# Life-Threatening Bradyarrhythmia After Massive Azithromycin Overdose

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A 9-month-old infant was inadvertently administered azithromycin 50 mg/kg, taken from floor stock, instead of the prescribed ceftriaxone. Shortly thereafter, she became unresponsive and pulseless. The initial heart rhythm observed when cardiopulmonary resuscitation was started was a wide-complex bradycardia, with a prolonged rate-corrected QT interval and complete heart block. The baby was resuscitated with epinephrine and atropine, but she suffered severe anoxic encephalopathy. Torsade de pointes and QT-interval prolongation have been reported after administration of macrolide antibiotics, including azithromycin, both intravenously and orally. This has occurred especially in the context of coadministered drugs that inhibit the cytochrome P450 (CYP) 3A4 isoenzyme, such as ketoconazole and astemizole. However, bradycardia with complete heart block has not, to our knowledge, been reported specifically with intravenous administration of azithromycin alone, either with therapeutic doses or overdose. Clinicians should be alerted about the potential of azithromycin to cause life-threatening bradycardia, and pharmacy systems should be implemented to ensure special care in the safe administration of this drug, especially when dispensed from a point-of-care source.

**Key Words:** bradyarrhythmia, azithromycin, macrolide antibiotics, QT-interval prolongation, QTc, torsade de pointes.

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Macrolide antibiotics have caused cardiac arrhythmias when given by rapid intravenous administration or in overdose.[1] Specifically, torsade de pointes has occurred with administration of erythromycin lactobionate, the most common intravenously administered macrolide.[2] We recently treated an infant who experienced life-threatening bradyarrhythmia after an overdose of intravenous azithromycin. As this drug is achieving widespread use in its intravenous form, and we are not aware of a report of arrhythmia resulting from an azithromycin overdose in a child without predisposing risk factors, we felt it important to alert clinicians about this potential complication.

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## Case Report

A 9-month-old infant weighing 9.2 kg was brought to another institution's emergency department with a 2-day history of fever and tugging at her ear. On arrival, her temperature was 105°F. Findings on physical examination were normal except for a dull, injected left tympanic membrane. She had no significant previous illnesses and had received no drugs other than acetaminophen, which was given in the emergency department shortly after her arrival. Intravenous ceftriaxone 500 mg was prescribed. In error, azithromycin 500 mg was taken from floor stock and administered

intravenously over 20 minutes.

The patient's medical record indicated specifically that azithromycin was administered, with the time of administration subscribed by a member of the emergency room staff (who was not the individual who performed the initial assessment of the patient). The medical record did not demonstrate pharmacist verification of the order, and the administration record was not initialed by emergency department staff to indicate that it had been checked against the original order.

Nineteen minutes after the start of the infusion and just before its termination, emergency department staff found the baby pulseless, cyanotic, and unresponsive. Chest compressions and bag-valve-mask ventilation were begun, followed by endotracheal intubation. When monitoring of the cardiac rhythm was started, a wide-complex bradycardia was observed, with third-degree atrioventricular block and an intrinsic pulse rate of 40 beats/minute (Figure 1). The rate-corrected QT interval was 0.62 seconds (normal < 0.45 sec[3]).

Intravenous epinephrine 0.1 mg was first given 12 minutes after the start of resuscitative efforts. Before sinus rhythm was restored 7 minutes later, epinephrine 0.1 mg and atropine 0.2 mg were each given 3 times, separated by approximately 1 minute. After restoration of sinus rhythm, one additional dose of epinephrine was given for a relative bradycardia of 60 beats/minute. In addition, sodium bicarbonate 30 mEq was given for documented metabolic acidosis; the first blood gas measurement demonstrated a pH of 6.89, partial pressure of carbon dioxide 52 mm Hg, and partial pressure of oxygen 316 mm Hg. After resuscitation, the patient's electrolyte concentrations were as follows: sodium 145 mEq/L (normal range 138–145 mEq/L), potassium 3.2 mEq/L (3.7–5.0 mEq/L), total carbon dioxide 16 mEq/L (22–32 mEq/L), and ionized calcium 2.52 mEq/L, (2.24–2.64 mEq/L).

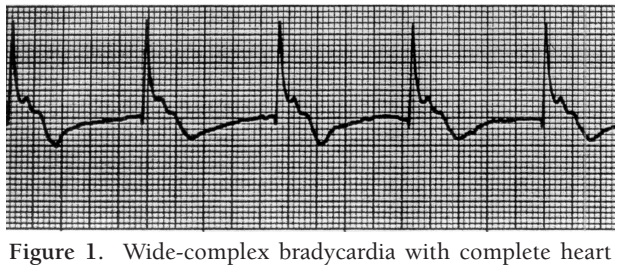

**Figure 1.** Wide-complex bradycardia with complete heart block initially observed in the patient.

Thereafter, sustained heart rate and blood pressure were maintained with epinephrine 0.1 µg/kg/minute and milrinone 0.5 µg/kg/minute; at the time of the patient's transfer to our institution, her systolic blood pressure was 84 mm Hg, diastolic blood pressure was undetectable, and pulse was 156 beats/minute. Her subsequent hospital course was complicated by acute respiratory distress syndrome and seizures; she survived, but with significant anoxic encephalopathy.

