Toxicological Considerations in the Trauma Patient

Spencer Greene, MD, MS, FACEP, FACMT
Director of Medical Toxicology and Assistant Professor
Henry J.N. Taub Department of Emergency
Baylor College of Medicine

Objectives

- Demonstrate how toxicological conditions may contribute to traumatic injuries
- Describe a rational approach to toxicology testing and address the limitations of urine drug screens
- Discuss the advantages and disadvantages of various sedatives and analgesics
- Explain how a multidisciplinary approach can best manage these complicated patients

Case 1

A tale from my misspent youth*

*Not the story of why I was almost kicked out of 5th grade
23 y/o male found minimally responsive in a car resting against a roadside tree. There are no skid marks and only slight damage to the car.

110/76  104  18  96.5  100%

Exam notable only for decreased responsiveness and cool, clammy skin.

What’s the differential?

Case 1

DDx of AMS

Structural/trauma
Toxic/metabolic
Infectious
Vital sign abnormalities
Behavioral

Immediate interventions

Secure airway
Ensure oxygenation and ventilation
Maintain euvoemla
Identify immediately-correctable conditions

Any thoughts?
Hypoglycemia → glucose

Benzodiazepine intoxication → flumazenil

Opioid intoxication → naloxone

Use as little as possible, but as much as necessary

Also consider for non-opioids:
- clonidine
- guanabenz
- brimonidine
- tetrahydrozoline
- dextromethorphan
- valproic acid

Naloxone

ACE inhibitors
- guanfacine
- α-methyldopa
- oxymetazoline
- tizanidine

Reversible conditions
Laboratory tests
• more on this momentarily

Imaging
• head CT
• conventional radiography

Electrocardiogram
• may provide a diagnosis
• may influence pharmacotherapy

Unexplained altered mental status

When to get head CT

At risk for intracranial catastrophe

Focal deficit

Laboratory tests to consider

Complete blood count
Thyroid function tests
Prothrombin time
Ammonia
RPR
Salicylates
Carbamazepine
Phenytoin
Lithium
Theophylline
Co-oximetry

Basic metabolic profile
Liver profile
Venous blood gas
HIV
Acetaminophen
Alcohol level
Phenobarbital
Valproic acid
Digoxin
Iron
Serum osmolarity
Laboratory tests to consider

Did I forget any tests?

Case 2

What’s the “U” for?

25 y/o female with a PMH of anxiety presents to the ED on Monday morning after a fall. She was apparently getting up from a chair when she slid over and struck her head against a desk. There was no loss of consciousness.

108/72 102 18 99% 101.3

She appears disheveled and she is not oriented to place or time. There is a small abrasion to the forehead but no hematoma and no deformities. Remainder of exam is unremarkable. She was reportedly normal the previous Friday.
CT head: no acute intracranial abnormalities
CT C-spine: no fractures or other deformities

ASA: undetectable
APAP: undetectable
ETOH: undetectable
UDS: (+) for PCP

Case 2

She is admitted for observation because of persistent AMS. She is pronounced dead 12 hours later. Cause of death is determined to be bacterial meningitis.

Problem with how the test is used
* designed for specific drugs/classes
* cannot test for vast majority of xenobiotics

Actual problems with the test
* False (+) results
* False (-) results
* Not available in clinically-meaningful timeframe
* It ain’t cheap

Useless Drug Screen
<table>
<thead>
<tr>
<th>Drug</th>
<th>UDS: true (+) results</th>
<th>PCP: true (+) results</th>
<th>UDS: false (-) results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dextromethorphan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketamine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methoxetamine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxylamine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tramadol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venlafaxine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clonazepam?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alprazolam?</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Amphetamines**
- the more “stuff”, the less merrier

**Benzodiazepines**
- designed to detect oxazepam
- does not reliably detect drugs that are glucuronidated

**Opioids**
- we do not detect synthetic opioids
- variable success with semi-synthetic opioids
Once more, with feeling

Case 3

45 y/o female presents to the ED via EMS after a suicide attempt. She tried to cut her neck with a box cutter before her roommate stopped her. The roommate is also concerned that the patient took some valproic acid tablets she is not prescribed, but the patient is not forthcoming with a history. Her VS are WNL and her exam is unremarkable except for a superficial wound to the neck.

Laboratory studies
- BMP: WNL
- LFTs: WNL
- ASA: undetectable
- VPA: undetectable
- APAP: undetectable
- ETOH: undetectable

Five hours after arrival she is encephalopathic. Her exam is otherwise unremarkable.

Laboratory studies remain the same, except VPA has risen from undetectable to 218 mg/L (reference range: 50 – 100 mg/L)
Serial laboratory testing for drugs with delayed and/or prolonged absorption:
- salicylates
- valproic acid
- carbamazepine
- iron
- phenytoin

It's not essential to know which medications do this. It's essential to know that some medications do this and whom to call for advice!

