

Februari 2003

## Macrolide antibiotics and myasthenia

### Introduction

Erythromycin was the first macrolide antibacterial drug approved for marketing in The Netherlands in 1967. At this moment the five macrolide antibiotics approved for marketing are erythromycin (Erythrocin® or Eryc®), spiramycin (Rovamycin®), roxithromycin (Rulide®), clarithromycin (Klacid®) and azithromycin (Zithromax®). The antibacterial spectrum of macrolides covers a broad range of pathogens, including Mycoplasma, Campylobacter, Hemophilus, Chlamydia and Legionella. Macrolide antibiotics are most frequently used in respiratory infections and skin infections. The antibacterial activity of macrolides is based on interference with protein synthesis, resulting in a bacteriostatic effect. The macrolide antibiotics are chemically and pharmacologically largely similar, resulting in a partly similar adverse reaction pattern; cross hypersensitivity and cross-resistance. The most frequent adverse effects of macrolides are gastrointestinal complaints, skin reactions and central nervous system reactions [1].

Myasthenia gravis is a rare disease of the neuromuscular junction, where the neuromuscular transmission is compromised by an autoimmune reaction resulting in a reduction of acetylcholine receptors. The clinical features are generalised weakness of voluntary muscles. The course of the disease is characterized by exacerbations, in the worst case leading to a life threatening myasthenic crisis. Exacerbations of myasthenia can be provoked by medication but for example also by infections [2]. Several classes of antibiotics can cause exacerbations of myasthenia gravis, for example aminoglycoside antibiotics, clindamycin and lincomycin [3].

The Netherlands Pharmacovigilance Centre Lareb received a report of exacerbation of myasthenia gravis in association with the use of the macrolide antibiotic clarithromycin. The Summary of Product Characteristics of clarithromycin does not mention myasthenia gravis as a contraindication or a warning. The contraindication myasthenia gravis also lacks in the SPCs of spiramycin, roxithromycin and azithromycin. The section "Special warnings and special precautions for use" of the SPC of erythromycin contains the following information: *Erythromycin can aggravate the symptoms of weakness on patients with myasthenia gravis* [4].

### Report

A 78-year-old male with myasthenia gravis experienced aggravated myasthenic weakness about one hour after the first intake of clarithromycin for an unspecified lung infection. Symptoms were a weakening of the masseters and dysarthria during long conversations. Symptoms resolved after changing the therapy from clarithromycin to amoxicillin/clavulanic acid. This case is reported by a neurologist. We have asked him for additional information.

### Other sources of information

#### Literature

A literature search revealed several references of case reports concerning myasthenia induced by macrolides. A recent case report concerns clarithromycin-induced myasthenic syndrome [5]. This case report describes a 28-year-old male with AIDS who was treated with clarithromycin for cerebral toxoplasmosis. He developed progressive loss of strength and trouble with swallowing and opening his eyes. These complaints started after the first dose of clarithromycin and progressed rapidly after each new dose. The clinical picture resembled

myasthenia gravis. Clarithromycin was withdrawn and the patient was treated with pyridostigmine. All symptoms disappeared within the next 6 hours.

Another case report describes a 25-year-old woman who experienced acute exacerbation of myasthenia gravis within 1 hour of ingesting a 500 mg oral dose of azithromycin for treatment of a respiratory infection [6]. She developed weakness of the legs and respiratory muscle failure, became comatose, requiring intubation and mechanical ventilation. She had had a previous exacerbation of myasthenia gravis associated with parenteral erythromycin 10 years earlier. Furthermore there are also case reports on aggravation of myasthenia gravis by erythromycin [7,8]. In both case reports the clinical symptoms started within approximately half an hour after intravenous erythromycin and symptoms resolved upon discontinuation of erythromycin.

Although not in all published cases an underlying infection could be ruled out as a cause of the myasthenia, the literature strongly indicates that the association between myasthenia and the macrolide antibiotics is applicable to the whole group of macrolides.

#### *Databases*

The Netherlands Pharmacovigilance Centre Lareb did not receive additional reports on the association between macrolide antibiotics and myasthenia. The database of the WHO Collaborating Centre for Drug Monitoring presently contains 35 reports on macrolide-induced myasthenia gravis-like syndrome, 22 on azithromycin (ROR 7.4; 95% CI 4.8-11.2), 6 on clarithromycin (ROR 1.4; 95% CI 0.6-3.1), 6 on erythromycin (ROR 1.01; 95% CI 0.5-2.3) and 1 on roxithromycin. The association between azithromycin and myasthenia gravis-like syndrome was the only statistically significant association. About 3-4 % of all the myasthenia gravis-like syndrome reactions in the WHO database are related to the use of macrolides.

#### *Mechanism*

Macrolides are thought to lead to neuromuscular blockade and exacerbation of myasthenia gravis through inhibition of the presynaptic release of acetylcholine. In patients without neuromuscular disease the administration of erythromycin lead to electromyographic findings resembling myasthenia-like changes without clinical weakness. The loss of motor unit contractions improved on administration of a cholinesterase inhibitor like neostigmine [9].

#### **Conclusion**

Due to the use of powerful immunosuppressive therapy and to the frequent weakness of respiratory musculature, resulting in difficulty clearing secretions, patients with myasthenia gravis regularly suffer from respiratory infections. Because of the need for antibiotic treatment and the known effects of different antibiotics on the neuromuscular junction, the choice for an appropriate antibiotic treatment for myasthenia gravis patients is often difficult.

Possible aggravation of myasthenia gravis is already mentioned in the SPC of erythromycin. The Lareb report combined with additional literature, database information and a plausible mechanism suggests that aggravation of myasthenia is most likely to be related to all macrolide antibiotics.

#### References

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