ACMT Position Statement: Determining Brain Death in Adults After Drug Overdose

Mark J. Neavyn¹ · Andrew Stolbach² · David M. Greer³ · Lewis S. Nelson⁴ ·
Silas W. Smith⁵ · Jeffrey Brent⁶ · Laura M. Tormoehlen⁷ · On behalf of the American
College of Medical Toxicology

Received: 9 January 2017 / Revised: 31 January 2017 / Accepted: 2 February 2017 / Published online: 2 March 2017
© American College of Medical Toxicology 2017

Keywords Brain death · Toxicology · Poisoning · Overdose

The position of the American College of Medical Toxicology, endorsed by the American Academy of Clinical Toxicology and the Society of Critical Care Medicine, is as follows:

We agree with the American Academy of Neurology (AAN) recommendation that the clinical determination of brain death should only be made in the absence of drug intoxication or poisoning. However, a drug screen and clearance calculation using five drug half-lives ($T_{1/2}$) are not sufficient to exclude intoxication in all cases. Drug screens are not sufficiently comprehensive to detect all drugs that may cause mental status depression. Even when the specific drugs are quantitatively identified, the use of kinetic data to determine

clinical effects is limited because drugs often have prolonged half-lives in overdose. For certain drugs and toxins, the duration of effect may extend beyond their detected presence in the vascular space. We recommend identification of drugs or toxins by careful history and targeted testing. An observation period of longer than five half-lives is appropriate when there is a possibility of an extremely large drug overdose, delayed drug absorption, delayed elimination, or interaction with another agent. In cases where brain death is considered but intoxication is unclear, consultation with a medical toxicologist or clinical toxicologist is recommended to guide decision-making regarding the timing or appropriateness of clinical testing, as clinical brain death determination cannot take place until intoxication is excluded.

While individual practitioners may differ, these are the positions of the ACMT, AACT, and SCCM at the time written, after a review of the issue and scientific literature.

The American Academy of Neurology (AAN) offers guidance for the diagnosis of brain death. Brain death is diagnosed clinically when an irreversible and proximate cause of brain injury is identified and no brain function is present upon clinical assessment [1, 2]. A prerequisite of the practice parameters for clinical testing is the absence of “drug intoxication or poisoning.” The only evidence available regarding brain death determination in the setting of intoxication derives from case reports. To determine the extent to which inaccurate brain death determination by clinical testing may occur in this setting, we conducted a review of the literature in MEDLINE and SCOPUS using the search terms “brain death mimic” and “brain death drug overdose” for the dates January 1, 1960 to June 10, 2015. A total of 1394 titles were reviewed for relevance to the topic, and only ten case reports of brain death mimicry were found (three baclofen [3, 4], two snake bites [5, 6], and one each of valproic acid [7], amitriptyline [8], mixed

The intent of this position statement is to reduce the likelihood of erroneous declaration of brain death in the setting of drug- or toxin-induced coma.

✉ Laura M. Tormoehlen
info@acmt.net

¹ University of Massachusetts Medical School, Worcester, MA, USA

² Johns Hopkins University, Baltimore, MD, USA

³ Department of Neurology, Yale University School of Medicine, New Haven, CT, USA

⁴ Department of Emergency Medicine, Division of Medical Toxicology, Rutgers New Jersey Medical School, Newark, NJ, USA

⁵ Department of Emergency Medicine, New York University School of Medicine, New York, NY, USA

⁶ University of Colorado School of Medicine, Aurora, CO, USA

⁷ Departments of Neurology and Emergency Medicine, Indiana University School of Medicine, Indianapolis, IN, USA

diazepam + ethylene glycol [9], bupropion [10], and phorate [11], an organic phosphorous compound).

