

Erythromycin-Induced Ototoxicity: A Case Report and Review of the Literature

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INTRODUCTION

Erythromycin is considered a safe antibiotic. However, advanced age, renal dysfunction, hepatic dysfunction, and high-dose erythromycin (≥ 4 g/day) are risk factors for erythromycin-induced ototoxicity. This condition usually presents as significant bilateral hearing loss, with tinnitus and vertigo occurring in a minority of cases. The ototoxicity develops quickly, with a typical onset of 3 to 4 days, and is usually reversible upon a reduction of the dose or discontinuation of the drug, although there are 4 published cases of irreversible ototoxicity. Erythromycin-induced ototoxicity may be an underrecognized adverse effect. Clinicians should be aware of the potential for this problem and should monitor for signs of ototoxicity, especially in patients with any of the known risk factors. We report a case of erythromycin-induced ototoxicity and review the literature on this adverse effect.

CASE REPORT

A 73-year-old woman (weight 50 kg, height 155 cm) presented to the emergency department on July 20, 1995, with a 3-day history of severe pain in the left upper quadrant. Three days before, she had undergone radiotherapy for non-Hodgkin's lymphoma of her left eye.

Her past medical history consisted of non-Hodgkin's lymphoma of the left orbit (stage 1AE), hypertension, osteoarthritis, hyperuricemia and mild renal dysfunction. She smoked (half a pack per day) and had no known drug allergies.

On examination, the patient was oriented, but restless, distressed, and in obvious discomfort. She was short of breath and had decreased air entry bilaterally, and crackles were heard in the left lower lobe. A chest

radiograph revealed left lower lobe infiltrates. Her temperature was 36.8°C, her heart rate was 126 beats/min, her blood pressure was 140/80 mm Hg, and her respiratory rate was 28 breaths/min.

Laboratory tests revealed that the white blood cell count was elevated ($22.6 \times 10^9/L$; normal range 4.0 to $11.0 \times 10^9/L$), the blood urea nitrogen level was elevated (13.6 mmol/L; normal range 3.0 to 7.0 mmol/L), and the serum creatinine level was elevated (201 $\mu\text{mol/L}$; normal range 3.5 to 97 $\mu\text{mol/L}$). The patient was hypokalemic (potassium level 3.3 mmol/L; normal range 3.5 to 5.0 mmol/L). All other laboratory test results were within normal limits. Arterial blood gas measurement showed that pH was 7.43 (normal range 7.35 to 7.45), partial pressure of oxygen was 66 mm Hg (normal range 80 to 100 mm Hg), partial pressure of carbon dioxide was 30 mm Hg (normal range 35 to 45 mm Hg), and bicarbonate was 20 mmol/L (normal range 21 to 28 mmol/L).

The preoperative diagnosis was ischemic colitis, although urgent laparotomy revealed that the abdomen was normal, with no intraabdominal pathology. Postoperatively, on July 21, she received single doses of gentamicin 80 mg IV and metronidazole 500 mg IV. A medical consult was requested because of the unexplained pain on her left side. On the basis of the chest radiograph and clinical symptoms, left lower lobe pneumonia was diagnosed, and the patient was started on cefuroxime 750 mg IV q12h and erythromycin lactobionate 1 g IV q6h (first dose of erythromycin was received on July 21 at 1600).

Over the weekend of July 23 and 24 (days 3 and 4 of erythromycin therapy), the nurse recorded in the chart that the patient was very hard of hearing. When the patient and her daughter were questioned on July 25, they both described the decrease in hearing as bilat-

eral with sudden onset. There were no signs of tinnitus or vestibular symptoms. There was no obstruction or other physical explanation for the ototoxicity. No audiograms were obtained during the patient's stay in hospital.

On July 23, the patient was receiving labetalol 100 mg PO bid, felodipine 10 mg PO daily, lisinopril 10 mg PO daily, cefuroxime 750 mg IV q12h, erythromycin 1 g IV q6h, salbutamol 5 mg by nebulizer q4h prn, ipratropium bromide 0.25 mg by nebulizer q4h prn, morphine 1 to 4 mg IV q1h prn, and dimenhydrinate 50 mg IV q4h prn. On July 21 and again on July 24, she received one dose of furosemide 20 mg IV (infusion rate unknown). The physician was informed that high-dose erythromycin can cause sudden, symmetrical hearing loss, particularly in elderly patients. As a result, erythromycin was stopped on July 25 (last dose was received on July 25 at 1000). By July 27, there were no further reports of decreased hearing, and the patient's hearing returned to preadmission status within 48 h of the drug being discontinued. It was decided to treat the resolving pneumonia with cefuroxime alone. The need for a macrolide was to be reassessed in 24 to 48 h if there was no further improvement in the pneumonia symptoms. The pneumonia gradually resolved, and the cefuroxime was discontinued on August 3 (day 14 of cefuroxime therapy). On August 4, the patient had completely recovered from the pneumonia, and on August 8, she was discharged home.

