Parkinson tedavisine farklı bir bakış

Nurgul Carkaci-Salli Ph.D.

Penn State College of Medicine
Department of Pharmacology
Substantia nigra and Parkinson's disease

PD, first described by James Parkinson in 1817, is a neurodegenerative disorder associated with specific neuropathological lesions.

3–5% of total neurons

substantia nigra pars compacta
Each connection between the CNS part of the autonomic nervous system and a peripheral organ contains two neurons connected in series. The cell body of the first neuron is located inside the CNS, but its efferent synapses are located inside a sympathetic or parasympathetic ganglion, outside of the blood brain barrier. The cell body of a second neuron is located in this ganglion.
The most commonly prescribed drug for PD is L-dopa. L-Dopa is the natural precursor for the metabolism of dopamine.

It is used as a treatment for PD patients to replace lost midbrain dopamine as, unlike dopamine itself, which is charged, it can cross the blood-brain barrier.

Experimental methods used at this time include deep brain stimulation, where electrodes are placed in the brain, which stimulate the thalamus and the implantation of stem cells. Transplantation of neural stem cells from fetal tissue into the PD striatum seems to be the most promising approach, as the fetal tissue not only appears to survive in the host, but also to replace the function of the damaged dopaminergic neurons.
<table>
<thead>
<tr>
<th>Type of agent</th>
<th>Dosing information</th>
<th>Max. Daily dose</th>
<th>Pharmacokinetics Parameters</th>
<th>% Bio-availability</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dopamine agonists</strong></td>
<td>Typical starting or maintenance dose (MD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>1.25-10 mg t.i.d</td>
<td>375-40 mg</td>
<td>0.5-2 hrs</td>
<td>90-96</td>
</tr>
<tr>
<td>Carbagoline</td>
<td>1-6 mg QD</td>
<td>2-6 mg</td>
<td>---</td>
<td>63-68</td>
</tr>
<tr>
<td>pergolide</td>
<td>0.5-1.0 mg t.i.d (MD)</td>
<td>3-5 mg</td>
<td>1-2 hrs</td>
<td>90</td>
</tr>
<tr>
<td>Pramipexole</td>
<td>1.0-5.0 mg t.i.d (MD)</td>
<td>4.5 mg</td>
<td>1-2 hrs</td>
<td>8-12 hrs</td>
</tr>
<tr>
<td>Ropinirole</td>
<td>2.5 mg t.i.d</td>
<td>9.24 mg</td>
<td>1.5 hrs</td>
<td>6 hrs</td>
</tr>
<tr>
<td><strong>Dopamine precursors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levodopa/carbidopa</td>
<td>25/100 mg t.i.d</td>
<td>400-800 mg</td>
<td>0.5-2 hrs</td>
<td>1-3 hrs</td>
</tr>
<tr>
<td>Long acting LD/CD</td>
<td>50/200 mg b.i.d</td>
<td>400-2000 mg</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Levodopa/benserazide</td>
<td>t.i.d-q.i.d dosing</td>
<td>400-800 mg</td>
<td>0.5-1 hr</td>
<td>1.5-2 hrs</td>
</tr>
<tr>
<td>Levodopa</td>
<td>50/200 mg b.i.d</td>
<td>500-1200 mg</td>
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</tr>
</tbody>
</table>

*Recommended useful maximum daily dose.

*Expressed as levodopa dose.

*Immediate-release formulation.
A COMT inhibitor is a drug that inhibits the action of catechol-O-methyl transferase. This enzyme is involved in degrading neurotransmitters. COMT inhibitors are used in the treatment of Parkinson’s disease.

Dopamine oxidation can occur either spontaneously in the presence of transition metal ions or via an enzyme-catalyzed reaction involving monoamine oxidase (MAO).
L-dopa depletion of L-tyrosine

L-dopa depletion of serotonin

L-dopa depletion of sulfur amino acids

Carbidopa in treatment
Arginase activity in immune cells is upregulated by certain cytokines such as IL-4, IL-10, and TGF-beta and by catecholamines. Since the release of these substances is increased after trauma, we hypothesized that arginase activity would also be increased in immune cells after trauma.

