Ethical Dilemmas
Brain Death and Overdose

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Disclosures

• I have no financial or personal interests to disclose
Objectives

1) Identify overdoses and toxins that have the potential to mimic brain death.
2) Recognize current guidelines for the determination of brain death.
3) Indicate any additional guidelines or testing that may be needed to determine brain death in the poisoned patient.
4) Establish what our (poison specialists/toxicologists) possible role is with regards to the overdose “brain dead” patient.

Case

- A 40 yr old female presents to the ED after a baclofen overdose
  - hypothermic and comatose
  - hemodynamically stable
  - dilated un-reactive pupils
  - absent corneal and oculocephalic reflexes
  - no response to external stimuli
• HD 1,2: warmed, brief period hypotension, posturing v. seizure like activity

• HD 3: EEG: no epileptiform discharges; burst suppression pattern on flat background, “poor prognosis”

![EEG waveform]

• HD 4: neurology consultation
  – no brainstem reflexes
  – flaccid extremities, no response to stimuli
  – apnea test: spontaneous breath vs. clonic-jerk at > 5 minutes, pCO₂ increases 34 to 64 mm Hg
  – neurology consultant: “The patient does not fulfill the clinical criteria for brain death”
• HD 4, cont.
  – family meeting by medical team, prognosis felt grim
  • family agrees to organ procurement and withdrawal support
• HD 5
  – plans in progress for organ harvest
  – While in surgical suite spontaneous eye opening noted

St. Joe’s “dead” patient awoke as doctors were about to remove organs

The state Board of Regents, the agency overseeing organ harvests in New York, has launched an investigation into the case of a woman who was declared brain dead and had her organs removed by a team of doctors. The woman, 27-year-old Jennifer Kaczorek, was declared dead by a doctor at St. Joseph’s Hospital in Syracuse on Feb. 12, 2015. The declaration came after Kaczorek suffered a head injury in an accident. After being declared dead, her organs were removed and donated to other patients.

But on Feb. 14, Kaczorek opened her eyes and began to speak. The hospital was shocked and the state’s Board of Regents was notified.

The board’s investigation found that Kaczorek was still alive when her organs were removed and that the hospital failed to follow proper medical protocols in declaring her dead.

The board has fined the hospital $28,000 and ordered it to take steps to prevent such incidents in the future.

The case has raised questions about the accuracy of medical determinations of death, particularly in cases where organs are to be donated.
Death?
A Definition of Irreversible Coma:
Report of the Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death

JAMA. 1968;205(6):337-340

“unresponsiveness and a lack of receptivity, the absence of movement and breathing, the absence of brain stem reflexes, and a coma whose cause has been identified”
Uniform Determination of Death Act

An individual who has sustained either:

1. irreversible cessation of circulatory and respiratory functions, or

2. irreversible cessation of all functions of the entire brain, including the brainstem, is dead

Evidence-based guideline update: Determining brain death in adults
Report of the Quality Standards Subcommittee of the American Academy of Neurology

**ABSTRACT**

Objective: To provide an update of the 1995 American Academy of Neurology guideline with regard to the following questions: Are there patients who fulfill the clinical criteria of brain death who recover neurologic function? What is an adequate observation period to ensure that cessation of neurologic function is permanent? Are complex motor movements that falsely suggest retained brain function sometimes observed in brain death? What is the comparative safety of techniques for determining apnea? Are there new ancillary tests that accurately identify patients with brain death?

Methods: A systematic literature search was conducted and included a review of MEDLINE and EMBASE from January 1988 to May 2009. Studies were limited to adults (aged 18 years and older).

Results and recommendations: In adults, there are no published reports of recovery of neurologic function after a diagnosis of brain death using the criteria reviewed in the 1995 American Academy of Neurology practice parameter. Complex spontaneous motor movements and false-positive triggering of the ventilator may occur in patients who are brain dead. There is insufficient evidence to determine the minimally acceptable observation period to ensure that neurologic function has ceased irreversibly. Apneic oxygenation diffusion to determine apnea is safe, but there is insufficient evidence to determine the comparative safety of techniques used for apnea testing. There is insufficient evidence to determine if newer ancillary tests accurately confirm the cessation of function of the entire brain. *Neurology* 2010;74:1911-1918
• Three necessary clinical findings (AAN):
  
  – coma *(with known cause)*
  
  – absence of brainstem reflexes
  
  – apnea

**Brainstem Reflexes**

– Absence of brainstem reflexes

• pupils, ocular movements, corneal reflex, facial muscle movement, pharyngeal and tracheal reflexes
Apnea Test

- the absence of respiratory effort with increasing pCO₂
  - pre-oxygenate, disconnect from ventilator
  - if no respiratory effort over 8-10 minutes and pCO₂ > 60 mm Hg (or > 20 mm Hg over baseline) = test positive
  - many inherent difficulties, underlying lung disease, abort if hypoxia (pO₂ remains > 90 mm Hg), hypotension
  - 10-20% patients either unable to perform or to complete