Laboratory testing

Some ingestants don’t typically require serial levels

On the other hand.....

The most common ingestion

The most commonly mismanaged ingestion

Toxicity is diagnosed or excluded with a single lab measurement obtained 4 – 24 hours post-ingestion
After 24 hours, toxicity is diagnosed or excluded by labs that assess for *end-organ damage*

- AST
- ALT
- prothrombin time
- creatinine

An undetectable APAP level after 24 hours means nothing.

The cause of – and solution to – all of life’s problems
A 46 y/o male - well-known to the trauma service because of frequent alcohol-related emergencies - presents to the ED after sustaining fractures to three right-sided ribs and a clavicle following a fall from standing.

120/80  94  12  96.5  98%

Exam reveals a chronically ill-appearing man in no acute distress. Tenderness noted to R chest and clavicle. Exam otherwise unremarkable.

Imaging only notable for aforementioned injuries.

Labs indicate an ethyl alcohol level of 422 mg/dL

Case 4

He is admitted to the trauma service and does well for the next five hours. He then becomes tremulous, tachycardic, and confused.

What’s responsible for the change in his condition?

How would you treat him?

50 trauma patients at risk for AWS admitted to ICU
TBI and stigmata of chronic alcoholism excluded
Ethanol infusion compared to diazepam 5 mg QID
  * Riker Sedation-Agitation Scale used as endpoint
  * greater under-sedation with ETOH group
  * no difference in over-sedation

Choosing a benzo

Logistical issues
• cost
• availability
Pharmacokinetics
• route
• onset of action
• duration

Costs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlordiazepoxide</td>
<td>25 mg</td>
<td>PO</td>
<td>$0.07</td>
</tr>
<tr>
<td>Diazepam</td>
<td>5 mg</td>
<td>PO</td>
<td>$0.10</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>1 mg</td>
<td>PO</td>
<td>$0.80</td>
</tr>
<tr>
<td>Diazepam</td>
<td>10 mg</td>
<td>IV</td>
<td>$2.40</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>2 mg</td>
<td>IV</td>
<td>$2.74</td>
</tr>
</tbody>
</table>

Kinetics

<table>
<thead>
<tr>
<th>Name</th>
<th>Peak effect</th>
<th>Half-life</th>
<th>Active metabolite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlordiazepoxide</td>
<td>PO: 2 hrs</td>
<td>6.6 – 25 hrs</td>
<td>yes 50 – 100 hrs</td>
</tr>
<tr>
<td>Diazepam</td>
<td>PO: 0.5 – 2 hrs</td>
<td>IV: immediate</td>
<td>yes 50 – 100 hrs</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>PO: 2 – 4 hrs</td>
<td>IV: up to 20 minutes</td>
<td>no</td>
</tr>
</tbody>
</table>
**Diazepam vs. Lorazepam**

- Diazepam 5 mg vs. lorazepam 1 mg
- Significantly less anxiety and depression in diazepam group
- Trend toward less craving in diazepam group
- Tachycardia significantly higher in lorazepam group
- 5% seizure incidence with lorazepam. None with diazepam.

**Diazepam vs. Chlordiazepoxide**

- Compared front-loaded diazepam vs. fixed-schedule chlordiazepoxide
  - Diazepam 20 mg given for CIWA-AR > 10
  - Chlordiazepoxide given every 6 hours using 10-day taper
  - Intervention group received average of 74 mg (e/t 222 mg)
  - Control group received average of 700 mg

  **Mean length of detoxification period**
  - 8.2 hours for intervention group
  - 242 hours for control group

**Symptom-Triggered vs. Fixed-Schedule Dosing**

- Randomized, double-blinded controlled trial
  - 22 patients treated with oxazepam PRN or placebo q 6h
  - 61 patients received oxazepam q 6h

  **Symptom-triggered approach resulted in:**
  - Less amount of benzodiazepine required 37.5 mg vs. 231.4 mg
  - Shorter duration of treatment 20 hrs vs. 62.7 hrs
Scheduled vs. PRN dosing

Prospective, randomized, double-blind controlled trial of 63 patients with moderate or severe AW

<table>
<thead>
<tr>
<th>Primary outcome measures</th>
<th>Scheduled</th>
<th>PRN</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total dose of lorazepam (mean ± SD)</td>
<td>18.0 (±6.5)</td>
<td>6.5 (±3.2)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Duration of desintoxication (mean ± SD)</td>
<td>47.6 (±5.0)</td>
<td>47.6 (±5.0)</td>
<td>p = 0.29</td>
</tr>
</tbody>
</table>

Dosing diazepam

Start with 5 – 20 mg

If symptoms are worsening: double the dose
If there is no improvement: give the same dose
If the patient is slightly improved: give half the previous dose
If symptoms have resolved: monitor for return of s/s
Do this q 10 minutes (IV) or q 30 minutes (PO)
Phenobarbital

Pharmacodynamic advantages over benzodiazepines
- different binding site on GABA receptor
- can work independently of GABA