Arginase II is coexpressed with nitric oxide (NO) synthase in smooth muscle tissue, such as the muscle in the genitals of both men and women. The contraction and relaxation of these muscles has been attributed to NO synthase, which causes rapid relaxation of smooth muscle tissue and facilitates engorgement of tissue necessary for normal sexual response. However, since NO synthase and arginase compete for the same substrate (L-arginine), over-expressed arginase can affect NO synthase activity and NO-dependent smooth muscle relaxation by depleting the substrate pool of L-arginine that would otherwise be available to NO synthase. In contrast, inhibiting arginase with ABH or other boronic acid inhibitors will maintain normal cellular levels of arginine, thus allowing for normal muscle relaxation and sexual response.

Recent studies have implicated arginase as a controlling factor in both male erectile function and female sexual arousal, and is therefore a potential target for treatment of sexual dysfunction in both sexes.
Serotonin

Serotonin is an example of a monoamine neurotransmitter, a chemical messenger that is passed between nerve cells. This hormone is mainly found in the gastrointestinal tract, the platelets and the central nervous system of animals and is thought to contribute to a sense of well being and happiness.

Serotonin is synthesized from the amino acid L-tryptophan via a short metabolic pathway that involves two major enzymes. These enzymes are: Tryptophan hydroxylase (TPH) Amino acid decarboxylase

The reaction in this pathway that is mediated by tryptophan hydroxylase is the rate limiting step, meaning that if this enzyme is blocked, the synthesis of serotonin would be stopped.

Tryptophan hydroxylase exists in two forms - TPH1 and TPH2. While TPH1 is found in several tissues, TPH2 is specifically found in nerves of the brain.
While serotonin in its primary form cannot reach the brain since it cannot cross the blood–brain barrier, the serotonin precursors tryptophan and its metabolite 5-hydroxytryptophan (5-HTP) do cross this barrier and reach the brain. These agents can be taken as dietary supplements to increase levels of serotonin in the brain.
Table 1.

<table>
<thead>
<tr>
<th>% Inhibition</th>
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<tbody>
<tr>
<td>Dienestrol</td>
</tr>
<tr>
<td>Apomorphine HCl</td>
</tr>
<tr>
<td>Propidium iodide</td>
</tr>
<tr>
<td>Luteolin</td>
</tr>
<tr>
<td>Benserazide HCl</td>
</tr>
<tr>
<td>Butoconazole nitrate</td>
</tr>
<tr>
<td>Deferoxamine mesylate</td>
</tr>
<tr>
<td>Levodopa</td>
</tr>
<tr>
<td>Dopamine</td>
</tr>
<tr>
<td>Carbidopa</td>
</tr>
</tbody>
</table>
Dopamine

- **Catecholamine**
  - Highest affinity for DR (vascular D1), moderate doses can activate beta 1, high doses can activate alpha1

- **Effects**
  - D1 – Gs- Vasodilation of renal, mesenteric, and coronary beds – affect renal function
  - Positive inotropic effect on myocardium through beta 1
  - Increases NE release from nerve terminals

- **Therapeutic Uses**
  - Congestive heart failure, shock

- **Adverse effects and Drug Interactions**
  - Similar to NE
**Norepinephrine**

- **Catecholamine**

- **Compared to Epinephrine**
  - = potency at beta 1
  - < potency at beta2 receptors
  - potent at alpha receptors

  Low doses do not cause vasodilation or decrease blood pressure

- **Topical or Injection (not oral)**

- **Therapeutic use**: vasoconstrictor

- **Adverse Effects and Drug Interactions**: similar to epinephrine, but greater chance of hypertension
Epinephrine