## Discussion

Macrolide antibiotics have been reviewed and found arrhythmogenic.[4] In some reports, QT prolongation degenerating to torsade de pointes occurred most frequently after administration of intravenous erythromycin lactobionate.[1, 2, 5, 6] Similarly, QT prolongation has been reported with administration of many other drugs, including the macrolide class. It has been asserted, although unproven, that any prolongation of the QT interval increases the risk of torsade de pointes.[7] Macrolides administered orally also prolong the QT interval, particularly when given in conjunction with a drug that inhibits their metabolism. A substantial risk of sudden death has been reported in patients taking oral erythromycin concomitantly with inhibitors of the CYP3A4 isoenzyme, such as the nitroimidazole antifungal agents (e.g., fluconazole and ketoconazole), diltiazem, verapamil, and troleandomycin,[8] as well as other agents such as benzodiazepines, cyclosporine, warfarin, protease inhibitors, rifabutin, tacrolimus, and theophylline.[4, 9]

Azithromycin, the macrolide administered to our patient, has not, to our knowledge, caused an arrhythmia when administered alone, either orally or intravenously. From January–December 2000, 156 reports were filed with the United States Food and Drug Administration's Adverse Event Reporting System (AERS) describing drug-related torsade de pointes.[10] Half (78) of these reports were attributed to administration of a macrolide antibiotic, and azithromycin was specifically identified in 23 (15%) of the total reports.

Most patients in the cases reported were taking numerous other drugs, and the AERS data do not distinguish arrhythmias specifically attributed to a particular macrolide administered alone. Therefore, these data do not clearly indicate that

azithromycin was the likely causative agent. The AERS data do not attribute any other arrhythmia specifically to a macrolide antibiotic, nor do they identify the administration route or whether the drug was given outside administration guidelines. Notwithstanding the absence of reports specifically describing an arrhythmia attendant to administration of azithromycin, the drug may affect the QT interval, even at therapeutic dosages.

Prolongation of the QT interval, albeit small, was reported in a study of 47 patients treated with azithromycin for 5 days.[11] Another study failed to document QT prolongation at conventional dosages.[12] Comparison of the various macrolide antibiotics to potentially prolong the QT interval indicated that azithromycin did not do so in an animal model at concentrations comparable to those encountered in the clinical setting.

Although our patient had significant QT prolongation, torsade de pointes was not observed. Life-threatening bradycardia has been reported after coadministration of verapamil with telithromycin[13] or clarithromycin,[14] and of erythromycin with digoxin.[15] Bradycardia with complete heart block was reported in an animal model studying drug-induced QT prolongation.[16] To our knowledge, however, there are no previous reports of humans developing bradycardia with complete heart block after azithromycin or other macrolide antibiotics administered alone. In the aforementioned animal study, bradycardia was attributed to a dose-dependent reduction in repolarizing potassium current.[16] Therefore, the hypokalemia (potassium concentration 3.2 mEq/L) noted in our patient, albeit mild, may have played a role in the genesis of the arrhythmia. Possibly, on the other hand, torsade de pointes was present in the infant before monitoring was begun, and the observed bradyarrhythmia was an agonal event.

Arrhythmias after intravenous administration of erythromycin have been correlated with the administration dose and infusion rate.[17] In our patient, more than 50 mg/kg of azithromycin—a 5–10-fold overdose—was given intravenously over 20 minutes instead of the recommended infusion time of 60 minutes. It is likely that both the amount of overdose and the rapidity of administration contributed to this incident. No other cardiopulmonary disease, electrolyte disturbance, or drug was present. In an analysis of the likelihood that this overdose had a role in causing the arrhythmia, a score of 5 was determined from the Naranjo scale, suggesting that the relationship was probable.[18]

The therapy for our patient's arrhythmia was in accordance with published guidelines for a child experiencing pulseless cardiac arrest,[19] and her sinus rhythm was restored with epinephrine and atropine. Although atropine is not included in the algorithm for pulseless cardiac arrest, it is recommended for symptomatic bradycardia unresponsive to epinephrine and in atrioventricular block. Administration of milrinone by the caregivers in the postresuscitation period was directed at improving perfusion; this drug has facilitated resuscitation and attenuated postresuscitation myocardial dysfunction.[20]

We emphasize that this incident was likely the result of an error in drug administration. All drugs, of course, should be administered in the right form, to the right patient, in the right dose, by the right route, at the right time. However, some agents represent a significantly greater risk than others; the macrolides are one such class. Point-of-care storage of drugs may increase the risk of incorrect administration due to lack of pharmacist participation. The American Society of Health-System Pharmacists recommends verification of all orders before drug administration, and that drugs administered by nurses in a health care organization be checked against the original orders.[21] They also recommend direct involvement of pharmacists in processing drug orders and in the procurement, distribution, and control of all drugs administered within the health care organization. They further recommend that floor stock be restricted to drugs used only in emergencies.[22]

## Conclusion

This case report emphasizes the likelihood that intravenously administered azithromycin may induce a life-threatening arrhythmia, as do other drugs in its class, when given at the wrong dose or infusion rate. Pharmacy systems should be implemented to intercept drug errors before administration, and to educate caregivers to be aware of the possible consequences of misadministration of all drugs, including the macrolide antibiotics.

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