Clinical Pharmacology & Toxicology Pearl of the Week

~Toxicologic Mimics of Brain Death~

Case:

- A 40-year-old male arrives to the ED after being found down by family for an unknown duration of time. He has a known history of depression, but no concerns noted by family of formal suicidality. He is on no prescription medications.
- On assessment, he is a GCS 3, with stable vital signs other than some respiratory depression (RR 8) and hypoxemia (SpO2 82%) – he is unresponsive to a total cumulative dose of 4 mg of naloxone.
- He is intubated and admitted to the ICU. Extensive workup including CT, MRI, LP do not reveal any acute explanatory pathology. EEG reveals no epileptiform discharges, however, does demonstrate global burst suppression.
- He remains GCS 3 off any sedation now 4 days later with clinical evidence brainstem dysfunction manifesting in a loss of corneal reflex and pupillary-light reflex. He demonstrates a very faint gag response; repeat neuroimaging remains completely normal.
- The patient's family is interested in potentially withdrawing care, as they are concerned he has brain death. However, the care team is concerned for potential toxicologic causes of brain death mimicry and are asking for advice on how long to monitor for recovery, or if specific testing could be conducted.

Background:

- Canadian guidelines exist to define brain death and death determination steps. *For full details, please refer to the referenced guideline by Shemie et al. (2023), as well as Lewis et al. (2023).* Important points surrounding this definition and its determination are as follows:
    - Brain death can result from cessation of blood circulation to the brain after circulatory arrest and/or from devastating brain injury; criteria include all the following:
        - Absence of consciousness shown by a lack of wakefulness and awareness in response to stimuli.
        - Absence of brainstem function as shown by complete cranial nerve testing.
        - Absence of the capacity to breathe shown by formal apnea testing.
    - Brain death assessment typically should be delayed 48 hours post ROSC. Additionally, the patient should be normothermic, and potential confounders of an accurate clinical assessment should be considered and excluded.
        - Potential confounders being intoxication, metabolic or other derangements contributing to altered mental status / neurologic function.
    - Brain death cannot be declared if there is <u>ANY</u> level of consciousness remaining and/or residual brainstem function, regardless of how diminished, or potential confounders remain.

- Brain death mimicry or a reversible brain death state is best defined as an unresponsive, intubated patient missing <u>SOME</u>, but <u>NOT ALL</u> brainstem reflexes, usually in the setting of confounders not yet addressed or excluded, such as intoxication (Murphy 2020).

- While many drugs may manifest as coma in overdose, few are known to cause loss of cranial nerve and brainstem reflexes; however, a recent narrative review identified 19 separate drugs (of 13 drug classes) reported to cause reversible brain death mimicry (Murphy 2020) (Table 1).

Drug / Toxin	***# of Reported Cases***	***Comments***
Snake Envenomation	13	• Duration: 2-4 days, with an average of 56.2 hours. • Prognosis: 46% of cases recovered to baseline; 15% with residual weakness – the remainder not reported. • All cases involving neurotoxic Elapidae, with one Viper suspected. • All cases occurred in India.
Baclofen	11	• Dose: Lowest dose to cause brainstem reflex loss = 450 mg; typically occurring >1g. • Duration: Up to 7 days, with a mean of 30 hours. • Prognosis: 55% of cases recovered to baseline; remainder unspecified.
Tricyclic Antidepressants	8	• Dose: Most seen with Amitriptyline 500-9000mg. • Duration: 2-72 hours, with a mean of 29 hours. • Prognosis: 62.5% of cases reported to recover to baseline; remainder unspecified. • Other TCAs reported include Doxepin and Amoxapine.
Bupropion	7	• Dose: Reported doses of 19.5-21g. • Duration: 24-48 hours, with a mean of 26.4 hours. • Prognosis: 6 surviving patients demonstrated complete recovery. • All cases reported exhibited seizures and/or status epilepticus, with three experiencing a cardiac arrest.
Alcohols (including Toxic Alcohols)	4	• Dose: Not reported. • Duration: Longest duration with ethylene glycol of up to 2 months in 2 separate cases (no EG levels reported); shortest duration of 40 minutes with ethanol. • Prognosis: Variable, but in some cases full recovery despite prolonged coma and brain death mimicry.
Valproic Acid	2	• Dose: Not reported. • Duration: Not reported; potentially up to 15 days. • Prognosis: Both reported cases recovered to baseline. • Somewhat confounded by concurrent hyperammonemia and cerebral edema secondary to valproic acid.
Pentobarbital (Barbiturates)	2	• Dose: 20g reported in 1 case; unclear amount in the other reported case. • Duration: 5-8 days • Prognosis: Both reported cases recovered to baseline.

Table adapted from data in Murphy et al. (2020)

- Single case reports exist for the following (Murphy 2021):
    - Carbamazepine
    - Bretylium
    - Lidocaine
    - Phorate
    - Thiacloprid
    - Magnesium
    - Succinylcholine
    - Tetrodotoxin
    - Zolpidem

- In addition to the above, novel psychoactive substances such as designer benzodiazepines have been implicated in brain death mimicry (Runnstrom 2020), as well as other illicit drugs such as GHB and GBL (GHB precursor) (Spungen 2023).

Challenges & Guidance:

- The strategy put forward by the American Academy of Neurology states that to sufficiently rule out intoxication as a confounder to a determination of brain death, the following should be met:
    - Exclude drug ingestion by history.
    - Ensure blood and urine drug screens are negative (if clinically indicated).
    - Ensure drug serum levels are therapeutic or subtherapeutic and not considered to contribute to the neurologic state.
    - Wait at least 5 half-lives of the drug in question.

