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Aggravation of Myasthenia Gravis by Erythromycin

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Erythromycin is not currently recognized as causing clinical aggravation of myasthenia gravis. We report the case of a patient who experienced exacerbations of myasthenia gravis subsequent to each of several doses of intravenous erythromycin. We suggest that erythromycin can cause clinical worsening in patients with disease of the neuromuscular junction.

May EF, Calvert PC. Aggravation of myasthenia gravis by erythromycin. Ann Neurol 1990;28:577–579

A wide variety of medications have been reported to exacerbate the weakness of patients with myasthenia gravis (MG). In addition, numerous agents interfere with neuromuscular transmission when given to individuals without underlying disease of the neuromuscular junction (NMJ) [1, 2]. In particular, several classes

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of antibiotics are known to interfere with neuromuscular transmission in clinical practice and in experimental models of the NMJ [3]. Erythromycin is not currently recognized as an agent that may clinically aggravate MG or induce weakness, although there is experimental evidence that it may [4]. We now report the case of a patient with MG in whom the administration of erythromycin was repeatedly associated with exacerbations of his clinical course, and discuss factors that may have predisposed to this phenomenon.

Report of a Case

A 38-year-old white man received the diagnosis of MG in November 1987, after a month's history of dysarthria and dysphagia. He was found to have an invasive thymoma, which was subtotally resected and irradiated. His symptoms were initially managed with pyridostigmine, but he ultimately required high doses of prednisone and azathioprine, as well as intermittent plasmapheresis. During exacerbations of the MG, the patient experienced dysphagia, dysarthria, and generalized weakness. He developed deep venous thrombosis in his calf and recurrent pulmonary emboli, for which he was orally anticoagulated. Propantheline was prescribed to counteract the muscarinic effects of pyridostigmine.

In July 1988, the patient presented with a temperature of 38.6°C and no other symptoms to suggest the source of an infection. Findings on physical exam were remarkable for a cushingoid appearance, bulbar and generalized fatiguability, and rales in the right lower lung field. Laboratory evaluation revealed a white blood cell count of 8,800/mm^3 and a possible left lower lobe infiltrate as determined by chest radiography. Medications at the time of admission included prednisone, azathioprine, pyridostigmine, warfarin, and propantheline at a dose of 15 mg, three times a day.

The patient received three intravenous doses of ceftizoxime at 8-hour intervals, but he continued to have fevers. His antibiotic regimen was changed to ceftazidime every 8 hours, and erythromycin, 1 gm, every 6 hours. The patient received his first dose of intravenous erythromycin at 12:00 noon with a simultaneous 75-mg oral dose of pyridostigmine, without complications. He received another 75-mg dose of pyridostigmine at 4:00 P.M., which was followed by a dose of erythromycin at 6:00 P.M. Approximately 30 minutes after the second dose of erythromycin was started, he noted the rapid onset of marked difficulty speaking, swallowing, and clearing secretions. These symptoms remained severe for approximately 1 hour but gradually cleared over the next 2 to 3 hours.

The dosage of erythromycin was decreased to 750 mg, and three more doses were administered at 4-hour intervals. Within 15 to 30 minutes of administration of each subsequent dose of erythromycin, the patient experienced deterioration of speech, swallowing, and coughing, even when pyridostigmine was administered 1 hour prior to the dose of erythromycin in an attempt to abort the deterioration. The oral temperature remained below 37.2°C throughout the period of his exacerbations. Potassium, calcium, and magnesium levels were normal, as were renal and liver functions. There was no temporal relationship between the episodes of deterioration and dosing of propantheline. The erythromycin was discontinued and the patient experienced no further episodes of dysarthria and dysphagia.

Discussion

Due to frequent weakness of the respiratory musculature, patients with MG are prone to pulmonary infections, especially when treatment of their disease requires powerful immunosuppressive medications. The question of what antibiotic to use for myasthenic patients is therefore frequently raised. Those antibiotics most commonly associated with neuromuscular blockade and exacerbation of MG include the tetracyclines, polymyxins, lincomycin, clindamycin, and aminoglycosides [3]. Mechanisms of action of these antibiotics at the NMJ include inhibition of the presynaptic release of acetylcholine (gentamicin [5], neomycin [5, 6], and tobramycin [6]) and depression of postjunctional sensitivity (clindamycin [7, 8], colistin [6], lincomycin [8, 9], neomycin [6], netilmicin [6], polymyxin B [10], and tetracycline [10]).

The use of erythromycin is generally not recognized as unsafe in myasthenic patients [1, 3, 11]. An early study suggested that erythromycin showed no neuromuscular blocking activity in a rabbit sciatic nerve–gastrocnemius muscle preparation [12]. A later study of electromyographic findings in normal patients taking erythromycin demonstrated myasthenic-like changes without clinical signs of weakness [4]. In that study, the response to supramaximal repetitive stimulation suggested a presynaptic effect of erythromycin. Also, the loss of motor unit potentials observed during sustained contraction was improved with intravenous administration of edrophonium. The effect of erythromycin at the NMJ is therefore certainly subtle and usually subclinical.

The case reported here demonstrates that in some circumstances, erythromycin can produce clinical worsening of MG. Our patient may have been particularly susceptible to the neuromuscular-blocking effect of erythromycin because his safety margin for neuromuscular transmission was reduced by multiple coexisting factors [13]. For one, severe MG profoundly affects function of the NMJ. Secondly, the presence of an underlying infectious process is known to be related to worsening of symptoms in myasthenic patients [14]. Also, the administration of propantheline may have further impaired neuromuscular transmission. Propantheline is used primarily for its antimuscarinic effects, but it can cause a curariform neuromuscular block through its action at nicotinic receptors [15]. Under normal conditions, the dose of propantheline administered to the patient is not expected to cause side effects, due to nicotinic blockade [16]. It remains unclear whether erythromycin alone could have caused worsening of the patient's MG or whether the pres-

ence of the other inhibitors of the NMJ was necessary to unmask erythromycin's effect.

In summary, erythromycin has been shown to cause subclinical presynaptic inhibition of the NMJ. The reported case demonstrates that erythromycin may, indeed, produce clinically obvious worsening of weakness in patients whose neuromuscular transmission is compromised. As such, erythromycin should be used judiciously in patients with disease of the NMJ, and in those in whom concurrent medications or other systemic disorders may predispose to impairment of neuromuscular transmission.

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Human Immunodeficiency Virus (HIV)–associated Myopathy: Immunocytochemical Identification of an HIV Antigen (gp 41) in Muscle Macrophages

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In a patient with acquired immunodeficiency disease syndrome (AIDS) and muscle weakness, a muscle biopsy specimen disclosed degeneration of muscle fibers, regeneration, and focal endomysial mononuclear inflammation. A conspicuous feature was the presence of perivascular macrophages within the endomysium that showed positive immunostaining for human immunodeficiency virus (HIV) (gp 41) antigen. HIV was not detected within myofibers. Our findings suggest an important role for the HIV-infected macrophage in the pathogenesis of this myopathy.

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The association between human immunodeficiency virus (HIV) infection and myopathy is well established [1–12]. The pathogenesis of the myopathy, however, is uncertain [12]. There may exist several different mechanisms for the damage to muscle fibers. These include: direct viral infection of muscle fibers or macrophages [1], autoimmunity [1, 5], and zidovudine-induced myotoxicity [9]. This report describes immunocytochemical evidence for HIV infection of the endomysial macrophage and therefore strengthens the view that macrophage infection is involved in the pathogenesis of AIDS-associated myopathy.

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