

Medications Side Effects and Interactions in Myasthenia Gravis Patients

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Pyridostigmine (Mestinon®)

- **Pyridostigmine** is an acetylcholinesterase inhibitor
- Cholinergic family of medications.
- It works by blocking the action of acetylcholinesterase and therefore increases the levels of acetylcholine.
- Came into medical use in 1955

Side Effects

- GI Symptoms: Abdominal cramps, diarrhea, nausea.
- GU: Urinary frequency.
- Muscle cramps and twitches.
- Increased tearing and saliva.
- Rx:
 - take with or after meals, smaller but more frequent doses.
 - Anticholinergic drugs: glycopyrrolate, hyoscyamine.
 - For diarrhea can use Imodium or Lomotil.

Cholinergic Crisis

- A potential major side effect of excessive anticholinesterase medication (pyridostigmine).
- Severe generalized weakness and respiratory failure.
- Difficult to distinguish from worsening myasthenia gravis.
- Cholinergic crisis is rarely seen with dose limitation of pyridostigmine to less than 120 mg every 3-4 hours.
- Diagnosed only when the over dose of pyridostigmine is confirmed, otherwise need to be assumed an MG crisis.
- Treatment:
 - Hold pyridostigmine and use atropine as needed.
 - Rule of thumb, **hold pyridostigmine with every MG crisis** to reduced pulmonary secretions and for potential cholinergic crisis.

Prednisolone (Prednisone)

(Steroids Exacerbation)

- Effective, first line immunosuppressant for MG
- May be assoc with worsening weakness early, more often with higher doses
- 42% patients begun on 40-80mg (1mg/kg) day developed clinical worsening
- Main predictors of Steroid-induced weakness are:
 - Older age
 - Severe bulbar symptoms (diff swallowing, breathing)
- Low dose initiation has been recommended. Usually start 5 mg daily, and increase weekly by 5 mg to goal dose.
- plasma exchange may limit steroid-induced weakness

Prednisolone (Prednisone) (Other Side Effects)

- Weight gain
- Worsening and new diabetes onset
- High blood pressure
- Cataract
- Psychiatric
- Osteopenia/Osteoporosis
- GERD and GI ulcers.
- Insomnia

Our Clinic Steroids Side Effect Patient Management Strategy

- 1- Take after meals in AM.*
- 2- Take vitamin D3 1000 units a day.*
- 3- Calcium supplements 1000 mg a day (can be replaced by Tums).*
- 4- Tums every AM before taking prednisone.*
- 5- If you have diabetes, you will need to contact your PCP to be placed on insulin sliding scale.*
- 6- You might need over the counter sleep meds as melatonin or Benadryl in case prednisone cause insomnia.*
- 7- Will see you in 3 months and consider tapering the dose if your symptoms stable.*
- 8- Some patients will need bone scan to screen for osteoporosis.*

Steroids Sparing Agents

- Group of medications used to lower or avoid the use of steroids.
- Oral: azathioprine (Imuran), mycopholate (Cellcept), cyclosporin, and Methotrexate.
- IVIG
- Rituxan
- Plasmapheresis
- eculizumab

Azathioprine (Immuran)

- Immunosuppressant, Reduces T and B lymphocytes
- Prodrug is converted to mercaptopurine, the active drug
- Mercaptopurine is deactivated by Thiopurine S-Methyltransferase (TPMT)

- Other side effects: GI symptoms, allergic reaction, fever, myalgia, flu-like symptoms, anemia (bone marrow suppression), liver toxicity, and malignancy with chronic use (Skin cancer)

TPMT and Azathioprine Toxicity

- Enzyme is reduced in 10% of Caucasians
 - need $\frac{1}{2}$ dose
- Enzyme absent in .3% (1/300)
 - need 1/10 dose
- Deficiency of enzyme may lead to bone marrow suppression (anemia, low WBC)
- Other reactions: pancreatitis and hepatitis
- Rx:
 - TPMT level screening before starting azathioprine
 - Monitor with weekly CBC x 1 month, biweekly for 2 months, then monthly
 - Start low dose and increase gradually.

Azathioprine and Drug Interactions

- Allopurinol (Zyloprim)
 - Inhibits elimination of AZA
 - May need lower doses of AZA
- ACE inhibitors (Lisinopril)
 - Anemia thought due to erythropoietin suppression
- Warfarin (Coumadin)
 - Inhibits action of warfarin
 - Follow INR closely when stopping or starting AZA

Other Oral Steroids Sparing Agents

- **Mycophenolate (Cellcept):**

- Generally safe
- Side effects: mainly GI, rarely bone marrow suppression.
- Need monthly CBC monitoring.

- **Cyclosporine:**

Side effects:

- Hypertension and nephrotoxicity are the most common effects.
- Progressive nephrotoxicity occurs in up to 10%.
- tremor, nausea, myalgias and flu-like symptoms.
- The risk of malignancy with long term use, primarily squamous cell skin cancer and lymphoma.
- Interact with many drugs.
- Kidney function and blood pressure need to be monitored regularly.

- **Methotrexate:** Oral or SC injections once weekly.

