بسم الله الرحمن الرحيم

DOPAMINE SCIENTIFIC TEAM

Parkinson's & Alzheimer's Drugs

FINAL | Lecture 8

﴿ إِنِّي تَوَكَّلْتُ عَلَى ٱللَّهِ رَبِّي وَرَبَّكُمْ ۚ مَّا مِن دَآبَّةٍ إِلَّا هُوَ ءَاخِذٌۢ بِنَاصِيَتِهَآ ۚ إِنَّ رَبِّي عَلَىٰ صِرَٰطٍ مُّسْتَقِيمٍ ﴾

Written by: Qusai Sharkas

Reviewed by: Almothana Khalil

PHARMACOLOGY

رحلة اليقين مع سورة يس

بِسۡمِ ٱللَّهِ ٱلرَّحۡمَٰنِ ٱلرَّحِيمِ

أَوَلَمۡ يَرَوۡاْ أَنَّا خَلَقۡنَا لَهُم مِّمَّا عَمِلَتۡ أَيۡدِينَآ أَنۡعَٰمٗا فَهُمۡ لَهَا
مَٰلِكُونَ ٧١ وَذَلَّلۡنَٰهَا لَهُمۡ فَمِنۡهَا رَكُوبُهُمۡ وَمِنۡهَا يَأۡكُلُونَ ٧٢
وَلَهُمۡ فِيهَا مَنَٰفِعُ وَمَشَارِبُۖ أَفَلَا يَشۡكُرُونَ ٧٣

يأمر تعالى العباد بالنظر إلى ما سخر لهم من الأنعام وذللها، وجعلهم مالكين لها، مطاوعة لهم في كل أمر يريدونه منها، وأنه جعل لهم فيها منافع كثيرة من حملهم وحمل أثقالهم ومحاملهم وأمتعتهم من محل إلى محل، ومن أكلهم منها، وفيها دفء، ومن أوبارها وأشعارها وأصوافها أثاثا ومتاعا إلى حين، وفيها زينة وجمال، وغير ذلك من المنافع المشاهدة منها، {أَفَلَا يَشْكُرُونَ} الله تعالى الذي أنعم بهذه النعم، ويخلصون له العبادة ولا يتمتعون بها تمتعا خاليا من العبرة والفكرة.

Central Nervous System

- Most of the drugs that affect the central nervous system (CNS) act by altering some steps in the neurotransmission process.

- They may act presynaptically by influencing the production, storage, release, or termination of action of neurotransmitters.

- Other agents may activate or block postsynaptic receptors.

- Several major differences exist between the neurons in ANS and those in the CNS, for example CNS communicates using 10 different neurotransmitters (ANS has norepinephrine and ACT).

Central Nervous System

- Most of the neurons in the CNS receive both excitatory and inhibitory potentials.
- Thus, several types of neurotransmitters may act on the same neuron, but each binds to its own specific receptors.
- The overall resultant action is due to the summation of individual actions of various neurotransmitters on the neurons.

Neurodegenerative diseases

General introduction; recall Pathology

- Include Alzheimer, Parkinson, Huntington diseases.
- Alzheimer affect some 4 millions Americans while Parkinson is affecting 1.5 millions Americans.
- They are devastating (destructive) illness, characterized by the progressive loss of selected neurons in discrete brain areas, resulting in characteristic disorders of movements, cognition or both.
- For example Alzheimer characterized by loss of cholinergic neurons, where as Parkinson is associated with a loss of dopaminergic neurons.

Parkinson

- Characterized by tremors, muscular rigidity, bradykinesia (slow in the voluntary movements). most patient are over 65 years old.

- The cause is unknown for most patients, rare to be secondary to viral encephalitis.

- Two main events happen in this devastating disease:

(1) Dopaminergic system appears to serve as a tonic

- Sustaining influence on the motor activity, rather than participating in specific movements.

Parkinson

Dopaminergic neuron makes thousand of synaptic contacts and modulates the activity of a large number of cells.

In Parkinson patients these nerves fire tonically rather than in response to specific muscle movements or sensory input.

