DRUGS IN MOVEMENT DISORDERS: TRUTHS, MYTHS AND MORE

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We will discuss commonly used medications in the movement disorder patient

• Who are our patients?

• What medications do we use?

• Why do we choose certain medications?

• What common side effects or interactions can occur?
Who are our patients?
Patients with:

- Parkinson’s disease *
- Essential tremor *
- Atypical parkinsonism (vascular parkinsonism, progressive supranuclear palsy, multiple system atrophy, corticobasal degeneration)
- Tic disorders
- Ataxia or cerebellar disorders
- Myoclonic disorders
- Huntington’s disease
What medications do we use?
Parkinson’s disease medications

• Carbidopa/levodopa

• Dopamine agonists

• Monoamine oxidase B (MAO B) inhibitors

• Catechol-O-methyl transferase (COMT) inhibitors

• Anticholinergics

• Amantadine
DDC inhibitors
- Prevent peripheral breakdown of levodopa

COMT inhibitors
- Prevent peripheral breakdown of levodopa

Levodopa
- Converted to dopamine within the brain

Dopamine agonists
- Post-synaptic mimicry of naturally occurring dopamine

MAO-B inhibitors
- Prevent further breakdown of dopamine
Carbidopa/Levodopa

• Carbidopa
  • decarboxylase inhibitor (prevents breakdown of levodopa in extra-cerebral tissues)
  • does not cross the blood brain barrier and therefore does not affect the CNS metabolism of levodopa
  • decreases the amount of levodopa required to produce a response by 75% and increases the plasma half life of levodopa from 50 minutes to 90 minutes

• Levodopa
  • amino acid that becomes dopamine by removal of a carboxyl group
Formulations

- c/l 10/100 (IR)
- c/l 25/100 (IR)
- c/l 25/250 (IR)
- c/l CR/SA 25/100
- c/l CR/SA 50/200
Parcopa

- Orally disintegrating tablets – not really a true “sublingual” preparation as it is still absorbed in the lower GI tract and not through the oral mucosa

- Similar pharmacokinetics to IR c/l with a slightly shorter time to Tmax

- c/l 10/100 mg, c/l 25/100 mg, c/l 25/250 mg

- Inactive ingredients include aspartame, phenylalanine and citric acid
Rytary

- Combination of IR and SA forms

- c/l 23.75/95 mg, c/l 36.25/145 mg, c/l 48.75/195 mg, c/l 61.25/245 mg

- Inactive ingredients include talc and gelatin

- Initial peak at 1 hour

- Plasma concentrations are maintained for 4-5 hours before declining

- Bioavailability of levodopa from Rytary is approximately 70% relative to IR c/l (dose conversion can be tricky)
• Caution in patients with cardiac history

• Placebo controlled study in patients with early PD – percent who reported ischemic CV adverse reactions
  
  • 2.4% (7/289) Rytary treated patients
  • 1.1% (1/92) placebo treated patients

• Active controlled study in patients with advanced PD – percent who reported ischemia CV adverse reactions
  
  • 0.7% (3/450) Rytary treated patients
  • 0% (0/471) of oral IR c/l treated patients

**these patients all had a previous history of ischemic heart disease or CV risk factors**
Duopa

- Enteral suspension of c/l (4.63 mg c/20 mg l per mL)
  - Maximum recommended dose is 2000 mg of levodopa over 16 hours (1 cassette)
  - Prior to initiating duopa, patients must be converted to IR c/l from all other forms of levodopa
  - Administered through a PEG-J tube (can be given short term through an NG tube if needed)
  - Peak plasma levels reached in 2.5 hours
  - Must be stored in freezer (-20 degrees C) and thawed in refrigerator (2-8 degrees C) prior to dispensing (12 week expiration after thawing)
  - Gastric emptying rate does not influence the absorption of duopa as it is administered by continuous intestinal infusion
  - 5% of patients (19/412) developed a generalized polyneuropathy – most often axonal sensorimotor polyneuropathy
Dopamine agonist

