



Toxin-Induced Seizures: Life-Threatening Forms of Withdrawal

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A 40 year old male presents to the trauma unit at Cook County Hospital after jumping from the 4th story of a burning hotel. There are obvious bilateral fracture/dislocations of his ankles, and he complains of back pain.

T 99 P 110 RR 24 BP 110/60

Alert, in moderate distress secondary to pain

CT head, chest, abdomen/pelvis negative

L-S L4 compression fracture

+ bilateral fracture dislocations of ankles

Over the next 24 hours the patient becomes increasingly anxious and agitated, noted to be diaphoretic.

HR 130 BP 160/90 RR 24 T 101

HEENT: PERRL at 6 mm

Ht: RRR S1S2 tachycardic

Neuro: Diffuse tremors noted bilateral UE's, followed by brief tonic clonic seizure.

Key Clinical Questions

What is your differential diagnosis for toxin-induced withdrawal?

What is the mechanism of action of withdrawal syndromes?

What is the timing and severity of seizures secondary to alcohol withdrawal?

In what scenarios should you suspect withdrawal from alcohol, Benzodiazepines, GHB, and Baclofen?

Key Learning Points

- Beware of the potential for Flumazenil to induce seizures in a benzodiazepine-dependent patient.
- Seizures in alcohol withdrawal usually begin six to eight hours after last consumption of alcohol, and tend to be self-limited.
- The mortality of delirium tremors has significantly dropped because of improvements in nursing care, and from the aggressive use of sedative hypnotics.
- GHB withdrawal can present very similarly to alcohol and sedative hypnotic withdrawal.
- Beware of Baclofen withdrawal in patients chronically on pumps.

Background, Risk Factors and Epidemiology

Ethanol use is pervasive in our society. With chronic alcoholism individuals are at high risk for the development of withdrawal should they not consume at a normal rate. Similarly, for patients on sedative hypnotic agents (Benzodiazepines, barbiturates, etc) they are also at risk for a similar withdrawal syndrome should they stop their medications. Often alcoholics stop drinking because they become ill, and cannot continue drinking. Other times they make an attempt to stop which gets them in trouble. Opiate withdrawal should be distinguished from other forms of withdrawal in that it is rarely a life-threatening event.

Definition

All human action is essentially disinhibition. Smooth movement requires a relaxation of inhibitory pathways. An individual becomes adapted to a drug or toxin over time. This means that the person makes physiological adaptations to accommodate the increased substance in the system. Withdrawal occurs when a drug or toxin is removed and adaptive changes persist producing dysfunction. This requires decreasing concentrations of the substance in the system. Withdrawal should be distinguished from tolerance in that tolerance is a blunted response to a drug despite increasing concentrations.

Drugs act as inhibitors at specific sites. Benzodiazepines work on GABA_A receptors, Opioids act on the opiate receptors, and Clonidine acts on the alpha 2 receptor.

Benzodiazepine Withdrawal

Ethanol is perhaps the classic form of withdrawal, and other forms of life-threatening withdrawal can be understood in that context. Benzodiazepine withdrawal clinically is very similar to ethanol and barbiturate withdrawal. The onset of Benzodiazepine withdrawal may be delayed because many agents have long half-lives of elimination, and active metabolites that will be in the system for days. Additionally, resolution may also take up to ten days.

The disinhibition syndrome is manifested by agitation, tachycardia, hypertension, fever or hyperthermia, and seizures.

Benzodiazepine Withdrawal Emergency Department Care

The treatment of Benzodiazepine withdrawal is similar to ethanol withdrawal. One should treat with Benzodiazepines as first line agents (Diazepam or Lorazepam). For a second line agent one can use barbiturates. A good rule of thumb of equivalence between Diazepam and Phenobarbital is that 10 mg of Diazepam is about equivalent to 30 mg of Phenobarbital.

Flumazenil, the Benzodiazepine antagonist should be avoided when managing Benzodiazepine overdose, particularly for - Benzodiazepine dependent patients. Spivey documented three cases of seizures after the use of Flumazenil when used to reverse Benzodiazepine overdose. If one was to find oneself in this predicament, treatment

options include high dose Benzodiazepines, Phenobarbital, or Pentobarbital. The duration of action of Flumazenil is between one to two hours, therefore one must be vigilant to observe beyond two hours to assess the patients return to baseline.