(2) Degenerating of the neurons responsible to release dopamine.

Thus, the normal inhibitory influence of dopamine on the cholinergic neurons is significantly diminished, which result in the overproduction of ACT. This trigger abnormal signaling, resulting in loss of muscles movements

Our goal in therapy is to replace dopamine sources, *exactly like we would treat a thyroidectomy patient with thyroid hormone supplements*

Levodopa and Carbidopa

- Levodopa is a metabolic precursor of dopamine. And used to restore the dopamine level in brain.

- In the new patient, the therapeutic response is consistent,

- while in advanced cases, the number of neurons decrease and fewer cells are capable of taking up Levodopa and converted to dopamine for subsequent storage and release. Subsequently, motor control fluctuation developed. The phenomena that called "wearing off"

Also called: on and off phenomenon

- Relief provides by Levodopa is only systemic, and it lasts only while the drug is present in the body.

Wearing off effect

- Replacement therapy of Parkinson's (and neurodegenerative diseases in general) does not reverse or slow down neuronal degeneration, and, over time, the number of neurons available to take up Levodopa and convert it to Dopamine will drop regardless, and thus patients become gradually less responsive to treatment.
- How do we combat this? By increasing the dose or number of doses, or by supplementing with other drugs
- The first thing you do if your patient starts becoming less responsive to treatment after 3-4 years is you increase the frequency of doses.
- Try to avoid increasing the dose itself, as that amplifies the adverse effects.

Levodopa and Carbidopa

- Dopamine itself does not cross the blood brain barriers, but its immediate precursor Levodopa is readily transport into the CNS and converted to dopamine in the brain.

- Large doses is required, because much of the drug is decarboxylated to dopamine by dopamine decarboxylase in the peripheral, resulting in side affects.

- To solve that, Levodopa is combined with Carbidopa, which is a dopamine decarboxylase inhibitor that does not cross the blood brain barriers.

- Thus Carbidopa, diminishes the metabolism of the Levodopa in the peripheral tissues, and increase the availability of Levodopa to the CNS (lower the dose four to five folds).

Levodopa and Carbidopa

- In two third of patient the combination is reduce the severity of the disease in the first few years, then a decline in response is experienced during the third to fifth year of therapy (“wearing off”)

- Adverse effect:

  (1) dopamine stimulate the emetic centre and may cause Nausea, vomiting.

  (2) dopamine has an action on the heart, and may cause tachycardia and ventricular extrasystolic.

  Remember that dopamine receptors are important players in the CVS

  (3) over activity of dopamine in the receptors in the brain may produce Hallucination, confusion and abnormal involuntary movements may occur, dyskinesia.

More about the adverse effects

- Vomiting:
  - If your patient complains of unbearable nausea and vomiting, you can prescribe antidopaminergic antiemetics *(Recall GI)*.
  - However, you should pick a drug that will achieve antiemetic effects without crossing the BBB, as you want it to antagonize dopaminergic receptors that cause vomiting without interfering with your treatment.
  - The drug of choice is Domperidone (Motilium).

- Inhibition of prolactin.
- Interactions with schizophrenia (*lecture 4*).

Next step if the wearing off effects continues: you can supplement with Selegiline (a MAO inhibitor that inhibits dopamine metabolism).

Selegiline

- is a drug used for the treatment of early-stage Parkinson disease. **Its an add-on drug** that is effective early after its administration but will lose its potency later on.
- Has been found to increase the dopamine level in the brain by selective inhibitor of dopamine metabolism.
- Selegiline exhibits little therapeutic benefit when used independently, but Enhances the action of Levodopa, and when administered together, Selegiline substantially reduce the required dose of Levodopa.
- When given at high doses, place the patient at high risk of hypertension.

Adverse effect profile? Since it increases dopamine, its adverse effects are the same as before.

Since it is a MAO type B inhibitor (B = Brain.) it works on the central nervous system, and it is therefore fine to consume products that are otherwise contraindicated with type A MAO inhibitors.

