Clinical Pharmacology & Toxicology Pearl of the Week

~ MPTP (1-methyl-4-phenyl-1,2,5,5-tetrahydropyridine)~

Case:

- ✓ A 25-year-old man presents to the ED with EMS direct from prison.
- ✓ He was found unresponsive in his cell: GCS 3, normotensive, slight bradycardia, respiratory rate 10 and shallow, sats low 90s, pupils equal at 2mm – fixed.
- ✓ GCS remains ~6 post repeat doses naloxone, patient is noted to hold left upper extremity in flexion and this extremity is described as 'rigid' – there are no other significant neuromuscular findings.
- ✓ The EMS team passes on the following question from the prison nurse, **"There is a bad batch of dope going around; he's not the only one we've sent in like this. Could the drugs be tainted with MPTP?"**

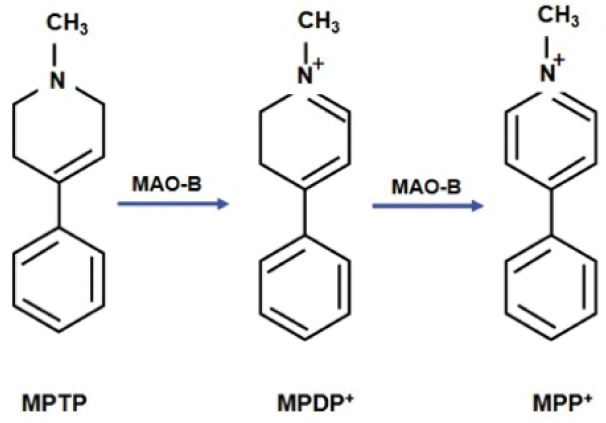
Background:

- ✓ MPTP was first identified amongst a group of recreational drug users in California in the 1980s but also appeared in the Vancouver drug scene during the same decade.
- ✓ Young patients were presenting unable to move or speak – appearing 'frozen' – with cogwheel rigidity that rapidly progressed over hours to days.
- ✓ The unifying historical feature was heroin use.
- ✓ These events in the United States overlapped with a period when drug legislation listed specific prohibited drugs, rather than a broader list of drugs with metabolites or drug classes. Narrow legislation encouraged rapid proliferation of underground drug manufacturing of molecules with just slightly deviated structure, to maintain the desired clinical effect, yet circumvent legislation.

- ✓ Mass spectrometry was used to identify a compound that was molecularly similar to meperidine; this novel compound was MPPP (1-methyl-4-phenyl-4-propionoxypiperidine), an opioid five times more potent than meperidine.

Biochemistry and Mechanism of Action:

- ✓ During the synthesis of MPPP, MPTP can be produced as a contaminant.
- ✓ MPTP does not have opioid effects, but it is lipid soluble and does structurally resemble dopamine and thus crosses the blood brain barrier where it enters astrocytes and undergoes metabolism by MAO-B enzymes to MPP+ (1-methyl-4-phenylpyridinium).
- ✓ MPP+ is taken up by dopamine releasing neurons, particularly dominant in the substantia nigra, and blocks aerobic metabolism at Complex I of the electron transport chain.
- ✓ Destruction of the substantia nigra, by free radicals and elevated intracellular calcium, effectively creates a state of irreversible drug-induced parkinsonism.
- ✓ Treatment options include levodopa, but also fetal neural tissue implants.
- ✓ MPTP is now used in primate models to replicate Parkinson's disease, to allow further research in pathophysiology and treatments.
- ✓ Recognition that MPP+ induces parkinsonism helped generate hypotheses for environmental causes of the condition, including herbicides such as paraquat.