- Issues and challenges with using the above framework are numerous:
    - Drug identification may not be possible by history.
        - Ex. The contents of street drugs are highly variable and not standardized, therefore historical information may be inaccurate.
    - Urine drug screens have limitations.
        - Urine immunoassay testing suffers from cross-reactivity and high false positive and negative rates, and there are also important caveats to the more sensitive and specific urine generalized toxicology panel (GTP).
    - The urine GTP (conducted using mass spectrometry) only tests for a finite number of predefined substances, potentially missing novel agents, or agents in question.
    - Presence of a drug or its metabolites in the urine cannot be used to assess the degree of intoxication, or temporal relationship to time of ingestion.
    - Serum drug level measurement is not available for all substances on a timely basis.
    - Available serum drug levels need to be interpreted with caution - a normal or negative serum level does not always equate to absence of clinical effect or toxicity.
        - The distribution of a drug into tissues (dependent on its volume of distribution, time since last dose, and other factors) makes the relationship of serum drug concentration to clinical picture difficult.
    - Half-lives are based on therapeutic use of a drug and cannot be fully relied on when a drug is taken in overdose.
        - This is due to significant changes in kinetics (absorption, distribution, metabolism, and elimination) that are not predictable.

- Taking the above into account, the following are suggestions to help identify and manage cases of potential brain death mimicry (Murphy 2020; Neavyn 2017):
    - The presence of normal neuroimaging in a comatose patient with loss of brainstem reflexes should prompt evaluation and consideration of potential brain death mimicry.
    - Identify potential for drug or substance exposure by history and targeted testing, where available.
        - Consider the potential limits to serum and urine testing as outlined above.
    - Where a suspect drug is identified, a minimum of 5 drug half-lives should lapse to ensure significant clearance – however, there is a low threshold to extend beyond this in suspect overdose settings, especially if there are any signs of improvement.
        - Where possible, case-based data can be used to provide further guidance on minimum monitoring times.
    - Consider the use of advanced ancillary testing to further support brain death mimicry or true brain death:
        - Assessment of cerebral blood flow (i.e., cerebral angiography, transcranial doppler, CT perfusion etc.)
            - It is unlikely that a drug would be the sole cause of cessation of cerebral blood flow, and this would support a non-reversible cause of brain death, regardless of intoxication.
        - EEG monitoring
            - EEG monitoring can help determine the presence of key differential considerations, such as non-convulsive status epilepticus as a confounder, or may point towards toxicologic changes (i.e., global burst suppression).
            - However, there are cases of brain death mimicry in which EEG days after presentation demonstrated no electrical activity (pentobarbital), only to eventually recover (Murphy 2020).
        - Consultation with Medical Toxicology can assist in decision making and can provide information on other potentially relevant testing on a case-by-case basis.

Additional notes:

- Paralytic xenobiotics or toxins are often far less reported as causes of brain death mimicry either because they are usually very short acting and hard to acquire outside of the medical environment (succinylcholine for example) or are unlikely to confound a brain death examination as an absence of deep tendon reflexes should alert a clinician to the possibility of a paralytic agent on board.

- Paralytic agents such as botulism, tetanus, strychnine, hemlock, nicotine / nicotinic alkaloids would be expected to have quite unique presentations with additional clues pointing away from confounding a brain death.

- There are case reports linking botulism to mistaken brain death. However, it isn't reported as a brain death mimic as often as other agents for the following reasons:
    - It is a rare disease
    - Pattern/length of time to progression and symptoms / history
        - GI botulism = begins with GI symptoms, and neuro symptoms follow along with anticholinergic features (e.g. dry mouth)
        - Wound botulism = the presence of a wound or history of IVDU, then focal symptoms progressing to widespread symptoms

Case Resolution:

- Given normal neuroimaging, concern for potential toxicologic confounders, as well diminished but not absent brainstem function, PADIS recommended further monitoring and history gathering.
- It is eventually discovered that the patient had ordered a substance online, in which was touted as being pentobarbital. In liaison with clinical biochemistry, specialized GC-MS analysis identified the presence of pentobarbital in patient serum samples.
- By day 8, the patient was extubated after demonstrating progressive return to baseline neurologic function and confirmed his ingestion as a means of self-harm.

References / Resources

1. Murphy L et al. Toxicologic confounders of brain death determination: a narrative review. *Neurocrit Care*. 2020;34(3):1072-89.
2. Shemie SD et al. A brain-based definition of death and criteria for its determination after arrest of circulation or neurologic function in Canada: a 2023 clinical practice guideline. *Can J Anesth*. 2023;70:483-557.
3. Runnstrom M et al. Overdose from designer benzodiazepine Diclazepam. *QJM*. 2020:122-4.
4. Lewis A et al. The 2023 AAN/AAP/CNS/SCCM pediatric and adult brain death/death by neurologic criteria consensus practice guideline. *Neurology*. 2023;13:e200189.
5. Spungen H & Spyres MB. The ToxIC NOSE (Novel Opioid and Stimulant Exposure): Report #11 from ToxIC's rapid response program for emerging drugs. *ACMT*.
6. Neavyn MJ et al. ACTM position statement: Determining brain death in adults after drug overdose. *J Med Toxicol*. 2017;13:271-3.

The Clinical Pharmacology (CP) physician consultation service is available Mon-Fri, 8am-5pm, excluding stat holidays. The on-call physician is listed in ROCA on the AHS Insite page. CP consultations are also available through Netcare e-referral, Specialist Link, and RAAPID. 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 April 2, 2025

Reviewed April 16, 2025