DISCUSSION

Erythromycin is considered a safe antibiotic, with gastrointestinal side effects (nausea, vomiting, diarrhea, and abdominal cramps) being the most common (occurring in 5% to 30% of patients).¹ Other adverse effects include thrombophlebitis (common) with IV administration and, rarely, QT interval prolongation and ventricular arrhythmias (including torsade de pointes), hepatotoxicity (in 0% to 10% of cases), hypersensitivity reactions (in less than 0.5% of cases), and ototoxicity.^{1,2}

Although erythromycin has been used since 1952, the first report of erythromycin-induced ototoxicity did not appear until 1973.³ The delayed recognition of an association between erythromycin and ototoxicity might be explained by the fact that large doses (4 g/day) were not used extensively before 1973.⁴ In 1993, Vasquez and colleagues⁵ found fewer than 50 case reports of this adverse effect. Nine articles, including both case reports and reviews,⁶⁻¹⁴ reporting 21 additional cases of erythromycin-induced ototoxicity were identified by a MEDLINE search for the period January 1991 to April 1998.

A prospective, case-control study published in 1992 reported a relationship between high doses of erythromycin and ototoxicity.¹⁵ In that study, 21% of patients (5/24) who received 4 g/day IV erythromycin experienced symptomatic ototoxicity (tinnitus in 3 patients and conversational hearing loss in 2 patients), which was confirmed by audiography. Patients who did not receive erythromycin or who received 2 g/day IV erythromycin did not experience ototoxicity. Mean peak serum erythromycin concentrations were significantly higher ($p < 0.05$) in the 5 patients who were affected (mean value 17.1 mg/L) than in the 25 erythromycin-treated patients who did not experience ototoxicity (mean value 10.4 mg/L). The authors concluded that erythromycin-induced ototoxicity is dependent on dose and on peak serum erythromycin concentration and may be an underappreciated side effect of erythromycin.¹⁵

The association between elevated peak erythromycin concentrations and ototoxicity is also supported by 2 case reports,^{16,17} which found elevated erythromycin concentrations (63 mg/L,¹⁶ 78 mg/L,¹⁶ and 100 mg/L¹⁷) in 3 patients with ototoxicity. In addition, one patient's ototoxicity improved after a change to a continuous erythromycin infusion from an intermittent infusion⁵ (serum erythromycin levels were not measured).

Sacristán and colleagues¹¹ also reported that erythromycin-induced ototoxicity is an underrecognized adverse effect, the incidence of which is underestimated. They reported 11 cases of suspected erythromycin-induced hypoacusis over a period of approximately 20 months in one hospital. All 11 patients were receiving 4 g/day IV erythromycin lactobionate. Three patients under the age of 60 years with no impairment of hepatic or renal function experienced erythromycin-induced ototoxicity. The authors suggested that there is an idiosyncratic component to this adverse effect.¹¹

Although the exact pathogenesis of erythromycin-induced ototoxicity is unknown, the central auditory pathway may be the site of action.^{4,9} Transient loss of waves I to III recorded by evoked auditory brain potentials coincided with erythromycin-induced ototoxicity.¹²

High blood concentrations of erythromycin may be involved in altering central nervous system function in addition to affecting hearing. Reports of reversible psychotic reactions, often in association with ototoxicity, have included confusion, slurred speech and diplopia,¹⁶ lack of control, abnormal thinking, a feeling of impending loss of consciousness and of being drugged,¹⁸ paranoia, and hallucinations.^{5,19,20}



Table 1. Risk Factors for Erythromycin-Induced Ototoxicity

Advanced age ^{11,21,23,24}
Renal dysfunction ^{4,9,11,14,21,23-25}
Hepatic dysfunction ^{4,9,11,14,21,23-25}
High-dose erythromycin (Ž 4 g/day) ^{4,9,11,14,15,17,23-25}

Our patient had characteristics that have been identified as risk factors for erythromycin-induced ototoxicity. She was elderly, had age-related changes in renal function, and was receiving high doses of erythromycin. Certain patients appear to be predisposed to this adverse effect. Although some believe that there is no predisposition related to gender,^{11,21,22} a few authors have found a predisposition to erythromycin-induced ototoxicity in women.^{14,23} It is generally agreed that elderly people^{11,21,23,24} with renal and/or hepatic dysfunction^{4,9,11,14,21,23-25} who are receiving high-dose erythromycin (Ž 4 g/day)^{4,9,11,14,15,17,23-25} are at increased risk.