Ethanol Withdrawal

Ethanol could be considered the ideal model to base one's understanding of the life-threatening withdrawal syndrome. Ethanol works by increasing inhibitory effects in the brain. The adaptive modulation with chronic ethanol consumptions revolves around the inhibitory effect at GABA_A, and the excitatory effect through NMDA. GABA_A is a Cl channel receptor. Some examples of GABA agonists are ethanol, Etomidate and Propafol. In withdrawal from ethanol there will also be a classic disinhibition syndrome. The patient will lose inhibitory control, hence having excess stimulation and release of glutamate, NMDA, Norepinephrine and serotonin.

Ethanol Withdrawal ED Presentation

Victor and Adams in 1953 wrote a classical description of the effects of ethanol on the neurological system. In addition they outlined a description of delirium tremens that is still quite applicable today. This is an article worth reading as a classic. The four phases of withdrawal leading to DTs that Victor and Adams describe include: tremulousness, seizures, hallucinations, and delirium. Seizures usually begin six to eight hours after the last consumption of ethanol. The seizure activity may also be seen prior to the onset of autonomic symptoms. These seizures are generally self-limited, and usually do not require much more than support and occasionally some Benzodiazepines. Seizures can be seen with ethanol concentrations greater than 100 mg/dl.

Mortality seen by Victor and Adams in DTs was in 15 out of 101 cases. Forty-three of these patients had other illnesses. Ten of the 15 fatalities had other illnesses. A key take home point is to discover why a patient has gone into withdrawal. If a patient has another illness that has prevented consumption of ethanol, then he or she is at greater risk for death.

Ethanol Withdrawal ED Care

Improvements in treatment have led to significant decreases in mortality from DTs. Moore in 1936 described the experience of treating DTs at Boston City Hospital from 1915-1935. In this series 2375 patients were admitted over that time period. The mortality in 1915 was 52%, and by 1935 it had dropped to 14%. The main reason for the decrease in mortality was the introduction of nurses, better treatment of dehydration, more limited use of physical restraints, and decreasing use of neuroleptics. Modern treatment involves the aggressive use of Benzodiazepines. Current mortality of DTs can be as low as 5%. An important concept in the treatment of DTs is kindling. It is felt that kindling in the brain leads to a self-perpetuating worsening of the DTs. In order to quickly stop the DTs one should treat aggressively with Benzodiazepines early. The endpoint of treatment is to achieve light sedation. Both Lorazepam and Diazepam have

pros and cons. My preference is for Diazepam. As it has a long half-life it will stay on board longer, and will potentially have a smoother taper.

Lorazepam	Diazepam
2 mg IV Q 15 min	5 mg IV Q 15 min
IM OK	IM not OK
Lack of hepatic metabolism	Long T ½ with metabolites
Good for cirrhotics	Accumulates in cirrhotics

Other options for treatment include Phenobarbital, Pentobarbital, and Propafol. One should avoid Phenothiazines. They can lower the seizure threshold, and potentially make hyperthermia worse. Beta-blockers have been reported by some, but they only block peripheral sympathetic effects, and do not help the CNS effects. Clonidine has been found to be ineffective. Phenytoin is a poor choice for toxin-induced seizures in general, and the same is true for alcohol withdrawal/DTs.

GHB Withdrawal

Gamma hydroxybutyrate (GHB) is a neuromodulator that has been abused as a street drug. It has been used as an agent for drug-facilitated sexual assault, and is also used by body builders as a bulk-enhancing agent. GHB can be obtained as GHB, 1,4 butanediol and gamma butyrolactone. The latter two chemicals are essentially converted *in vivo* to GHB.

The following table compares the properties of GHB with other agents that cause life-threatening withdrawal.

Substance	Onset/Duration	Autonomic Instability	Mechanism
GHB	Hours/5-12 days	Mild-Mod	GHB, GABA _A , GABA _B
Benzos	1-3 days/5-9days	Moderate	GABA _A
Ethanol	12-96h/8d	Mod-Severe	GABA _A , NMDA
Baclofen	Hours/10-14d	Moderate	GABA _B

Treatment of GHB withdrawal requires recognition first and foremost. Often just symptomatic treatment may only be required. Both the Benzodiazepines and Propafol have been used successfully.

