Transpl Int (1994) 7: 62–64

BRIEF REPORT

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Erythromycin ototoxicity in liver transplant patients

Received: 18 December 1992
Received after revision: 6 April 1993
Accepted: 16 April 1993

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Abstract We report on three liver transplant patients who developed erythromycin-related ototoxicity. This complication has been described in renal transplant patients and in patients with liver dysfunction, but to our knowledge it has not yet been reported in liver transplant patients. The influence of hepatic dysfunction, common renal failure, and the interaction between cyclosporin and erythromycin in the development of erythromycin ototoxicity are discussed.

Key words Liver transplantation, ototoxicity · Ototoxicity, liver transplantation · Erythromycin, liver transplantation
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Introduction

Erythromycin is a macrolide antibiotic that was discovered in 1952 by McGuire et al. in the metabolic products of a strain of *Streptomyces erythreus*. The ototoxic effect of this antimicrobial agent was not reported until 1973, when high doses of intravenous erythromycin were administered for the first time in the treatment of patients with pneumonia caused by *Legionella pneumophila* [14]. Since then erythromycin ototoxicity has been mainly described in other patient populations receiving large doses (> 4 g/day) or in patients with renal and hepatic dysfunction [1].

Liver transplant patients frequently present liver graft dysfunction and renal failure [10], and they are prone to developing infections likely to be treated with erythromycin, such as atypical pneumonia. These patients could, therefore, run the risk of developing erythromycin-related ototoxicity. However, to date, this complication has not been reported in liver transplant patients.

In the current report, three liver transplant patients who developed ototoxicity during erythromycin lactobionate administration for the treatment of respiratory tract infections are described. The three patients presented bilateral hearing loss without tinnitus or vertigo, which reversed after discontinuation of the drug. All three patients had renal failure and one showed severe liver dysfunction. The influence of hepatic and renal abnormalities on erythromycin ototoxicity and the possible role of the interaction between cyclosporin A (CyA) and erythromycin on the development of this complication are discussed.

Case reports

Case 1

A 51-year-old woman received a liver transplant in 1989 and was retransplanted in 1990 because of an uncontrollable graft rejection. She developed a chronic rejection of the second graft. Nine months after the liver retransplantation, while staying at the hospital for treatment of multiple vertebral fractures that developed following aggressive steroid therapy, she presented fever, dyspnea, considerable deterioration in her general status, and bilateral lung infiltration according to chest X-ray. Intravenous treatment with 1 g/12 h ceftriaxone and 1 g/8 h erythromycin was started. At the time anti-

Table 1 Variations in cyclosporin blood levels (ng/ml) measured by monoclonal RIA before (Pre-eryth), during (Eryth), and after (Post-eryth) erythromycin administration

Case	Pre-eryth	Eryth	Post-eryth
1	453	1470	256
2	304	535	393
3	245	422	256

biotic therapy was initiated, biochemical data showed a marked cholestasis with serum bilirubin of 62 mg/dl, alkaline phosphatase of 2433 U/l and gamma glutamyl transpeptidase of 2156 U/l, and moderate renal failure with serum creatinine of 2.0 mg/dl. The patient was receiving maintenance therapy with 200 mg/12 h oral CyA, 15 mg/24 h prednisone, and 150 mg/24 h ranitidine. An almost complete bilateral hearing loss appeared on the 3rd day of antibiotic treatment that markedly improved after stopping erythromycin administration. Since a causative organism of pneumonia could not be isolated, cotrimoxazole, ganciclovir, and imipenem were empirically added to ceftriaxone. However, patient status became progressively worse and she died 14 days after the diagnosis of pneumonia had been made. Necropsy was not allowed by the patient's relatives. A considerable increase in blood trough CyA levels, measured by monoclonal RIA, was observed during erythromycin treatment (Table 1).

Case 2

A 56-year-old man who had received a liver transplant 14 months earlier was readmitted to the hospital because of fever, leukocytosis, and right upper lobe condensation as revealed in the chest X-ray film. With the presumed diagnosis of community-acquired pneumonia, i.v. treatment with 1 g/12 h ceftriaxone and 1 g/6 h erythromycin was started. At the time the antibiotic therapy was initiated, the patient showed normal standard liver function tests and moderate renal failure, with a serum creatinine of 1.9 mg/dl. The patient was receiving maintenance therapy with 125 mg/12 h CyA, 10 mg/24 h prednisone, and 150 mg/24 h ranitidine. On the 2nd day of antibiotic therapy, the patient complained of marked bilateral hearing loss. Erythromycin administration was immediately discontinued and 1 g/12 h josamycin was given orally in its place. The patient's hearing returned to normal 48 h after erythromycin withdrawal. Cultures from blood, sputum, and cultures, cytology, and methenamine silver nitrate stain from bronchoalveolar lavage at bronchoscopy were negative.

