Pharmacologic Treatment of Parkinson’s Disease

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Disclosures

- NO SIGNIFICANT FINANCIAL, GENERAL, OR OBLIGATION INTERESTS TO REPORT
Learning Objectives

- Recognize the 4 cardinal features of parkinsonism
- Describe the mechanism of action, indications, and adverse effects of medications used to treat Parkinson disease (PD)
- Be able to apply the above knowledge to make recommendations to treat the symptoms of a patient with PD
Overview

- Brief review of Parkinson’s disease (PD)
  - Clinical manifestations
  - Pathophysiology

- Pharmacologic treatment of PD
  - Levodopa/carbidopa
  - COMT inhibitors
  - Dopamine agonists
  - MAO-B inhibitors
  - Amantadine
  - Anticholinergics
Clinical Features

- Second most common neurodegenerative disorder

- Incidence and prevalence increase with age
  - Incidence of PD in recent Olmstead County study:
    - 1/100,000 between ages of 30-39
    - 17/100,000 between ages of 50-59
    - 93/100,000 between ages of 70-79

- Risk factors
  - Higher risk in males, Hispanics
  - Lower risk associated with smoking and caffeine use
  - Several genetic mutations
Clinical Features

- Motor symptoms
  - Rest tremor
  - Bradykinesia
  - Rigidity (with cogwheeling)
  - Postural instability
Clinical Features

- Non-motor symptoms
  - Olfactory disturbances
  - Sensory symptoms
  - Gastrointestinal disturbances (e.g. constipation)
  - Urinary symptoms (nocturia, frequency, urgency)
  - Orthostasic intolerance and other signs of dysautonomia
  - Sleep disorders
  - Dementia
  - Depression
Pathophysiology

- Loss of dopaminergic neurons in the substantia nigra pars compacta
Figure 2 - Corticostriate projections.
GP: globus pallidus; SN: substantia nigra; SNL: subthalamic nucleus of Luys.
Dopamine
Levodopa/Carbidopa

- Trade name: Sinemet
- Levodopa is dopamine precursor
- Carbidopa is a peripheral dopa decarboxylase inhibitor

Dosage
- Initial: 25/100mg tab p.o. t.i.d.
- Adjust based on response up to total of 200/2000mg/day
Levodopa/Carbidopa

- Wearing off phenomenon
- Motor Fluctuations
- Freezing
  - Apomorphine: injectable dopamine agonist
- Dyskinesias
Levadopa/Carbidopa

- Adverse effects
  - Dyskinesias
  - Impulse control disorders (e.g. pathologic gambling)
  - Orthostatic hypotension
  - Nausea
  - Somnolence
  - Psychosis
  - Exacerbation of glaucoma
  - NMS with abrupt withdrawal
COMT inhibitors

- Entacapone (Comtan)
- Tolcapone (Tasmar)

Mechanism of action: inhibit catechol-O-methyl transferase, prolonging action of levadopa

Dosage:
- 200mg with each dose of levadopa/carbidopa up to total daily dose of 1600mg/day
COMT Inhibitors

- Adverse reactions
  - Dyskinesias
  - Diarrhea
  - Orthostatic intolerance
  - Psychosis
  - Nausea
  - Orange-brown discoloration of urine
  - Hepatic failure with tolcapone
Dopamine Agonists

- Ergot derivatives
  - e.g. Bromocriptine
  - No longer widely used due to risk of cardiac valvular fibrosis

- Non-ergots
  - Pramipexole (Mirapex)
  - Ropinirole (Requip)
Dopamine Agonists

- **Mechanism of action:** Bind to D2 (and also D3, D4) receptors, activating dopaminergic circuits

- **Dosage:**
  - Pramipexole: 0.125mg p.o. t.i.d., titrating up to 4.5mg/total daily dose as needed
  - Ropinirole: 0.25mg p.o. t.i.d., titrating to 1mg p.o. t.i.d. over 4 weeks and then up to 24mg/total daily dose as needed
  - Both are also available in extended release formulations
Dopamine Agonists

- Adverse effects
  - Somnolence
  - Orthostatic hypotension
  - Nausea
  - Peripheral edema
  - Hyperhidrosis
  - Impulse control disorders
  - Dyskinesias
  - Psychosis
MAO Inhibitors

- **Non-selective:** selegiline (Eldepryl)
  - Available both p.o. and transdermally
  - Risk of hypertensive crisis with tyramine

- **Selective (MAO-B):** rasagiline (Azilect)
  - Dosage: 0.5mg p.o. q.a.m., can increase to 1mg if needed
  - Possibly neuro-protective
MAO-B Inhibitors

- Adverse effects:
  - Somnolence
  - Nausea
  - Orthostasis
  - Psychosis
  - Rarely, serotonin syndrome if taken in conjunction with tricyclic antidepressants
Amantadine

- Trade name: Symmetrel
- Mechanism of action: possible dopamine agonist and/or reuptake inhibitor
- Useful in treatment of dyskinesias and tremor
- Dosage:
  - 100mg p.o. b.i.d. up to 400mg/day as needed
- Adverse effects:
  - Peripheral edema, livedo reticularis
Anticholinergics

- Benztropine (Cogentin)
- Trihexyphenidyl (Artane)
- Diphenhydramine (Benadryl)

- Mechanism of action: restore natural balance of dopamine and acetylcholine in the basal ganglia
- Useful in treating tremor in younger patients
Anticholinergics

- Adverse effects:
  - Encephalopathy
  - Tachycardia
  - Xerostomia and xerophthalmia
  - Constipation
  - Urinary retention
Basic Principles

- Levadopa/carbidopa still the drug of choice
- COMT inhibitors for “wearing off”
- Dopamine agonists probably almost as effective as levadopa/carbidopa and useful for younger patients
- Rasagiline possibly neuroprotective
- Amantadine for dyskinesias
- Anticholinergic agents for tremor-predominant disease in younger patients
Questions?

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