Azithromycin: more lethal than chloramphenicol?

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Abstract. Azithromycin is commonly used in sexual health and respiratory medicine, often when the diagnosis is presumptive. A recent article by Ray *et al*. reported that 1 out of 20 000 courses of low-dose azithromycin was associated with (sudden) cardiovascular death (including 1 out of 4000 courses in high-risk cardiovascular patients), ascribing these deaths to azithromycin itself. Here, we critique the actual study and examine conflicting data from randomised control trials, animal studies and observational data.

Introduction

Azithromycin is commonly used in sexual health medicine. The Melbourne Sexual Health Centre has dispensed over 24 700 prescriptions for azithromycin to ambulatory patients since 2004 (including 4069 in 2012), primarily to treat nongonococcal urethritis, although an azithromycin responsive organism (e.g. *Chlamydia trachomatis* or *Mycoplasma genitalium*) is only confirmed in ~30% of such patients.[1] Furthermore, azithromycin is prescribed for sexual contacts whom clinicians have not assessed, a practice used extensively internationally and supported by randomised control trials.[2]

However, a recent report by Ray *et al*. indicated oral azithromycin resulted in 47 additional acute cardiovascular (mostly sudden) deaths per million courses.[3] The death rate (1 out of 21 277 courses) exceeds that ascribed to high-dose oral chloramphenicol (1 out of 21 671),[4] now essentially abandoned because of toxicity. Alarmingly, the death rate amongst high-risk cardiovascular patients was five-fold higher, and estimated at 245 excess cardiovascular deaths per million courses or 1 out of 4082 patients, with confidence limits stretching to 1 out of 1736 courses. On face value, this should be of great concern to sexual health physicians. However, we suggest caution be exercised interpreting their findings, based on a critique of the published report, and conflicting evidence arising from multiple randomised control trials, animal data, observational studies and extensive clinical experience. Given the potential impact of the association, we feel it appropriate to detail some of these issues here.

Basis for the study

The lead author has published numerous articles investigating the relationships between medications and sudden cardiac death.[5–10] The current article studied 5-day courses of oral azithromycin, presumably the standard Z-Pak (Pfizer; 500 mg on day 1, then 250 mg on days 2–5; a total of 1.5 g; peak serum concentration: 0.31–0.41 mg L^{-1}[11,12]), although results would reasonably apply to chlamydia treatment doses (1 g stat; peak serum concentration 0.82–1.07 mg L^{-1}[13,14]) used by sexual health physicians, as the authors discuss a potential link between azithromycin serum (rather than tissue) concentrations and the risk of cardiovascular death.[15,16] The authors build a narrative around cardiac arrhythmia and torsades de pointes (TdP) stating: 'Our study was prompted by evidence that azithromycin is pro-arrhythmic...' Seven case reports (none of which resulted in death) are cited with disparate findings: QT prolongation with no TdP, QT prolongation with TdP and TdP without QT prolongation.[17–23] In five cases, the cumulative dose was 1 g or less, one case occurred at day 7 (total: 3.5 g azithromycin) and one case was in a foreign language. Issues such as sepsis, concurrent use of proarrhythmic drugs, hypokalaemia, congenital QT prolongation and underlying cardiomyopathy and dysrhythmia, however, confound the cases. Two citations[21,22] have striking word-for-word similarities suggestive of plagiarism, partially undermining the basis upon which the study was predicated (this issue has been brought to the attention of the relevant journal). For example, Matsunaga *et al*. in 2003[21] described the following clinical picture:

> '*Upon presentation, the patient's blood pressure was 126/72 mmHg, heart rate 90 bpm, respiratory rate 26 pm, temperature 38.1°C, and SpO2 was 93% on room air. He had left basal crackles but no signs of right ventricular failure. Chest X-ray revealed new left basal opacity. White blood cell count was 16.1/mm3, 93% of which were neutrophils.*

> *Arterial blood gas showed pH of 7.49, pCO2 35,*
> *pO2 61, HCO3 26, SaO2 93% on room air.'*

Russo *et al.* in 2006[22] described their patient with exactly the same parameters:

