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Bradycardia and Hypothermia Complicating Azithromycin Treatment

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Conflict of interest: None declared

Patient: Male, 4
Final Diagnosis: Febrile neutropenia
Symptoms: Fever
Medication: Azithromycin
Clinical Procedure: —
Specialty: Infectious Diseases

Objective: Unusual or unexpected effect of treatment

Background: Azithromycin is a macrolide antibiotic widely used to treat respiratory, urogenital, and other infections. Gastrointestinal upset, headache, and dizziness are common adverse effects, and prolongation of the rate-corrected electrocardiographic QT interval and malignant arrhythmias have been reported. There are rare reports of bradycardia and hypothermia but not in the same patient.

Case Report: A 4-year-old boy given intravenous azithromycin as part of treatment for febrile neutropenia complicating leukemia chemotherapy developed hypothermia (rectal temperature 35.2°C) and bradycardia (65 beats/minute) after the second dose, which resolved over several days post-treatment, consistent with persistence of high tissue azithromycin concentrations relative to those in plasma. A sigmoid E_{max} pharmacokinetic/pharmacodynamic model suggested a maximal azithromycin-associated reduction in heart rate of 23 beats/minute. Monitoring for these potential adverse effects should facilitate appropriate supportive care in similar cases.

Conclusions: Recommended azithromycin doses can cause at least moderate bradycardia and hypothermia in vulnerable pediatric patients, adverse effects that should prompt appropriate monitoring and which may take many days to resolve.

MeSH Keywords: Azithromycin • Bradycardia • Hypothermia

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/905400

Background

Azithromycin is a broad-spectrum macrolide antibiotic used to treat respiratory, urogenital, and other infections [1]. Gastrointestinal upset, headache, and dizziness are common adverse effects, and prolongation of the rate-corrected electrocardiographic QT interval (QT_c) and malignant arrhythmias have been reported [2], as have rare instances of bradycardia [3,4] and hypothermia [5].

We report the case of a child who developed both hypothermia and bradycardia after administration of therapeutic azithromycin doses.

Case Report

A 4-year-old boy in the delayed intensification phase of treatment for B cell lymphoblastic leukemia was admitted with fever, cough, and coryza. He had no other illnesses and had taken no recent corticosteroid therapy. He was started on 1.7 g intravenous piperacillin (100 mg/kg) plus tazobactam every 6 hours for febrile neutropenia [6], but this was changed to intravenous ceftriaxone 850 mg daily after 1 dose when admission hematology showed he was not neutropenic. His fever continued and he developed neutropenia (0.5×10^9/L) on the third day of hospitalization. His leukemia chemotherapy was withheld and piperacillin/tazobactam plus 380 mg of intravenous amikacin daily was recommenced. Thoracic CT scan appearances at that time were consistent with a fungal/atypical respiratory infection and he was started on 60 mg intravenous liposomal amphotericin B daily plus 170 mg (10 mg/kg) intravenous azithromycin followed by 85 mg (5 mg/kg) daily as a result. Piperacillin, tazobactam, and amikacin were continued.

Within 3 hours of the second azithromycin dose, he developed bradycardia (heart rate 75 beats/minute) when asleep. Five hours later, the bradycardia had worsened (65 beats/minute), his systolic blood pressure had fallen (110 to 80 mmHg), and he had become hypothermic (rectal temperature 35.2°C). Septic shock was diagnosed and, after intravenous fluids, the pulse rate and blood pressure increased. Blood cultures proved sterile, and serum electrolytes and venous blood gas analysis were normal. A nasopharyngeal aspirate showed picornavirus and parainfluenza RNA detected by PCR. Over the next 24 hours the patient experienced further episodes of bradycardia and hypothermia requiring use of a temperature management system. Electrocardiographic monitoring showed a $QT_c \leq 480$ msec$^{-0.5}$. Liposomal amphotericin B was withheld and 310 mg intravenous vancomycin was added on the seventh day of hospitalization. The azithromycin was ceased after the third dose and the bradycardia and hypothermia improved over the next 72 hours. The bradycardia had resolved by the tenth day of admission and the hypothermia by the eleventh day.