Baclofen Withdrawal ED Presentation

Baclofen is an agent that is used in intrathecal pumps, and when they malfunction can leave to a life-threatening withdrawal syndrome. One should consider this in patients with muscular dystrophy or other illnesses involving spasticity.

The clinical picture includes high fever, altered mental status, exaggerated rebound spasticity, muscle rigidity, rhabdomyolysis, multi-system organ failure and death. Twenty-seven cases have been reported to the manufacturer including six deaths. Reasons for pump failure (which leads to withdrawal) can include catheter malfunction, low volume in pump reservoir, battery running out and human error. Treatment should focus on re-starting the pump, treating with a GABA-ergic agonist drugs, Oral or enteral Baclofen, or Benzodiazepines.

Consultations and Admission

Patients requiring significant doses of Benzodiazepines should be admitted to an intensive care setting. Patients with mild withdrawal may be managed on a general medical floor, but should not have standing orders for Benzodiazepines written. The patient should be closely monitored and re-evaluated before and after all doses of a sedative hypnotic.

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Patient Outcome

Initially the clinicians were sidetracked by trauma issues, and for the search for occult pathology. After several hours a history was obtained revealing that the patient was taking multiple Benzodiazepines prescribed by several practitioners. Initially the patient was given 100 mg Diazepam just in order to achieve light sedation. A total of 400 mg of Diazepam was given over the next 2 days. After that time a taper of Diazepam done by reducing the total daily dose by 10% was undertaken until the patient was weaned off Diazepam.

Annotated Bibliography

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Excellent clinical description and definition of the GHB withdrawal syndrome.

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THE CLASSIC alcohol withdrawal paper! This is really worth a read if you want to appreciate the original observations of alcohol use and withdrawal.

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Not a drug widely used today, but perhaps we should be. This is a nice review of an experience with Phenobarbital for alcohol withdrawal.

Questions

- 1. Flumazenil is most appropriately used in the setting of:**
 - a. Combined overdose of TCAs and Benzodiazepines
 - b. Procedural sedation
 - c. As part of the coma cocktail
 - d. Barbiturate withdrawal

- 2. Seizures in the setting of alcohol tend to be:**
 - a. Refractory to normal therapy
 - b. Solely due to concomitant trauma
 - c. Due to a co-ingestant
 - d. Self-limited

- 3. The decrease in mortality secondary to delirium tremens is most likely due to:**
 - a. The use of neuroleptics
 - b. The liberal use of physical restraints
 - c. The use of antipyretics
 - d. The improvement in nursing and supportive care

- 4. Which of the following are NOT considered to be life-threatening withdrawal syndromes?**
 - a. Opiates
 - b. Alcohol
 - c. Benzodiazepines
 - d. Barbiturates
 - e. Baclofen

- 5. Which of the following drugs is most likely to be associated with withdrawal in a patient with muscular dystrophy with an indwelling pump?**
 - a. Baclofen
 - b. Diazepam
 - c. Propofol
 - d. GHB

Answers

1. Answer b.

Flumazenil should not be used in the setting of combined TCAs and Benzodiazepine overdose. Cases of precipitating dysrhythmias with this specific overdose. It should also not be used as part of a routine coma cocktail, and should only be used in very selective cases (e.g. a toddler who gets into an adult's Benzodiazepine. It will be ineffective in barbiturate withdrawal. Flumazenil is most appropriately used for procedural sedation.

2. Answer d.

Seizures associated with alcohol withdrawal are generally self-limited. If a patient presents with status epilepticus in this setting another reason e.g. trauma, other ingestant, etc should be explored.

3. Answer d.

Previously, the high mortality of DTs was because of poor treatment of dehydration, the use of physical restraints which led to rhabdomyolysis. Antipyretics have no role in the treatment of DTs. Excellence in nursing and supportive care has led the way to a mortality rate of approximately 5%.

4. Answer a.

Alcohol, Benzodiazepines, barbiturates, and baclofen are all examples of life-threatening withdrawal syndromes. Opiate withdrawal should not lead to hyperthermia. If one observes hyperthermia in suspected opiate withdrawal, it is wise to reconsider the diagnosis.

5. Answer a.

Of the agents listed only baclofen is used in an indwelling pump to control spasticity. Cases of baclofen withdrawal are being reported with increased frequency from this pump malfunction.