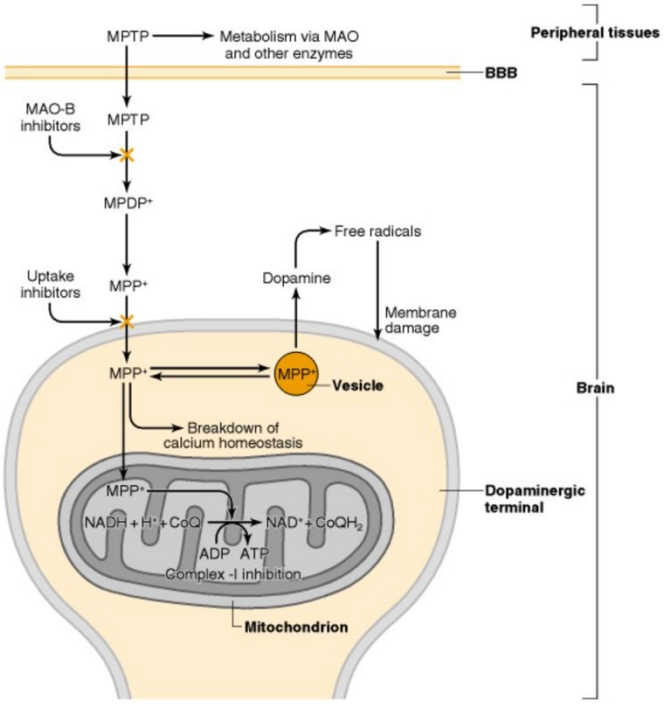


Figure 45-6

From: MPTP-Induced Parkinsonian Syndrome

Basic Neurochemistry: Molecular, Cellular and Medical Aspects. 6th edition.
Siegel GJ, Agranoff BW, Albers RW, et al., editors.
Philadelphia: Lippincott-Raven; 1999.

Case Resolution:

- ✓ The patient's clinical status and level of consciousness improved over ~48hrs, returning to baseline with no lingering neuromuscular abnormalities.
- ✓ His general urine tox panel was positive for: morphine, fentanyl, amphetamines, benzodiazepines, and cocaine.
- ✓ MPP+ was not a likely contributor to his presentation, or other similar cases at the time. As od April 2023, there has been no MPPP/MPTP/MPP+ detected in the current or recent Alberta illicit drug supply (recognizing limitations and delays in public health and law enforcement drug testing programs).
- ✓ The most likely culprit drug in this case was an opioid +/- benzodiazepine.

In general, for Drug Induced Movement Disorders:

- ✓ Consider broad differential of drug-induced movement disorders, including akathisia, tremor, serotonin syndrome, acute dystonic reaction, neuroleptic malignant syndrome, parkinsonism, and tardive dyskinesia.
- ✓ Consider broad range of culprit medications: dopamine receptor blockers, SSRIs/SNRIs, antiepileptics, lithium, TCAs, amiodarone, opioids, methylphenidate/amphetamines, calcium channel blockers, organophosphates, carbon monoxide, cyanide, methanol.
- ✓ Knowing the causative drug may not change management. Treat the symptoms of the patient in front of you!

References:

1) Duma SR, Fung VS. Drug-induced movement disorders. Aust Prescr. 2019 Apr;42(2):56-61. doi: 10.18773/austprescr.2019.014. Epub 2019 Apr 1. PMID: 31048939; PMCID: PMC6478951.
2) Kopin IJ. Features of the dopaminergic neurotoxin MPTP. Ann N Y Acad Sci. 1992 May 11;648:96-104. doi: 10.1111/j.1749-6632.1992.tb24527.x. PMID: 1637076.
3) Langston, JW. The case of the frozen addicts: how the solution of a medical mystery revolutionized the understanding of Parkinson's disease. 2014
4) Sian J, et al. MPTP-Induced parkinsonian syndrome. Basic Neurochemistry: Molecular, Cellular and Medical Aspects. 6th ed. Philadelphia: Lippincott-Raven; 1999.

The Clinical Pharmacology (CP) physician consultation service is available Mon-Fri, 8am-5pm. The on-call physician is listed in ROCA on the AHS Insite page. CP consultations are also available through Netcare e-referral and Specialist Link. You can also find us in the Alberta Referral Directory (ARD) by searching "Pharmacology" from the ARD home page. Click HERE for more details about the service.

The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414 (AB and NWT) or 1-866-454-1212 (SK). Information about our outpatient Medical Toxicology Clinic can be found in Alberta Referral Directory (ARD) by searching "Toxicology" from the ARD home page.

More CPT Pearls of the Week can be found HERE.

Created: May 3, 2023

Reviewed: March 11, 2025