Our patient's ototoxicity was most likely induced by high-dose erythromycin, given the temporal relationship (the ototoxicity occurred within 48 h after the initiation of erythromycin therapy and resolved within 48 h of discontinuation of the drug) and the presence of several known risk factors for erythromycin-induced ototoxicity (Table 1). The nature of our patient's ototoxicity is typical of most reported cases. The onset was sudden, the ototoxicity was bilateral and affected speech frequencies, and its resolution was prompt after the discontinuation of the erythromycin. Audiography was not performed, and serum concentrations of erythromycin were not measured. Most case reports describe significant hearing loss;^{5,15} tinnitus^{5,15,17,19,23,24,26-30} and vertigo^{5,30} are reported in a minority of cases. Typically, the hearing loss is bilateral and sensorineural^{5,20,23-25} and develops quickly, with average onset of 3 to 4 days^{5,23} (range after first dose²⁰ to 13 days¹⁹). After discontinuation of the drug or dose reduction, the ototoxicity diminishes rapidly (on average, over 1 day²³) and resolves within about 7 days.^{5,23} Although the hearing loss is usually reversible, there is one published case each of persistent bilateral sensorineural hearing loss,²¹ bilateral residual high-tone sensorineural hearing loss,²⁴ irreversible bilateral labyrinthic hypoflexia,²⁸ and persistent tinnitus.³¹ It is not known whether permanent damage is more likely if diagnosis and treatment are delayed.

Some cases illustrate the unpredictability of this adverse effect. For example, erythromycin-induced ototoxicity has occurred in young patients, including people 17, 18 and 34 years of age.^{27,32,33} Patients with normal renal function^{3,22,26,28,29} and normal hepatic

function^{16,28,29} have been affected, as well as patients who have received less than 4 g/day of erythromycin.^{16,21,24,32} Since erythromycin-induced ototoxicity has occurred in association with a variety of routes of administration (IV,^{24,25} oral,^{24,27,32,33} and intraperitoneal¹⁶) and salt forms, including the lactobionate,^{3,5,11,12,14,15,17,19-21,23,26,28-30} stearate,^{7,24,27,32} and gluceptate,²² ototoxicity probably occurs independent of the erythromycin route and salt form.^{11,14,17,21-23,30}

Our patient also received small, single doses of 2 other known ototoxic agents: gentamicin and furosemide (which have cochlear toxicity rates of approximately 2% and 6.4%, respectively);^{25,34} however, we believe that these agents contributed little, if anything, to the ototoxicity. Concurrent use of other ototoxins was not associated with erythromycin-induced ototoxicity in the 1992 case-control study reviewed earlier.¹⁵

All aminoglycosides can cause auditory and vestibular toxic effects by damaging the sensory hair cells of the inner ear. Auditory or cochlear damage is characterized by high-frequency hearing loss, which usually occurs before conversational-tone hearing loss. Whereas vestibular symptoms generally improve within 3 to 4 months, deafness tends to be permanent, since hair cell degeneration is irreversible.^{2,35} Potential risk factors for aminoglycoside-induced ototoxicity include elevated serum aminoglycoside peak and trough levels, prolonged duration of treatment, impaired renal function and the concomitant use of other ototoxins.^{2,25}

The loop diuretics (furosemide, ethacrynic acid, and bumetanide) can cause hearing impairment, tinnitus or deafness, and (rarely) vestibular damage. Most cases are immediate and transient; however, irreversible deafness may also occur. Risk factors include the rapid parenteral administration of high doses, impaired renal function and the concomitant use of other ototoxins.² The risk of ototoxicity can be reduced by infusing furosemide at a rate not exceeding 15 mg/min.²⁵

Most (85% to 95%) of an erythromycin dose is eliminated as inactive metabolites and unchanged drug by biliary excretion, 5% to 15% being eliminated renally as unchanged drug.³⁶ Because erythromycin is eliminated primarily by nonrenal routes, dosage modification is not usually recommended in patients with renal dysfunction, unless the patient's glomerular filtration rate is less than 10 mL/min.³⁷ However, dose reduction or an extension of the dosing interval may be required in patients with severe liver disease.³⁶ Despite these recommendations, high-dose erythromycin (Ž 4 g/day) is a risk factor for ototoxicity, and doses of 1 g IV q6h should be reserved for patients with highly



suspected or documented *Legionellae pneumophila* pneumonia.

Erythromycin-induced ototoxicity may be an underrecognized adverse effect. Clinicians should be aware of the potential for this problem and should monitor for sensorineural hearing loss, tinnitus, and vertigo, especially in patients with any of the known risk factors. In patients experiencing potential erythromycin-induced ototoxicity, the need for erythromycin therapy should be re-evaluated, and discontinuation or dosage adjustment should be considered.

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