- Ropinirole (Requip)
  - Agonist at D2 and D3 receptors, stimulates postsynaptic D2 receptors in basal ganglia
  - Rapidly absorbed, peak concentration in 1-2 hours with a half life of 6 hours
  - Inactive ingredient: anhydrous lactose

- Pramipexole (Mirapex)
  - Same mechanism of action as above
  - Peak concentration in 2 hours, half life 8-12 hours (12 hours in elderly population)

- Rotigotine (Neupro)
  - Same mechanism of action as above
  - Patch form, continuous 24 hour delivery of medication
  - Contains sodium metabisulfite – can cause allergic reactions in patients with sulfite sensitivity
• Apomorphine
  • Injectable form (subcutaneous)
  • Rapid absorption, peak concentration in 4-12 minutes, half life of 30 minutes
  • Need to used in conjunction with antiemetic – trimethobenzamide (Tigan)
  • Cannot use with ondansetron – several reports of profound hypotension and LOC
  • Caution in patients with sulfite sensitivity – contains sodium metabisulfate

• Pergolide, bromocriptine (rarely used)
MAO-B inhibitor

- Rasagiline (azilect)
  - Irreversibly inhibits the action of MAO-B enzyme -- decreases the breakdown of dopamine in the brain and inhibits the reuptake of dopamine at the presynaptic receptor
  - 5 times more potent than selegiline
- Selegiline
  - Amphetamine metabolite – can have a stimulant effect causing insomnia, anxiety and hallucinations
COMT inhibitor

- Entacapone/Tolcapone
  - Reversible, peripherally acting COMT inhibition -- decreases the breakdown of dopamine
  - Increases the half life of levodopa by 30-50% (from 1.5 to 2.5 hours)
  - Rapidly absorbed, Tmax of 1 hour. Bioavailability not affected by food
  - Used mostly for patients with "wearing off" prior to next dose
  - Not used alone must be given with levodopa
  - Can cause increased dyskinesias, diarrhea, abdominal pain
  - Tolcapone with 3 patients deaths due to development of fulminant hepatitis
Anticholinergics

• May be of benefit for “tremor predominant” PD

• Trihexyphenadyl (Artane), benztropine (Cogentin)

• Side effects:
  • Dry mouth
  • Blurred vision
  • Constipation
  • Urinary issues
  • Memory issues/confusion
  • Hallucinations
Amantadine

- Antiviral drug originally developed to prevent influenza but was found to improve mild motor symptoms in PD patients

- May help to reduce dyskinesias secondary to levodopa use, but benefit if transient

- Side effects:
  - Hallucinations
  - Confusion
  - LE edema
  - Livedo reticularis
Droxidopa

- Synthetic amino acid precursor which acts as a prodrug to norepinephrine

- Unlike NE, droxidopa can cross the BBB

- Used for neurogenic orthostatic hypotension

- Used in Asia since 1989, FDA approved here in February 2014

- Inactive ingredient: gelatin

- Caution when used in combination with other agents that increase BP (midodrine, triptans)

- Caution in patients with pre-existing CHF, ischemic heart disease or arrhythmias
New drugs in development

- New COMT inhibitors
- New MAO-B inhibitor
- New dopamine agonists
- Adenosine A (2A) receptor antagonists (proposed to block unwanted activity of receptors in the BG)
- Alpha-adrenergic receptor antagonists (proposed to help balance the GABA activity in the BG)
- Serotonergic agonists (proposed to enhance the transmission of serotonin)
- Neuroprotective medications
- Pioglitazone (DM drug)
- Isradipine
- Glutathione
- Growth Factor Neurturin
Essential tremor medications

- Topiramate (topamax)
- Primidone (mysoline)
- Propranolol (inderal)
- Clozapine
- Metoprolol
- Mirtazapine
- Atenolol
- Gabapentin
- Zonisamide
- Pregabalin
- Alcohol
- Benzodiazepines
- Botulinum toxin
Topiramate

- Exact mechanism of action unknown for tremor control but blocks voltage-dependent sodium channels, augments GABA activity and antagonizes glutamate