- Generally safe
- Side effects: GI symptoms, myalgias and flu-like symptoms.
- Chronic use: malignancy and interstitial lung disease.
- CBC and CMP monthly monitoring

IVIg

- Used for moderate to severe MG, resistant to classic immunomodulating agent and for MG crisis.
- Not directly impacting MG
- Common reaction: Rash, headache, nausea, fever, blood pressure liability.
- More severe reaction:
 - Aseptic meningitis.
 - Nephrotoxicity. (need frequent kidney function monitoring)
 - anaphylactic reaction.
 - Hypercoagulability as strokes, DVTs, PE, and MI. (risk factors control)

PLEX

- Used during MG crisis, and sometime as maintenance therapy.
- Common reaction: hypotension, bleeding disorder, port infection, electrolytes disturbance
- Rare: Seizure, rash, allergic reactions.

Rituxan

- Monoclonal antibody against B cell membrane marker CD20. Originally developed to treat B cell lymphomas
- Particularly effective in patients with MuSK-positive MG and refractory Achr Abs MG.
- IV infusions every 3-6 months.
- Side effects:
 - Generally safe
 - Hypotension
 - Allergy
 - Headaches
 - GI symptoms.
 - Patients may be more susceptible to certain infections

Eculizumab (Soliris)

- **Eculizumab (Soliris):** is a humanized monoclonal antibody that binds to C5 and inhibits the formation of C5b-induced membrane attack complex.
- Recently approved for AChR-positive MG
- given IV infusion starting at least two weeks after vaccination for meningococcal meningitis
- Side effects:
 - increases the risk of life-threatening Neisserial infections, including *N. meningitidis*, associated with a 1000-fold to 2000-fold increased incidence of meningococcal disease
 - infusions are generally well tolerated.
 - Commonly reported adverse events in clinical trials include headache nasopharyngitis, diarrhea, upper respiratory infection, arthralgias, and nausea

MG and Drugs Interactions

Neuromuscular Blockers

- Curare, vecuronium, botulinum toxin
- Leads to prolonged neuromuscular blockade
- Worsens and prolongs anesthetic paralysis and respiratory paralysis
- Notify anesthesiologist of MG prior to surgery
- Botox should be avoided in MG.

IV Contrast

- Rare reports of weakness and respiratory paralysis after contrast-enhanced CT scanning, etc.
- May occur in patients with severe generalized MG and respiratory weakness
- In a careful review of 136 MG patients who received contrast, the complication rate was 5.1%, similar to non-MG patients
- Caution is recommended, but IV contrast is not contraindicated.

Vaccinations

- Patients with disorders of the thymus may have less protection from live (attenuated) virus vaccines
- Live virus vaccines should be avoided
- yellow fever, measles, rubella, mumps , some H1N1
- Flu shot, Pneumovax are recommended

Antibiotics

- Zithromycin (Z-Pack)
- Telithromycin (Ketek)
- Levofloxacin (Levaquin)
- Ciprofloxacin (Cipro)
- Tetracyclines
- Aminoglycosides
 - Gentamycin
 - Tobramycin less of a problem
- **Penicillins, cephalosporins, metronidazole, sulfa drugs are safest agents in MG**

Statins

- Myalgias noted in 13%, resolved after drug stopped.
- MG worsening in 11%
- Occurred within 1-16 weeks of statin treatment
- Safe for the majority, but monitoring is needed

MG and Dentistry

Table II. Drugs used in dentistry that may interfere with myasthenia gravis*

<i>Drug type</i>	<i>Relatively contraindicated</i>	<i>Use with caution</i>	<i>Safe</i>
Local anesthetics	Procaine (Novocaine) [†]	Lidocaine [†] Mepivacaine [†] Bupivacaine [†] Prilocaine [†]	
Sedative/hypnotics		Morphine and derivatives [‡] Narcotics [‡] Benzodiazepines [‡] Hypnotics [‡] Barbiturates [‡]	Acetaminophen N ₂ O/O ₂ sedation
Anti-inflammatory drugs		Corticosteroids [§]	NSAIDS Aspirin
Antibiotics	Erythromycin [†] Gentamicin [†] Neomycin [†] Polymyxin B [†] Bacitracin [†] Clindamycin [†]	Metronidazole Tetracycline Vancomycin	Penicillin and derivatives

MG and other Adverse Effects

- MG can be exacerbated by
 - Infection
 - was it the infection or the antibiotic?
 - Systemic illnesses
 - Thyroid disease
 - Present in 11% with MG
 - Excessive heat
 - Exercise
 - Pregnancy

Panel 2: Medications that might exacerbate MG

Contraindicated

- D-penicillamine

Use with great caution

- Telithromycin (use only if no other option is available)

Will exacerbate weakness in most patients with MG

- Curare and related drugs
- Botulinum toxin
- Aminoglycosides (gentamycin, kanamycin, neomycin, streptomycin, tobramycin)
- Macrolides (erythromycin, azithromycin)
- Fluoroquinolones (ciprofloxacin, levofloxacin, norfloxacin)
- Quinine, quinidine, procainamide
- Interferon-alfa
- Magnesium salts (intravenous magnesium replacement)

Might exacerbate weakness in some patients with MG

- Calcium channel blockers
- Beta-blockers
- Lithium
- Iodinated contrast agents
- Statins (causal relationship in these cases might be questionable given the widespread use of these agents)

Thanks!