> '*Upon presentation, the patient's blood*
> *pressure was 126/72 mmHg, heart rate 90*
> *bpm, respiratory rate 26 pm, temperature*
> *38.1°C, and SpO2 was 93% at room air. He*
> *presented left basal crackles but no signs of*
> *right ventricular failure. Chest X-ray revealed*
> *new left basal opacity. White blood cell count*
> *was 16.1/mm3, 93% of which were neutrophils.*
> *Arterial blood gas showed pH of 7.49, pCO2 35*
> *mmHg, pO2 61 mmHg, HCO3 26 mmol/L, SaO2*
> *93% at room air.'*

To our knowledge, there is only one report of arrhythmic death associated with azithromycin (anoxic brain injury after ventricular tachycardia);[24] the patient was hypokalaemic and it was not clear if the patient actually took the prescribed azithromycin.

Randomised control trials

Importantly, Ray *et al.* do not discuss six randomised placebo-controlled trials in high-risk cardiovascular patients, all showing that azithromycin *reduced* mortality (albeit nonsignificantly, odds ratio: 0.91[25]), including sudden death.[26–31] The largest (WIZARD) trial,[30] utilising azithromycin at a dosage of 1800 mg over 3 days, followed by 600 mg azithromycin weekly for 11 weeks, indicated the benefit was greatest early (a 30% reduction in mortality and recurrent acute myocardial infarction; $P < 0.05$) and favoured those patients with the highest ongoing cardiovascular risk: smokers, males and diabetics. The SPACE trial showed a similar trend.[32]

Mammalian studies

In at least four mammalian models, TdP could not be induced by azithromycin,[33–36] despite specific efforts to do so including supratherapeutic high-dose intravenous infusions, coadministration of chloroquine and use of experimental atrioventricular block and hypokalaemia. Indeed, Milberg *et al.* characterised a mechanism that potentially explains why azithromycin did not induce TdP even in the presence of QT prolongation, and further demonstrated that azithromycin actually suppressed TdP previously provoked by erythromycin.[34]

Observational cohort data

The issue of drug induced corrected QT (QTc) prolongation leading to TdP is the subject of anecdotal case reports and long lists of implicated drugs have been compiled from adverse drug reaction reports, with an ascribed mortality of 4.5%.[37] A prospective 12-month observational study reported that 251 out of 900 patients admitted to advanced cardiac units had prolonged QTc intervals.[38] Interestingly, the use of 'QT-prolonging medication' (azithromycin was included in that category) was not actually associated with prolonged QTc intervals (36% v. 31%, $P = 0.18$). Rather, QTc prolongation was associated with sepsis, among other things ($P = 0.001$). Thus, azithromycin may be a surrogate marker for sepsis-induced arrhythmia, rather than the cause. Significantly, no episode of TdP occurred among these 251 high-risk cardiac patients admitted with prolonged QTc, despite comorbidities including hypokalaemia, hypomagnesaemia, sepsis and ongoing use of QT-prolonging drugs. Further, a prospective study of 47 healthy adults taking azithromycin (3 g over 5 days) found no significant increase in the QTc interval.[39] At the maximal limits of these observations, the following theoretical mathematical progression could be formulated: (a) 1 in 50 patients on azithromycin get prolonged QTc, (b) 1 in 250 patients with prolonged QTc get TdP and (c) 1 in 20 patients with TdP progress to sudden death. Hence, it would take at least 250 000 courses of azithromycin to get one sudden death, more than ten-fold above that reported by Ray *et al.*

Clinical experience

High-dose IV azithromycin is extensively used in monitored intensive care unit patients with multiple comorbidities where potentially lethal ventricular arrhythmias (including TdP) should be more common than in community settings. Considering that very few episodes of TdP (perhaps 1 in 20) result in death,[37] the data from Ray *et al.* suggest that ~1 in 1000 patients prescribed azithromycin would develop TdP, and ~1 in 200 high-risk cardiovascular patients. It seems likely that this would have been observed and reported more widely in routine azithromycin use in monitored patients.