Azithromycin was measured in available plasma samples using liquid chromatography-mass spectrometry [7] and pharmacokinetic/pharmacodynamic (PK/PD) modelling was performed using NONMEM (v 7.2.0, ICON Development Solutions, Ellicott City, MD). Plasma azithromycin concentrations and clinical data were available at 16 time-points (Figure 1). A two-compartment PK model with first-order elimination from the central compartment provided the best fit (Table 1). Overall azithromycin exposure, the simulated C_{max}, and the terminal elimination half-life were consistent with values after intravenous dosing based on data from studies of oral azithromycin in this age group [8]. A PK/PD model was developed incorporating heart rate during sleep. Observations before the final azithromycin dose were excluded to minimize the confounding effect of active infection. A negative sigmoid E_{max} model

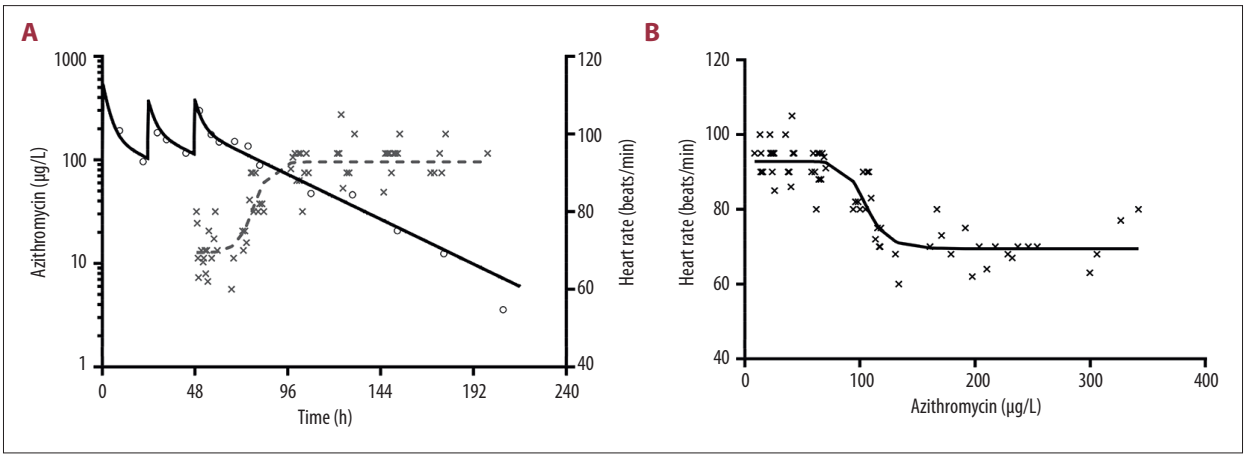

Figure 1. (**A**) Time *vs.* concentration (black open circles) and resting heart rate (grey crosses) plotted with model curves (black solid line and grey dashed line, respectively). (**B**) Pharmacodynamic relationship between resting heart rate and azithromycin concentration with actual observations as black crosses and model as solid black line.

Table 1. Model parameters for the pharmacokinetic/pharmacodynamic model along with secondary pharmacokinetic variables.

Parameter	Value	Published range [8]
Pharmacokinetic model		
Clearance (L/h)	18.1	
Central volume of distribution (L)	305	
Inter-compartmental clearance (L/h)	46.2	
Peripheral volume of distribution (L)	451	
Proportional residual variability (%)	12.8	
Additive residual variability (µg/L)	8.54	
Secondary parameters		
Distribution half-life (h)	2.4	
Terminal elimination half-life (h)	33	31.6±6.6*
Simulated maximum concentration (µg/L)		
First dose	530	224±120*
Second dose	368	
Third dose	378	
Total area under the curve to infinity (µg.h/L)	18.785	7.364±2.604*
Pharmacodynamic model		
Baseline heart rate (beats/min)	92.9	
Half maximal effective concentration (EC50) (µg/L)	105	
Maximal effect (Emax) (beats/min)	–23.4	
Hill coefficient	11	
Additive residual variability (beats/min)	26.8	

* Children aged 0.5-5 years receiving multiple doses of azithromycin suspension (10mg/kg then 5 mg/kg Days 2–5) with values based on sampling after the last dose (steady state) and to be interpreted against oral bioavailability of 40–50%.

adequately described the association between plasma azithromycin and heart rate (Figure 1), the maximal azithromycin effect being a reduction of 23 beats/min.