“Evidenced-Based Guideline Update: Determining Brain Death in Adults” suggests that the clinician should exclude the presence of a central nervous system (CNS)-depressant drug effect by “history, drug screen, and calculation of clearance using five times the drug’s half-life.” [2] However, there may be limitations to this approach. The specific drug responsible for intoxication may not be identified by history or drug screening. Drug screening in the clinical setting is not comprehensive, so a negative drug screen does not exclude intoxication. Routine urine toxicologic immunoassays have limited sensitivity, even for common drugs, and a “negative” urine drug screen should not be used to exclude drug intoxication, and a “positive” urine drug screen cannot be used to assess the extent or degree of intoxication. For example, a typical opiate screen does not reliably identify oxycodone and hydrocodone and does not identify synthetic opioids such as fentanyl or buprenorphine, and a typical benzodiazepine screen does not reliably identify clonazepam. In contrast, a “positive” urine drug screen by itself is not confirmatory, but in the setting of an appropriate history, clinical presentation and physical examination can support intoxication.

Although most hospital laboratories can readily measure serum concentrations of some common drugs in overdose, including lithium, digoxin, phenobarbital, phenytoin, and valproic acid, there are many drugs that cannot be measured in a clinically relevant time frame. When drug concentrations are available, the distribution of the drug into tissues may complicate the relationship between concentration and clinical effect.

In cases in which drug concentrations are not available but a specific drug is suspected, experts recommend waiting five half-lives prior to clinical determination of brain death [2]. This figure is likely derived from the mathematical observation that 0.5^5 (50% elimination, five times) equals 0.03125, suggesting that only 3% of a drug remains following five half-lives. However, this approach may not be appropriate in every case. If a patient was exposed to an exceedingly large quantity of drug or toxin, 3% of the original dose could potentially still have clinical effects. In addition, the pharmacokinetics of many drugs will be altered in patients with organ failure [12, 13]. Furthermore, the pharmacokinetics of absorption and elimination of a drug in large dose may be different than published pharmacokinetic data suggest, which are typically obtained following therapeutic dosing, generally in healthy subjects without co-exposures [14].

The reasons for prolonged half-lives in overdose are numerous. Delays in gastric emptying and gut hypomotility may result from fasting status, from overdose itself, or from co-ingestion of opioids or anticholinergic drugs, and controlled-

release drugs have a prolonged absorption phase [15, 16]. Hypoperfusion of the gastrointestinal tract, secondary to hypotension and/or splanchnic vasoconstriction, can slow absorption [17]. Hypothermia may slow drug metabolism [18]. Enterohepatic recirculation may play a role in elimination of certain drugs. Mechanisms of metabolism may be saturated in overdose [14]. As an example of prolonged half-life in overdose, many references indicate the half-life of baclofen is approximately 2–4 h, but in overdose, the duration of effect far exceeds the recommended five half-life calculation [3]. Reported cases of coma mimicking brain death secondary to baclofen overdose have described a duration of coma of up to 7 days [3, 4]. Furthermore, pharmacokinetic elimination (i.e., “normal” or negative serum concentration) does not equate to pharmacodynamic duration of effect (i.e., drug remaining at the target organ receptor). Finally, published pharmacokinetic data may not account for pharmacodynamic or pharmacokinetic interactions [19].

Ancillary testing to assess cerebral blood flow, including cerebral angiography, transcranial Doppler, and single photon emission computed tomography, has been used to assist in the determination of death when the examination is felt to be potentially unreliable [2]. No publication was found to suggest that a drug or toxin could be the sole cause of cessation of cerebral blood flow and it is unlikely that such a drug effect exists; however, no study has been performed to answer this question.

The requirement to identify a proximate and irreversible cause of brain injury should prevent clinical brain death determination in overdose patients [4]. Therefore, we recommend identification of drugs or toxins by careful history and targeted testing. Five drug half-lives should be considered an absolute minimum period to ensure clearance. A longer period is necessary when there is a possibility of an extremely large drug or toxin exposure, likelihood for delayed drug absorption or elimination (relevant organ failure), pharmacokinetic or pharmacodynamic interactions, saturable elimination kinetics, or interactions with another agent. In cases where brain death is considered but intoxication is unclear, a medical toxicologist or clinical toxicologist can be consulted to guide decision-making regarding clinical testing, as clinical brain death determination cannot begin until intoxication is excluded. In the absence of an on-site toxicologist, one can be consulted via a local poison center at 1-800-222-1222.

