Parkinson’s Disease - Medical Management

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Talk Overview
- Therapeutic Principles
- Therapeutic Choices
- Medications available for PD
- Treatment available for PD
- Treatment of complications
- Future pharmacotherapies

Introduction

Pathophysiology

Dopamine

Pathology
Questions about Treatment of PD

- Are there drugs available to slow the rate of progression?
- Which drug first?
- When should Levodopa be introduced?
- How are complications from levodopa prevented?

Therapeutic Principles

- Optimise independent functioning for as long as possible
- Individualize therapy
- Exercise Program – muscle stretching, enhances mental attitude and improves motor performance

Therapeutic Choices available

- Initial medication may depend on age and severity of symptoms
- Multidisciplinary approach
- Lifelong treatment
- Many drugs developed
- Dopamine replacement therapy is the major medical approach to treating the disease

Replace Dopamine

- Levodopa-mainstay of treatment for PD
- Improves rigidity and mobility
- Oral and duodenal continuous infusion
- Levodopa - metabolic precursor of dopamine.
- Levodopa is taken into dopaminergic neuron terminals and converted into dopamine by enzymes.

Levodopa

- Combined with agents (inhibitors) reduces breakdown in the gut and bloodstream and enhances delivery to the brain

\[
\text{Sinemet} = \text{Levodopa} + \text{carbidopa} \\
\text{Madopar} = \text{Levodopa} + \text{benserazide} \\
\text{Stalevo} = \text{Levodopa} + \text{carbidopa} + \text{entacapone}
\]
Levodopa

The Advantages of Levodopa
- The most effective symptomatic treatment
- Improves ADL and thus quality of life
- Well tolerated
- Provides antiparkinsonian benefit over the entire course of the disease
- All PD patients will eventually require levodopa therapy

Limitations of chronic Levodopa therapy
- Disabling motor and sensory complications may develop – correlates with severity of PD and long-term levodopa therapy
- ‘wearing off’ (end of dose failure)
- ‘on-off’ phenomenon. The ‘off’ state – return of PD symptoms often abruptly
- Dyskinesias – involuntary movements, frequently not bothersome and related to peak dose

Motor fluctuations: On-off

Dyskinesia: extra movements
1. Peak-dose dyskinesia usually occurs at the time of peak dose levodopa
2. Less commonly, dyskinesia can occur either side of the peak dose
3. OFF state dyskinesia (pre meds)
Prevention of side-effects of Levodopa

- Wearing off -
  - Aim to prolong response to levodopa
  - Combine L-dopa with agent that inhibits the breakdown of dopamine-Comtess, Eldepryl

- Sudden offs-
  - Adjunctive treatment with dopamine agonists.

- Dyskinesias-
  - Adjunctive dopamine agonist and lower dose of levodopa

Response to Levodopa may vary in relation to meals

- Levodopa is absorbed only from the small intestine,
- A full meal with delayed gastric emptying - delay and weaker response to Levodopa when taken with the meal
- Better and faster response if taken before the meal

Prevention of side effects of Levodopa

- Controlled release preparations of Levodopa –
  - Sinemet CR and Madopar CR
  - Benefit – prolonged absorption
  - increased bioavailability - improves wearing-off symptoms

May increase dyskinesias

Prevention of side effects of Levodopa

- Adjunctive therapies
  - Comtess, Tasmar, Eldepryl, Azilect - improve wearing-off and on-off symptoms
  - Enhance bioavailability of levodopa by preventing breakdown of dopamine

STALEVO

Combination of Levodopa/carbidopa/COMT inhibitor(Comtess)
- Prolonged benefit from levodopa
- Offers smoother and more consistent plasma levels of levodopa
- Up to 15% of a dose of Stalevo reaches the brain

DUODOPA

- Combination levo-dopa/carbidopa
- Given via small tube inserted directly into small bowel
- Dose adjustments
- Considered in certain refractory cases
**Dopamine Agonists**
- Levodopa sparing
- In combination with Levodopa may improve motor symptoms – wearing-off and on symptoms, dyskinesias
- Mirapexin, Requip, Parlodel – oral admin

**Dopamine agonists – side effects**
- Confusion and hallucinations in the elderly
- Swelling of the legs (oedema)
- Sleepiness and sleep attacks

**Dopamine agonists**
- Transdermal administration – Neupro Patch – 24 hour delivery of drug
- Subcutaneous administration APO-go Rescue therapy for intractable ‘offs’

**Other Therapies**
- Anticholinergics – Akineton, Kemadrin
  - May help tremor
  - Side effects – confusion
- Amantidine – Symmetrel
  - Promotes release of dopamine
  - May help reduce dyskinesias
  - Mild effect on symptoms
- Surgery – Deep brain stimulation

**Potential Future Therapies**
- Reverse / arrest disease progression
- Combination therapies – to prolong Levodopa effect and decrease side effects
- Neuroprotective agents
- Surgery

**Patient’s Role**
- Be well informed and keep updated
- Medication diary – dose adjustments and side effects
- Drug dispenser
- Be aware of effects of treatment – both good and bad
- Nutrition
- Exercise
- Apply for long term disability scheme (Long Term Illness Book)