Catechol-O-methyltransferase (COMT) inhibitors

Another option, another **add-on drug.**

- When peripheral dopamine decarboxylase activity is inhibited by Carbidopa, a significant concentration of 3- O-methyldopa is formed and compete with Levodopa for active transport into the CNS.

- Inhibition of COMT by **Entacapone** and **Tolcapone** leads to decrease the plasma concentration of 3-O- methyldopa, increase the central uptake of dopamine.

- Both of these agents have been demonstrated to reduce the symptoms of “wearing off” phenomena seen in patient on Levodopa-Carbidopa.

Catechol-O-methyltransferase (COMT) inhibitors

- Their adverse effects include diarrhea, postal hypotension, hallucination, and sleep disorders.
- Tolcapone produces hepatic necrosis and only used with patients in whom other mediators failed.

Dopamine receptors agonist

Specifically, D1 receptors, as those are generally affected in the disease.

- This group includes
  (1) two older agents, Bromocriptine and Pergolide.
  (2) two newer agents, Ropinirole and Pramipexole.

- These agents has longer duration of action than that of Levodopa, thus have been effective in patients exhibiting fluctuation in their response to Levodopa.

- Initial therapy with the newer agents is associated particularly with less risk of developing dyskinesias and motor fluctuations in compare to Levodopa.

- These agents are ineffective in patient who have shown no therapeutic response to Levodopa.

Bromocriptine and Pergolide

Doctor didn't explicitly say these two are not required, but instead said:
"قدام هدول بدناش اياهم"

- Are dopamine receptors agonists, Pergolide being more potent.
- Their side effects are similar to that of Levodopa, however the Hallucination, confusion are more common, while dyskinesia is less frequent.
- Series cardiac problems may develop, particularly with patients with myocardial infarction.
- In addition, both agents have the potential to cause pulmonary fibrosis

Ropinirole and Pramipexole

- They alleviate the deficit in both patients who have never treated with Levodopa and in patients with advanced Parkinson disease taking Levodopa.

- They may delay the need to employ Levodopa in advanced Parkinson, and may decrease the dose of Levodopa in advanced Parkinson.

- Pramipexole interact with Cimitidine, which inhibit the renal secretion of Pramipexole and result in a 40 % increase in the half life of Pramipexole.

- Their main side effect are nausea, hallucination, and hypotension.

Dopamine receptor agonists

- These are standalone drugs, not add-ons, and are given instead of Levodopa and Carbidopa. Their adverse effect profile is similar to previously discussed drugs, yet hallucinations are exacerbated and are more common in patients (affecting ~17% of the population) and are therefore considered second-line drugs given to patients who did not tolerate the adverse effect of our previously discussed regimen.
- Because they are not as selective as the body's naturally synthesized Dopamine, they lead to a state of heightened reward-seeking behavior and reduced impulse control, referred to as " a dirty old man" where the patient may become more compulsive (gambling, shopping, etc...) and hypersexual (inappropriate and vulgar).

Amantadine

Not very important and not widely used anymore

(NOT REQUIRED)

- It was accidentally discovered that antiviral drug Amantidine (effective in the treatment of influenza A, not B) has an antiparkinsonism action.
- It cause an increase in the release of dopamine, blocking cholinergic receptors, block some of the NDMA glutamate receptors.
- Adverse effect includes restlessness, agitation, hallucination.
- Amantadine is less officious than Levodopa and tolerance develops more readily, However, it has lower side effects.

Antimuscarinic agents

- Blockage of the cholinergic transmission and produce effects similar to rise of dopaminergic transmission

- Much less efficacies than Levodopa and play only an adjuvant role in antiparkinsonism therapy.

Atropine analogues

- **Benztropine** and **Biperidine** are similar, although individual patient response more favorably to one drug.

- Blocking of the cholinergic transmission produces effects similar to augmentation (rise) of dopaminergic transmission.

- These agents may cause mood change and produce dryness of the mouth and visual problems. Interfere with the gastrointestinal peristalsis. And are contraindicated in glaucoma.

These are also add-on drugs, used because they have a synergistic effect similar to increasing dopamine levels.