**Catecholamine**

Non-selective but higher affinity for beta adrenergic receptors

**Effects**

- **Blood Pressure**
  - Low dose – decrease (beta 1)
  - High dose – increase (beta 1 + beta 2 + alpha 1)

- **Vascular Effects**
  - Constrict cutaneous blood flow (alpha 1)
  - Blood flow to skeletal muscles is increased (beta 2)

- **Smooth Muscle**
  - Muscle/receptor type dependent
    - GI relaxed – alpha and beta activation
    - Heart contraction (+ chronotropic and inotropic action) – beta activation
    - Uterus relaxation – beta 2 activation
    - Bronchial relaxation – beta 2 activation
Glutathione is not an essential nutrient for human, since it can be synthesized in the body from the amino acids L-cysteine, L-glutamic acid and glycine, it does not have to be present as a supplement in diet. The sulfhydryl group (SH) of cysteine serves as a proton donor and is responsible for its biological activity. Cysteine is the rate limiting factor in cellular glutathione biosynthesis.
- Management of L-dopa depletion of serotonin

- Management of dopamine fluctuations with L-tyrosine

- Management of sulfur amino acid depletion by L-dopa

- Management of paradoxical amino acid reactions
L-DOPA dozunun ayarlanması
Bugüne kadar olan bütün bilgiler L-DOPA’nın Parkinson tedavisinde en yüksek potansiyele sahip olduğunu göstermiştir, fakat hastalarda görülen olumsuz yan etkilerin azaltılması için verilecek doz her hastaya özel ayarlanmalıdır.

Parkinson hastalarının tedavisinde L-DOPA miktarı belirlenirken dopamin ve serotonin dengesinin ayarlanması, 5-hidroksitriptofan, L-tirozine ve sülfür amino asitlerinin vücuttaki kullanımının ayarlanmasını sağlamaktır.

Serotonin seviyesinin ayarlanması
Çözüm L-DOPA tedavisi ile birlikte 5-HTP almaya başlamak, yada serotonin reuptake inhibitörlerinin kullanılmaya başlanmasıdır, tedaviye başlandığında organik katyon transportör essey yapılması ve bunun sonucuna göre serotonin-dopamin dengesinin sağlanmasını sağlayacaktır.

Dopamin seviyesindeki dengesizliğin L-tyrozin ile ayarlanması
L-DOPA arttırılması yerine L-tirozin arttırılması problemleri çözebilir. On-off etkisinin kontrol altında tutulmasını sağlayacak L-tirozin dozu günde 20 000mg civarındadır.

Sülfür amino asitlerinin azalmasının kontlolu
Çözüm hergün düzenli olarak uygun seviyede sülfür aminoasitlerinin kaybı karşılayacak düzeyde takviyesidir.
Ilacdan kaynaklanmayan tetikleyici faktorlerin elemine edilmesi (enfeksiyonlar, vucudaki elektrolit dengesinin bozulması, susuz kalma gibi)

Halihazırda uygulanan tedavi yönteminin gözden geçirilmesi
- Anti Parkinson ilaclarının azaltılması
- Risk faktörü yüksek olan ilacların azaltılması – Antikolinerjik ilacların durdurulması (deprenyl, Amantadine)
- Dopamin agonistlerinin azaltılması yada durdurulması
- Levodopa dozunun azaltılması

Kalici psikoz

Parkinson hastalığı-Dimensia

Kolin esteraz inhibitörlerinin ilavesi (rivastigmine, 3mg-12 mg/h)

Kalici psikoz

Anti psikotiklerin ilavesi
- quetiapine yatmadan önce 25mg ile baslanıp gerektiginde günde 200mg'a kadar artırılır
- clozapine yatmadan önce günde 6.25-12.5mg, 6.25mg yavaş istenmeyen bir yan etki gorulunceye kadar artırılır, haftalık kansayımı yapılmalıdır

(Poewe, 2008)
THANK YOU