Myasthenia Gravis

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Goals of this presentation

- Introduction to myasthenia gravis (MG)
- Review the reported effects of telithromycin on MG.
- Clinical recommendations.

What is myasthenia gravis?

Myasthenia gravis (MG) is a rare autoimmune disease, in which an immunological attack on the neuromuscular junction produces ineffective transmission of impulses from motor nerves to muscle, resulting in weakness.

Epidemiology of MG

- Incidence – ~5,000 new cases/year in US
- Estimated US prevalence - 35,000 to 70,000 (~1:5,000)
- Since it can be hard to diagnose, the true prevalence is probably higher.

What are the symptoms of MG?

- In most patients with MG, eye muscles are affected first, producing double vision or drooping eyelids.
- Weakness usually spreads from the eyes to other muscles, especially those that control chewing, swallowing and talking.
- Weakness in MG can be mild or severe and can be life-threatening if respiratory or oropharyngeal muscles are affected.

Myasthenic “crisis”

- Acute weakness of respiratory or oropharyngeal muscles requiring ventilatory support
- There usually is a defined precipitating event:
  - Infection
  - Medications
  - Systemic disease, eg hyperthyroidism

Medications that exacerbate MG

- Antibiotics
  - Aminoglycosides – Hokkanen, 1964
  - Macrolides
  - Fluoroquinolones
  - Polymixin, colistin
- Cardiovascular drugs
  - Quinine, quinidine, procainamide
  - β-blockers
  - Ca^{++} channel blockers
- Corticosteroids

Telithromycin in MG

- Exacerbations reported in
  - 60 MG patients worldwide (2.1/million exposures)
  - 29 MG patients in US (5.0/million exposures)
- 7 “MG-associated” deaths worldwide – 3 US

Evidence that telithromycin exacerbates MG

- Strong temporal relationship
  - acute onset of worsening (hours)
  - rapid resolution
- Repeated Ketek-related episodes in some patients

The European Agency for the Evaluation of Medicinal Products
Post-authorisation evaluation of medicines for human use

London, 23 April 2003
EMEA/8837/03

EMEA PUBLIC STATEMENT
PRECAUTION REGARDING USE OF TELITHROMYCIN (KETEK®) IN PATIENTS WITH MYASTHENIA GRAVIS

- Not recommended for use in MG unless other therapeutic alternatives are not available.
- MG patients on Ketek should immediately seek medical attention if their symptoms worsen.
- MG patients taking Ketek should be carefully monitored.
- If symptoms worsen, adequate supportive measures should be undertaken and the medication should be discontinued.

“Ketek-associated” fatalities in MG

- 7 reports worldwide, 3 US
  - 2 possible/probable Ketek-induced exacerbation
  - 2 unlikely related
  - 1 anaphylactic reaction
  - 1 mesenteric thrombosis
  - 1 “hearsay”

Conclusions: telithromycin in MG

- Telithromycin can induce MG exacerbations, including fatal crisis.
- This was recognized by ex-US post-marketing surveillance (EMEA) prior to FDA approval.
- 3014 included 5 MG patients
  - 2 received Ketek, without exacerbation
  - This study would not have identified MG exacerbations

Conclusions: telithromycin in MG

- FDA approval included caution for MG.
- Recognition of MG exacerbations has led to dissemination of risk information:
  - Modified package insert
  - “Dear Doctor” letters
  - Notification of disease-specific organizations
  - Physician education

Clinical recommendations re: telithromycin in MG

- Not recommended for use in MG unless no other reasonable choice is available.
- The exacerbation risk should be compared with
  - Exacerbation risk of alternative antibiotics, e.g. macrolides, fluoroquinolones.
  - Specific risk of the infection to the MG patient
- The potential for acute, severe worsening must be recognized.
- Should be administered in a controlled environment with monitoring for worsening, preferably in hospital for patients with oropharyngeal or respiratory muscle weakness.