- Rapid absorption, peak plasma concentration within 2 hours

- Not extensively metabolized, 70% is excreted unchanged in the urine

- Inactive ingredient: lactose monohydrate
Primidone

- Exact mechanism of action unknown for tremor control

- Metabolized to phenobarbital which acts as a GABA<sub>a</sub> receptor agonist and antagonist at some subtypes of glutamate receptors

- Phenobarbital is metabolized by the liver and induces many P<sub>450</sub> isozymes (especially CYP<sub>2B6</sub>)

- Inactive ingredients: lactose monohydrate, sodium lauryl sulfate, talc
Propranolol

• Non-selective beta-adrenergic receptor blocking agent

• Rapidly absorbed with peak plasma concentration from 1-4 hours after oral dose

• High first pass metabolism by the liver (P450 system), only approximately 25% of propranolol reaches the systemic circulation

• Inactive ingredient: gelatin
Why we choose certain medications...

What common side effects or interactions can occur?
PD

- There is no “correct” starting medication – this will vary by providers and depending on patient profile

- Often use dopamine agonists first for younger patients

- Need to take into account co-morbidities and side effects
ET

• Guidelines from the AAN 2011
  
  • Propranolol (regular or long acting) or primidone (Level A)
  
  • Topiramate, atenolol, gabapentin, sotalol (Level B)
  
  • Insufficient evidence for amantadine, clonidine, clozapine, pregabalin, zonisamide, metoprolol, nicardipine (Level U)
Side effects/interactions
Carbidopa/levodopa

• Nausea

• Mood/behavioral changes

• Daytime somnolence

• Orthostatic hypotension
• Dark urine or sweat due to increased urinary excretion of dopamine (more commonly seen in patients also taking entacapone)

• High protein diet may delay the absorption of levodopa due to competition for binding as both are transported across the small intestine by the same amino acid transport system

• Excessive stomach acidity may also delay the absorption of levodopa due to a delay in stomach emptying into the small intestine

• Iron salts (often a part of a multivitamin) also may reduce the amount of levodopa available to the body by forming chelates with the carbidopa and levodopa
• Good initial choice for ???

• “Older” patients with suspected PD
• Patients with significant mood disorder (other than depression or anxiety)
Dopamine agonists

- Mood/behavioral changes (more common in DA than with levodopa)
  - obsessions, compulsions, impulse control disorders – sexual, gambling, shopping...
  - hallucinations

- Daytime somnolence (sleep attacks)

- Leg edema

- Orthostatic hypotension
• Ropinirole is metabolized by P450 enzyme system (CYP1A2)

• Drug level altered by enzyme inducers (smoking, omeprazole) and inhibitors (ciprofloxacin, verapamil, grapefruit juice, cumin, tumeric)

• Hormone replacement therapy also reduces clearance (estrogen effect)
Pramipexole is not metabolized by P450 enzymes (90% of drug excreted in urine unchanged)

For renal impairment
  • Cr clearance 30-50 mL/min -- maximum dose is 0.75 mg tid
  • Cr clearance 15-30 mL/min – maximum dose is 1.5 mg daily
• Rotigotine patch has aluminum backing – must be removed before cardioversion or MRI

• Heat may increase drug absorption – avoid direct heat source (heating pads, electric blankets, heat lamps, hot tubs, hair dryers, prolonged direct sunlight)
• Good initial choice for ???

• “younger” patients with PD symptoms
• Patient with mild PD symptoms
• Patient with restless legs syndrome
Topiramate

- Cognitive slowing
- Numbness and tingling of fingers and toes
- Weight loss (average of 5 lbs – mechanism unclear)
- Metallic taste with drinking “dark sodas”
• Decreased sweating and hyperthermia

• Reduce dose in patients with renal impairment (Cr clearance <70 mL/min)

• Risk of secondary angle closure glaucoma (myopia, eye pain, ocular redness) and visual field deficits

• Risk for metabolic acidosis – caused by renal bicarbonate loss
  • Caution in conditions which would predispose patients to acidosis – renal disease, severe respiratory disorders, diarrhea, ketogenic diet, some drugs – metformin – can lead to fatigue, renal stones, altered mental status, weakness