Compliance with Ethical Standards

Source of Funding for the Project None.

Conflicts of Interest None.

References

- Practice parameters for determining brain death in adults (summary statement). The quality standards subcommittee of the American Academy of Neurology. *Neurology*. 1995;45(5):1012–1014.
- Wijdicks EF, Varelas PN, Gronseth GS, Greer DM. American Academy of N. Evidence-based guideline update: determining brain death in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2010;74(23):1911–8.
- Ostermann ME, Young B, Sibbald WJ, Nicolle MW. Coma mimicking brain death following baclofen overdose. *Intensive Care Med*. 2000;26(8):1144–6.
- Sullivan R, Hodgman MJ, Kao L, Tormoehlen LM. Baclofen overdose mimicking brain death. *Clin Toxicol*. 2012;50(2):141–4.
- John J, Gane BD, Plakkal N, Aghoram R, Sampath S. Snake bite mimicking brain death. *Cases J*. 2008;1(1):16.
- Sodhi R, Khanduri S, Nandha H, Bhasin D, Mandal AK. Brain death—think twice before labeling a patient. *Am J Emerg Med*. 2012;30(7):1321. e1321-1322
- Auinger K, Muller V, Rudiger A, Maggiorini M. Valproic acid intoxication imitating brain death. *Am J Emerg Med*. 2009;27(9):1177. e1175-1176
- Yang KL, Dantzer DR. Reversible brain death. A manifestation of amitriptyline overdose. *Chest*. 1991;99(4):1037–8.
- Marik PE, Varon J. Prolonged and profound therapeutic hypothermia for the treatment of “brain death” after a suicidal intoxication. Challenging conventional wisdoms. *Am J Emerg Med*. 2010;28(2):258. e251-254
- Mundi JP, Betancourt J, Ezziddin O, Tremayne B, Majic T, Mosenifar Z. Dilated and unreactive pupils and burst-suppression on electroencephalography due to bupropion overdose. *J Intensive Care Medicine*. 2012;27(6):384–8.
- Peter JV, Prabhakar AT, Pichamuthu K. In-laws, insecticide—and a mimic of brain death. *Lancet*. 2008;371(9612):622.
- Philips BJ, Lane K, Dixon J, MacPhee I. The effects of acute renal failure on drug metabolism. *Expert Opin Drug Metab Toxicol*. 2014;10(1):11–23.
- Verbeeck RK. Pharmacokinetics and dosage adjustments in patients with hepatic dysfunction. *Eur J Clin Pharmacol*. 2008;64(12):1147–61.
- Sue YJ, Shannon M. Pharmacokinetics of drugs in overdose. *Clin Pharmacokinet*. 1992;23(2):93–105.
- Adams BK, Mann MD, Aboo A, Isaacs S, Evans A. Prolonged gastric emptying half-time and gastric hypomotility after drug overdose. *Am J Emerg Med*. 2004;22:548–54. doi:10.1016/j.ajem.2004.08.017.
- Buckley NA, Dawson AH, Reith DA. Controlled release drugs in overdose. Clinical considerations Drug Safety. 1995;12(1):73–84.
- Howland MA. Pharmacokinetic and toxicokinetic principles. In: Hoffman RS, et al., editors. Goldfrank’s toxicologic emergencies. 10th edition. New York: McGraw-Hill; 2015. p. 110–23.
- van den Broek MP, Groenendaal F, Egberts AC, Rademaker CM. Effects of hypothermia on pharmacokinetics and pharmacodynamics: a systematic review of preclinical and clinical studies. *Clin Pharmacokinet*. 2010;49(5):277–94.
- Jann M, Kennedy WK, Lopez G. Benzodiazepines: a major component in unintentional prescription drug overdoses with opioid analgesics. *J Pharm Pract*. 2014;27(1):5–16.