Azithromycin-induced myasthenic crisis: Reversibility with calcium gluconate

Sir,

Infections that precipitate acute exacerbations of myasthenia gravis (MG) are managed with antibiotics which themselves have the potential to worsen MG. We report the case of a boy with MG in whom intravenous (iv) azithromycin caused sudden worsening of motor symptoms necessitating endotracheal intubation. The respiratory weakness improved within a few minutes of inravenous (iv) calcium gluconate administration followed by improvement in limb power. Such a rapid reversal suggests that azithromycin probably acts presynaptically suppressing acetylcholine release. Since there is no harmful effect of iv calcium gluconate in postsynaptic defects, we advocate such treatment in all cases of acute worsening of MG due to antibiotics or other substances with less clear site of action.

Several antibiotics are known to worsen myasthenia gravis (MG). Still their administration becomes necessary in dire situations. Aminoglycosides are well known to worsen MG.[1] About some newer antibiotics, such adverse effects are not clearly known. However, there are some anecdotal reports of exacerbation of MG with macrolides, such as azithromycin and telithromycin.[2,3] No definite remedy is known for such worsening. We report a case of acute worsening of MG with a macrolide antibiotic azithromycin, which dramatically improved with intravenous (iv) administration of calcium gluconate. As trials on human beings are not possible in specific situations, experience gained over a period of time makes our understanding better. It is for this reason that pharmacovigilance efforts should continue even long after marketing of drugs.

A 13-year-old boy presented to the emergency services with acute onset painless difficulty in swallowing with drooling of saliva for two days and generalized weakness for one day. He had had similar symptoms twice in the last one year; on both the occasions, he had responded to iv steroids administered empirically without getting a definite diagnosis. Examination revealed bilateral ptosis without other extraocular weakness, pharyngeal weakness with a nasal twang in voice, neck weakness, and proximal limb weakness. Fatigability could be demonstrated in all groups of muscles. There were no sensory signs and deep tendon reflexes were normal. The child had tonsillitis with bilateral tonsilar hypertrophy. Chest X-ray and CT revealed pneumonia involving left lower lobe without any mediastinal enlargement to suggest thymic hyperplasia. With the provisional diagnosis of MG, a neostigmine test was performed to which the response was immediate and significant. In addition to low dose oral steroids (prednisolone (10 mg/day) and pyridostigmine (60 mg thrice a day)) that he received for two days, iv azithromycin (500 mg single dose infused in one hour) was administered in view of the evidence of active tonsilitis and pneumonia. Within 10minutes of receiving iv azithromycin, the child started having respiratory distress, became cyanosed and unresponsive. He was immediately intubated, put on mechanical ventilator, and administered iv calcium gluconate. Ten minutes later he regained consciousness and started flexing his neck and moving his limbs against gravity. He was put off the ventilator after two hours and could be easily extubated the next day. Over the next 10 days, the dose of prednisolone was gradually increased while pyridostigmine was continued. The ptosis and extraocular paresis improved almost completely, the nasal twang in speech decreased, and the swallowing improved. At the time of discharge, the boy was able to walk and perform his self-care activities.

Aminoglycoside antibiotics are well known to impair neuromuscular transmission, which can be partially reversed by cholinesterase inhibitors and aminopyridines.[1,4,5] Some animal studies have suggested reversal of neuromuscular transmission block by the infusion of iv calcium.[4] Other antibiotics including tetracyclines, sulfonamides, penicillins, amino acid antibiotics, and fluoroquinolones have either been associated with anecdotal reports of increased weakness in myasthenic patients or implicated from *in vitro* studies to adversely affect neuromuscular transmission.[6-8]

Intravenous administration of calcium gluconate is known to potentiate the presynaptic release of acetylcholine (Ach) resulting in the reversal of drug-induced presynaptic block. The dramatic improvement in our patient with iv calcium administration suggests that worsening of myasthenia after azithromycin injection was probably due to presynaptic suppression of Ach release. The worsening of the patient was very rapid and necessitated immediate resuscitative measures. As a result, immediate evaluation of deep tendon reflexes or pupilary size could not be made. Once the patient was stabilized and detailed examination performed, no difference in the neurological signs could be recorded. Since prednisolone was being administered at a small dose, it is unlikely that the worsening was related to its use. However, no conclusion regarding worsening of myasthenia with azithromycin or improvement with iv calcium can be made on the basis of experience with a single patient and more experience in this regard will be contributory.

Various agents belonging to the same antibiotic group are known to affect transmission at different levels, for example, while tobramycin is known to suppress Ach release at the presynaptic level, netilmycin acts postsynaptically by blocking the binding of Ach to receptors, and clindamycin, lincomycin, and colistin affect transmission at both pre as well as postsynaptic levels.[8,9] In this context, our finding of rapid recovery with iv calcium suggests that azithromycin produces primarily a presynaptic block.

Myasthenic crises are often precipitated by infections which require antibiotic administration. Nearly every antibiotic ever studied has demonstrated some deleterious effect in case series or anecdotal reports. This poses a challenging dilemma for clinicians as infections must be adequately treated to control myasthenia. When using newer antibiotics with unknown effects, any myasthenic worsening should alert the clinician to the possibility of antibiotic use as the cause thereof. As several antibiotics have been known to act presynaptically, iv calcium can be empirically administered in such situations.

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