They cause blurry vision (hence contraindicated in glaucoma), urinary retention, constipation, and tachycardia (atropine is used in resuscitation)

Drugs used to treat Alzheimer disease

- Pharmacological intervention for Alzheimer disease is only palliative (calming) and provides modest short-term benefit.

- None of the current therapeutic agents alter the underlying neurodegenerative process.

- Current therapeutics are aimed at either

  (1) improving cholinergic transmission within the CNS

or

  (2) preventing the excitotoxicity actions of NMDA glutamate receptors in selected brain areas.

Apolipoprotein E and Alzheimer’s Disease

- **Apolipoprotein E (especially the ApoE ε4 isoform) is the strongest genetic risk factor for sporadic Alzheimer's disease because it alters lipid transport and protein clearance in the brain.** Normally, ApoE helps remove Amyloid beta from the extracellular space, supports synaptic repair, and maintains neuronal membranes. However, the ApoE ε4 variant has a different structure that reduces amyloid-β clearance, promotes its aggregation into plaques, increases neuroinflammation, and worsens neuronal repair mechanisms. This results in earlier and more extensive accumulation of amyloid plaques and downstream Tau protein pathology, accelerating neurodegeneration and increasing the risk and earlier onset of Alzheimer disease.

Acetylcholinesterase inhibitors

- Recall Neostigmine and physostigmine, used to wake patient after anesthesia and for atropine toxicity respectively. Physostigmine works both centrally and peripherally while Neostigmine works peripherally. They are not selective enough for the purposes of treatment, so **we use the drugs in the following slide**:

Acetylcholinesterase inhibitors

- Many studies have linked the progressive loss of cholinergic neuron and, presumably cholinergic transmission within the cortex, to the memory loss that hallmark (trademark) symptoms of Alzheimer disease.
- Inhibition of Acetylcholinesterase within CNS will improve cholinergic transmission,
- Examples on this group are **Donepezil**, and **Galantamine**.
- At best these agents provide a modest reduction in the rate of loss of cognitive functioning in Alzheimer disease.
- Common adverse effect include anorexia, muscles gramps, and diarrhea

Adverse effects include typical cholinergic effects and are mild, in general, because these drugs are relatively selective to the CNS.

NDMA receptors antagonist

- Over stimulation of glutamine receptors, particularly of the NMDA type, has been shown to result in excitotoxic effects on neurons, and is suggested as a mechanism for neurodegenerative processes.

- Antagonist of NDMA glutamine receptors are often neuroprotective, preventing the loss of neurons following ischemic and other injuries.

- **Memantine** is an example and has shown to prevent or slow the rate of memory loss in Alzheimer dementia, even in patient with moderate to sever cognitive losses.

- **Memantine** is well tolerated, with few dose related adverse effects, which include confusion and restlessness.

Dr. Malik says this one is not that important and that "بدكم تعرفوه اعرفوه".

PHARMACOLOGY QUIZ LECTURE 8

رسالة من الفريق العلمي

قال الله تعالى :

قُلْ إِنَّ صَلَاتِي وَنُسُكِي وَمَحْيَايَ وَمَمَاتِي لِلَّهِ رَبِّ الْعَالَمِينَ ﴿١٦٢﴾ لَا شَرِيكَ لَهُ ۖ وَبِذَٰلِكَ أُمِرْتُ وَأَنَا أَوَّلُ الْمُسْلِمِينَ ﴿١٦٣﴾

سورة الأنعام

أي قل -أيها الرسول- لهؤلاء المشركين: إن صلاتي, ونسكي, أي: ذبحي لله وحده, لا للأصنام, ولا للأموات, ولا للجن, ولا لغير ذلك مما تذبحونه لغير الله, وعلى غير اسمه كما تفعلون, وحياتي وموتي لله تعالى رب العالمين. لا شريك له في ألوهيته ولا في ربوبيته ولا في صفاته وأسمائه, وبذلك التوحيد الخالص أمرني ربي جل وعلا وأنا أول من أقر وانقاد لله من هذه الأمة.

(التفسير الميسر)

Scan the QR code or click it for FEEDBACK

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			