Critique of the study by Ray *et al*

Several problems relating to the study design should be addressed. First, the veracity of death certificates is compromised by the 25% error rate acknowledged by the authors, using a computerised verification algorithm developed and validated in-house.[40] The use of International Classification of Diseases 9 (ICD9) codes 798.2 ('unexplained' death), 798.8 ('unattended' death) and 799.9 ('unknown' death) raises doubts over the exact nature of the deaths. Given that there were only 112 cardiovascular deaths across the three main cohorts (azithromycin 29, amoxicillin 42 and null group 41), physician review of deaths seems feasible, making the data more robust and helping to mitigate concerns raised by researchers about the accuracy of 'validation' committees.[32,41] Second, it seems unavoidable (given the large size of the cohorts) to assign 'presumptive' diagnoses, for which antibiotics were prescribed based on (1) a predetermined algorithm of 'likely' diagnoses and (2) recent Medicaid encounters. However, the data would be more reliable if the authors had excluded the ~30% of encounters (over 720 000 instances) where clinical data were absent and no antibiotic indication could be assigned, primarily due to telephone prescribing. Exhaustive propensity scoring for underlying comorbidities cannot adequately compensate for contemporaneous clinical parameters such as fever, respiratory rate and blood pressure. This is underscored by a higher rate of respiratory pathology (bronchitis, pneumonia, respiratory symptoms, chronic obstructive pulmonary disease

and other respiratory problem) among patients prescribed azithromycin (44.9%) compared with amoxicillin (27.4%), the clinical import of which is acknowledged by the authors and substantiated by higher use of β-agonists (themselves implicated in sudden cardiac death[42]). With propensity scoring adjustment, respiratory pathology is calculated at 45.1% versus 44.8%, respectively. However, across such large cohorts, even a small 0.3% difference accounts for over 1000 high-risk respiratory patients, where some (or perhaps most) of the 18 excess deaths (allowing for the 1 : 4 ratio) may clearly be attributable to the underlying illness rather than the azithromycin itself. Third, one way to evaluate clinically how well these cohorts were matched at baseline is to observe the early noncardiovascular mortality, which presumably relates to antibiotic indication and reasonably reflects the severity of the illnesses for which the antibiotic was prescribed. Curiously, during the initial 48 h, no patients in the azithromycin group suffered a noncardiovascular death, compared with 11 and 15 for the amoxicillin and no antibiotic groups, respectively; at 72 h, the noncardiovascular deaths were 1, 19 and 28, respectively. Again, allowing for the 1 : 4 patient ratio, one would expect at least three or four early azithromycin deaths to be noncardiovascular in nature. How, then, might the data be clinically explained? It is improbable that the azithromycin group was actually healthier than the null group at baseline, as the groups were matched, except for antibiotic indication. Also, it would be contentious to conclude that azithromycin is potent enough to reduce noncardiovascular mortality so quickly, although azithromycin potency may explain the remarkably low noncardiovascular mortality seen after day 4 of therapy (four azithromycin deaths *v.* 50 amoxicillin deaths). Rather, the most plausible explanation for the minimal early noncardiovascular mortality is that some of the early cardiovascular deaths were incorrectly assigned. Fourthly, no allowance is made for compliance, which is a major issue when assigning adverse drug events in population-based studies. Under research conditions, compliance with the 5-day azithromycin z-pak is reported to be 82–93%.[43,44] An estimate of 10% noncompliance would, *pro rata*, reassign three (of 29) azithromycin deaths to the null group (41 deaths), an issue that is not relevant to the amoxicillin group, as the death rate was equal to those who took no antibiotics. It would be interesting to know what effect a net shift of six deaths would have on the hazard ratios. Fifthly, we note in passing that their critical azithromycin mortality cumulative graph (see fig. 1 of Ray *et al.*[3]) appears to be incorrectly plotted – flat-lining at day 5 instead of day 6.

Summary

Good science is about meticulous observation. Retrospective research predicated on poorly scrutinised references and based around patient cohorts for whom antibiotic indications and the cause of death are imprecisely known is hazardous, particularly when it contradicts prospectively collected data. We suggest that further study of the association between azithromycin and sudden death is warranted. In the meantime, azithromycin should be used appropriately to control sexually transmissible diseases and other infections.

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