antibiotic such as a macrolide or fluoroquinolone is medically necessary due to preferential bacterial susceptibility or patient allergies, every effort should be made to correct modifiable risk factors (eg, electrolyte abnormalities) and, if possible, to avoid polypharmacy with multiple QT-prolonging drugs.

- For patients who have multiple risk factors for QT prolongation in whom treatment with a known QT-prolonging medication is still deemed in the patient’s best interest, strong consideration should be given to in-patient administration and monitoring until the treatment has been completed. With careful consideration of modifiable and nonmodifiable risk factors as well as a little extra caution when prescribing potential QT-prolonging medications such as azithromycin, the clinical benefit of these often-advantageous medications can be maximized and the incidence of these tragic but rare drug-induced sudden cardiac deaths can be reduced.

REFERENCES


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