• Kidney stones (occurs in approximately 1.5% of patients) – suspected due to inhibition of carbonic anhydrase which reduces urinary citrate excretion and increases urinary pH
Primidone

- Sedation
- Ataxia
- Vertigo

- Use with caution in patients on other sedative drugs (muscle relaxants, benzodiazepines, opiates) or with chronic ETOH use

- Phenobarbitol is metabolized by the liver and induces many P450 isozymes (especially CYP2B6) therefore dosage adjustments need to be made for patients with hepatic failure

**Notify other providers when starting this medication as it may alter the levels of other medications (statins, mental health medications...)**
Propranolol

- Fatigue
- Bradycardia
- Hypotension
- Worsening of depression
- Worsening of asthma

- Use with caution in diabetics on insulin (may mask symptoms of hypoglycemia)

- SJS
- SLE-like reaction
• Chronic renal failure has been associated with a decrease in propranolol metabolism via downregulation of P450 activity resulting in a lower "first-pass" clearance = higher peak plasma levels in patients with renal failure as well as in patients with hepatic failure

• P450 inhibitors increase plasma levels of propranolol (amiodarone, cimetidine, fluoxetine, paroxetine, ciprofloxacin, fluconazole)

• P450 inducers decrease plasma levels of propranolol (phenytoin, phenobarbital, cigarette smoking)
Other interesting facts...
Glaucoma

- Levodopa therapy is contraindicated in patients with narrow/closed angle glaucoma.

- While levodopa primarily is a dopaminergic agent, there may be cross-over onto cholinergic receptors.

- These receptors are generally responsible for pupil dilation which can cause narrowing of the angle which can increase eye pressure.

Angle Closure Glaucoma: The angle formed by the cornea and the iris narrows, preventing the aqueous humor from draining out of the eye. This can lead to a rapid increase in intraocular pressure. Source: The Mayo Clinic (www.mayoclinic.com)
Melanoma

• Overall risk for cancer in patients with PD is lower but risk for malignant melanoma is higher (4x increased risk)

• Unclear etiology – initially suspected due to relationship between dopamine and melanin (dopamine is precursor of melanin), but more complex than that – new genetic studies going on as studies finding early PD patients with melanoma (not treated with levodopa)
From the current literature there is:

- Consistent data supporting an association between cutaneous melanoma and PD
- A possible association between non-melanoma skin cancers and PD
- Insufficient data to conclude on the association between L-dopa and melanoma in PD patients
- Insufficient data to conclude on the association between MAO-B inhibitors, DA or other anti-parkinsonian drugs and melanoma or other skin cancers in PD patients
- Insufficient data about the risk factors for skin cancer in PD patients and therefore no EBM recommendations regarding the need for periodic dermatological screening
• When you order carbidopa/levodopa a box pops up that says “ok to take pyridoxine with this combination”….what is this all about?

• Pyridoxine (B6) may reverse the effects of levodopa by increasing the rate of decarboxylation, but carbidopa inhibits this action
• To eat or not to eat....

• Protein competes with levodopa for transport across the small intestine and can decrease its absorption/plasma concentration.

• Protein rich foods increase the bioavailability of propranolol by about 50%.

• Patients who take levodopa on an empty stomach will often complain of nausea, can add additional carbidopa 25 mg to each dose or instruct patients to take with carbohydrate meal.
• Can these medications be stopped abruptly or do they need to be tapered?

• There is a risk of neuroleptic malignant syndrome with abrupt discontinuation of sinemet or a dopamine agonist, but this is rare

• Primidone must be tapered off as metabolite is phenobarbitol – increased risk of seizures with abrupt discontinuation

• Propranolol must be tapered off due to risk of rebound hypertension if abruptly stopped
Conclusions...

- Variability in medication and dosing regimen between providers
- No “one correct” starting medication for all patients
- New medication trials currently underway
- Providers need to be aware of side effects, inactive ingredients and pharmacology/pharmacokinetics of medications
Questions?
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