During erythromycin administration, blood trough levels of CyA markedly increased; they returned to previous levels after erythromycin therapy was discontinued (Table 1).

Case 3

A 35-year-old man who had received a liver transplant 13 months earlier and who was receiving maintenance therapy with 150 mg/12 h CyA, 20 mg/day prednisone, and 150 mg/day ranitidine was admitted to the hospital because of fever and dyspnea that had lasted 3 days. The chest X-ray film showed extensive bilateral lung infiltration. The diagnosis of atypical pneumonia was suspected and intravenous treatment with 1 g/12 h ceftriaxone, 1 g/6 h erythromycin, as well as 7 mg/kg per 8 h trimethoprin and 30 mg/kg per 8 h sulfamethoxazole was started. Upon admission, liver function tests were normal and serum creatinine was 4.4 mg/dl. The patient developed a moderate bilateral hearing loss on the 2nd day of antibiotic therapy that completely resolved 48 h after the discontinuation of erythromycin administration. Blood and sputum cultures were negative, but methenamine silver nitrate stain from bronchoalveolar lavage showed *Pneumocystis carinii.* Cotrimoxazole treatment was continued for 21 days, after which the pneumonia was completely resolved. The blood trough levels of CyA before, during, and after erythromycin administration are shown in Table 1.

Discussion

Erythromycin-related ototoxicity is an uncommon, adverse effect revealed by neurosensory hearing loss that appears within the first 48 h of treatment and reverses after discontinuation of the drug [13]. However, there have been few reports of persistent hearing loss and persistent labyrinthitis [3, 4, 9], suggesting that erythromycin ototoxicity may be permanent if the antibiotic is not discontinued or its dosage reduced [19]. Hearing loss, usually bilateral, may be accompanied by tinnitus and vertigo, but in some cases psychiatric and generalized central nervous system symptoms, such as confusion, fear, lack of control, or acute psychotic reactions, have been reported [20]. The ototoxic mechanism of erythromycin in humans is not well established. However, the demonstration that i.v. administration of erythromycin in animals causes alterations in the auditory brain stem evoked responses without changes in cochlear function [18], together with the fact that some patients developing erythromycin-related ototoxicity also present central nervous system clinical manifestations, suggest that central auditory pathways may be the site of action in humans.

Erythromycin is a macrolide antibiotic extensively, metabolized by the hepatic microsomal system in which cytochrome P-450 serves as a terminal oxidase. Erythromycin is also oxidized by cytochrome P-450 to its major N-demethylated metabolite, forming a stable, inactive complex with reduced cytochrome P-450 which, in turn, depresses the activity of selected mono-oxigenases of this enzymatic pathway [2]. As a consequence, in the presence of liver dysfunction, erythromycin dosage should be adequately reduced. In liver transplant patients, mild hepatic dysfunction is commonly present [10], especially in the early postoperative period, and may contribute to increased erythromycin serum levels and ototoxicity. This mechanism most probably accounted for the situation of our case 1, who showed considerable liver dysfunction, evidenced by a marked cholestasis at the time of erythromycin therapy.

Another important point related to erythromycin in liver transplant patients is the interaction with drugs commonly used in these patients. Erythromycin-CyA interaction has been described in renal transplant patients [5, 7]. The mechanism proposed for this interaction is not clear, but the inhibiting effect of cytochrome P-450 by erythro-

mycin could be the main factor increasing CyA levels during concomitant administration of erythromycin and CyA [6, 11, 16] as occurred in our patients. Although measurements of erythromycin levels were not taken in our patients, it could be speculated that sharing the same metabolic pathway, the simultaneous administration of erythromycin and CyA could also increase erythromycin levels, contributing to the ototoxic effects [12]. Moreover, it should be kept in mind that ranitidine also has an inhibitory effect on the cytochrome P-450 enzymatic system [15] and might, therefore, enhance erythromycin toxicity.

Although only 4%–15% of the erythromycin administered is excreted unchanged in the urine, recent data document a dramatic alteration in erythromycin kinetics in patients with renal failure, which may explain why approximately 70% of erythromycin-related ototoxicity has been in patients with renal failure [8]. Kroboth et al. reported a serum half-life for erythromycin of 7.3 h, compared with 2 h in normal subjects [8]. Renal failure, a common finding affecting 50% of liver transplant patients [17], was present in the three cases reported. This suggests that a combination of liver dysfunction, renal failure, and drug interactions may account for the erythromycin-induced ototoxicity in liver transplant patients. Since the cases reported here involved 3 of a total of 11 patients treated with erythromycin during the same period of time – an incidence of 27% – one can conclude that an adequate reduction in the doses and careful monitoring of blood levels of erythromycin and CyA should be recommended in these patients.

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