COMA

- Definition:
  - Coma is a state of unconsciousness in which a person cannot be awakened fails to respond normally to noxious stimuli; lacks a normal wake-sleep cycle; and does not initiate voluntary actions
COMA

• Clinical evaluation
  – establish irreversible and proximate cause of coma
    • exclude presence of CNS-depressant drug effect, absence neuromuscular blocking drugs
    • correct electrolyte, acid/base disturbances, endocrine disturbances
  – correct hypothermia (defined T > 36º C)

COMA

• Drug Overdose (AAN)
  – Drug Levels
  – Drug Screening and History
  – 5 half-life “rule”
Coma
Consideration #1 – Drug Levels

• **Drug Levels – Pros**
  – Readily Available
    • lithium
    • digoxin
    • phenobarbital
    • phenytoin
    • valproic acid
    • ethanol
    • ASA/APAP

  – Sometimes Available
    • e.g./methanol

• **Drug Levels – Cons**
  – many drugs cannot be measured in a clinically relevant timeframe.
  – drug concentrations does not always equal clinical effect
    • Distribution issues
      – Ex. lithium
## Coma Consideration #2 – Drug Screening/History

### Cons
- **Specific** drug responsible for intoxication may not be identified by history or drug screening.
- **Drug Screening not comprehensive** - Neg. drug screen does not exclude intoxication or overdose.
- **Limited Specificity** - Immunoassay - a “negative” urine drug screen should not be used to exclude drug intoxication.

### Pros
- a “positive” urine drug screen by itself is not confirmatory, however, drug intoxication can be supported with:
  - appropriate history
  - appropriate clinical presentation
  - appropriate physical examination
Coma
Consideration #3 – 5 Half-Life rule

- Pros
  - Easy to conceptualize
  - May be relevant in some overdoses
Coma
5 – half lives

• Cons
  – Pharmacokinetics data based on therapeutic dosing
    • Toxicokinetics may be very different
  – Prolonged half-lives in overdose
    • Delays in gastric emptying and gut hypomotility
      – fasting status
      – overdose itself
      – opioids or anticholinergic drugs
      – controlled-release drugs
      – hypoperfusion of the gut
    • Enterohepatic circulation
    • Multi-Compartment movements

Half Life
Baclofen

![Graph showing half life of Baclofen with therapeutic and OD levels.](attachment:image.png)
Drugs that Mimic Brain Death

- Based on Case Reports
  - baclofen
  - snake bites
  - valproic acid
  - amitriptyline
  - mixed diazepam and ethylene glycol
  - bupropion
  - phorate

- Maybe consider
  - carisoprodol
  - barbiturates
  - benzodiazepines
  - any CNS depressant that can cause coma

Three necessary clinical findings (AAN):

- coma (with known cause)
- absence of brainstem reflexes
- apnea

WHAT ABOUT ANCILLARY TESTS?
Confirmatory/Ancillary

- Confirmatory tests are optional in adults
  - Cerebral perfusion
    - conventional angiography
    - transcranial doppler
    - radionucleotide (HMPAO) brain scan
    - CT angiography, MRI/MRA
  - Brain activity
    - EEG
    - Brainstem somatosensory evoked potentials

Neurology 2010;74:1911-1918

Angiography
Nuclear Brain Scan

PET Scan

<table>
<thead>
<tr>
<th>Vegetative state</th>
<th>Minimally conscious state</th>
<th>Fully conscious</th>
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Objectives
#1. Identify overdoses and toxins that have the potential to mimic brain death.

- baclofen
- snake bites
- valproic acid
- amitriptyline
- diazepam
- ethylene glycol
- bupropion
- phorate
- carisoprodol
- barbiturates
- benzodiazepines
- any CNS depressant that can cause coma

Objectives
#2. Recognize current guidelines for the determination of brain death.

- Three necessary clinical findings (AAN):
  - coma (with known cause)
  - absence of brainstem reflexes
  - apnea
**Objectives**

#3. Indicate any additional guidelines or testing that may be needed to determine brain death in the poisoned patient.

- **Ancillary Tests**
  - Cerebral Perfusion Scanning
  - Brain Activity tests
    - EEG

  *Confirmatory tests are not mandatory in adults.
  *Confirmatory tests are usually mandatory in pediatrics.

**Objectives**

#4. Establish what our (poison specialists/toxicologists) possible role is with regards to the overdose “brain dead” patient

- identification of drugs or toxins should be done by careful history and targeted testing.
- five drug half-lives should be considered an absolute minimum period to ensure clearance.
- a longer period may be appropriate when there is reasonable chance of delayed drug absorption or elimination.
- in cases where brain death is considered but intoxication is unclear, a medical toxicologist or clinical toxicologist can be consulted.
References

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