Discussion

There have been 2 previously reported cases of severe bradycardia associated with azithromycin [3,4], and 3 additional cases of hypothermia in a brief report from 1 pediatric unit [5]. Of the 2 bradycardia cases, 1 was a 9-month-old infant who was accidentally given a high (50 mg/kg) dose of azithromycin and then developed a wide-complex bradycardia, prolonged QT_c, and complete heart block [4]. The second involved a man with human immunodeficiency virus infection who developed marked QT prolongation and sinus bradycardia after a single 500-mg dose of intravenous azithromycin [3]. The 3 cases of azithromycin-associated hypothermia were all in children [5]. The first was a 3.5-year-old girl with tonsillopharyngitis who became unresponsive and had a rectal temperature of 34.4°C after the third daily 10 mg/kg azithromycin dose. The azithromycin was ceased on the fifth day and her hypothermia resolved. The second case was a 5-year-old girl who developed a rectal temperature of 35°C after the second daily dose of 200 mg azithromycin for tonsillopharyngitis. The hypothermia persisted for 4 days after treatment was discontinued. The third case was a 5-year-old boy treated with 200 mg azithromycin daily for otitis media, whose rectal temperature was 35.7°C 12 hours after the third dose. The hypothermia resolved over the next 24 hours.

The present case is the first to show a clear dose-response relationship between plasma azithromycin concentrations after therapeutic doses and bradycardia in a severely ill child. This observation, and the rarity of previous reports of azithromycin-associated bradycardia [3,4], suggest that our patient had underlying latent disease of the sinus and/or atrio-ventricular node which was unmasked by azithromycin treatment, albeit not severe enough to warrant cardiologic intervention [9]. Although azithromycin has a relatively weak pro-arrhythmic potential through inhibition of the rapid component of

delayed rectifier K+ current channel compared with other macrolides [10] and our patient's QT_c prolongation was not marked compared with that in other severely ill pediatric patients [11], bradycardia is a risk factor for azithromycin-associated malignant arrhythmias when the QT_c is prolonged [12]. In addition to electrocardiographic monitoring in cases such as ours, management should include withdrawal of other medications associated with QT_c prolongation and correction of significant electrolyte abnormalities, including hypokalemia.

The potential causes of non-environmental hypothermia include infections, shock, and pharmacotherapy [13]. Whether our patient's hypothermia was due to azithromycin rather than other factors is unknown, but, in addition to similar pediatric cases [5] and reports of hypothermia with other macrolides [14], the resolution of hypothermia was protracted in parallel with that for bradycardia and consistent with the persistence of high tissue concentrations of azithromycin relative to those in plasma [15]. Although bradycardia was not a reported feature of the 4 previously reported cases of macrolide-associated hypothermia in children [5,14], hypothermia is a recognized cause of bradycardia [16] and a bidirectional relationship cannot be excluded in our case. Hypothermia can cause or contribute to multi-organ failure but cardiotoxic effects appear rare, at least in adults [17]. Thus, coexistent bradycardia and hypothermia, as in our patient, who responded to supportive care, may not increase the risk of adverse outcomes.

Conclusions

This case provides evidence that recommended azithromycin doses can cause at least moderate bradycardia and hypothermia in vulnerable pediatric patients, which are adverse effects that may take days to resolve. Monitoring, including rectal temperature, heart rate, and QT_c, should allow identification of these potential complications and facilitate appropriate supportive care.

Conflicts of interest

None.

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