Variable dosing options
- range from 1 – 20 mg/kg

Potential complications
- hypotension
- respiratory depression
- immediate availability
- onset of action

Phenobarbital for acute alcohol withdrawal: a prospective randomized double-blind placebo-controlled study

Jonathan Rosenson, SC, Carol Clemente, SC, Barry Gore, SC, Leslie Visa, SC, Sarah D’Amico, SC, “Randomized, double-blind, placebo-controlled trial of 10 mg/kg
- treatment group had lower ICU admission rates (8% vs 25%)
- no difference in adverse events
Chill, bro

Case 5

26 y/o male is brought in by police for agitation. He was found at the bus station screaming and running around, knocking over garbage cans. He reportedly has a history of methamphetamine abuse

160/101  135  20  100.1

Very agitated, diaphoretic. Pupils 7 mm, reactive

Moving all extremities well. Too well, in fact! Remainder of exam not possible because of agitation

How would you control his agitation?
Benzodiazepines
- lorazepam
- midazolam

Antipsychotics
- haloperidol
- olanzapine
- ziprasidone

Diphenhydramine

Ketamine

**Sedation options**

A Prospective, Double-blind, Randomized Trial of Midazolam versus Haloperidol versus Lorazepam in the Chemical Restraint of Violent and Severely Agitated Patients

Randomized, prospective, double-blind trial

Intramuscular midazolam vs. haloperidol vs. lorazepam

Midazolam has faster onset and more rapid arousal

<table>
<thead>
<tr>
<th>Sedation options</th>
<th>onset (min)</th>
<th>arousal (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>midazolam</td>
<td>18.3</td>
<td>81.9</td>
</tr>
<tr>
<td>haloperidol</td>
<td>28.3</td>
<td>126.5</td>
</tr>
<tr>
<td>lorazepam</td>
<td>32.2</td>
<td>217.2</td>
</tr>
</tbody>
</table>

Management of Acute Undifferentiated Agitation in the Emergency Department: A Randomized Double-Blind Trial of Droperidol, Ziprasidone, and Midazolam

Randomized, prospective, double-blind trial of 144 patients
- 50 treated with droperidol 5 mg IM
- 46 treated with ziprasidone 20 mg IM
- 48 treated with midazolam 5 mg IM

Midazolam had shortest time to adequate sedation
- 15 minutes vs 30 minutes for antipsychotics
Comparison of midazolam 5 mg, haloperidol 5 mg, haloperidol 10 mg, ziprasidone 20 mg, and olanzapine 10 mg

Primary outcome was percentage of patients adequately sedated at 15 minutes

Diphenhydramine
- interferes with heat dissipation
- altered mental status
- QT prolongation
- lowers seizure threshold

Haloperidol
- extrapyramidal side effects
- lowers seizure threshold
- QT prolongation
A 44-year-old female with no PMH presents to the ED via EMS after an intentional ingestion. She reportedly took several handfuls of an OTC sleeping product in a suicide attempt. She is confused and difficult to understand.

- **Blood Pressure**: 140/84
- **Pulse**: 144
- **Respirations**: 18
- **Oxygen Saturation**: 99%
- **Temperature**: 101.3°F

- **Pupils**: 8 mm, minimally reactive
- **Bowel Sounds**: Diminished
- **Skin**: Hot, dry

Patient confused, agitated, mumbling. No clonus or hyperreflexia. Not following commands.

On the other hand…

**Antimuscarinic toxicity**

- Altered mental status
- Mumbling speech
- Tachycardia
- Mydriasis*
- Anhidrosis
- Urinary retention
- Ileus
- Variable blood pressure
- Hyperthermia
- Seizure

**Antimuscarinic toxicity**

- Antihistamines
- Phenothiazines
- Low-potency and benzepine antipsychotics
- Benztpoline
- Tricyclic antidepressants
- Carbamazepine and oxcarbazepine
- Orphenadrine
- Cyclobenzaprine
- Tolterodine and oxybutynin
- Amantadine
- Dicyclomine
- Plants containing atropine, scopolamine, and/or hyoscyamine
What’s the best way to treat this delirium?

**Antimuscarinic toxicity**

**Physostigmine**

- Inhibits cholinesterase
- Tertiary carbamate
- Antidote for antimuscarinic toxicity
- Works as non-specific reversal agent
- Surrounded by unnecessary controversy

**A Comparison of Physostigmine and Benzodiazepines for the Treatment of Anticholinergic Poisoning**

- Physostigmine controlled agitation and reversed delirium in 96% and 87% of patients, respectively
- Median dose 2.2 mg
- Benzodiazepines controlled agitation in 24% of patients and did not reverse any delirium
- Patients treated initially with physostigmine had a 7% incidence of complications vs. 46% of patients initially treated with benzodiazepines
- Faster recovery time with physostigmine
  - 12 hrs vs. 24 hours
Retrospective study of 39 adult patients who received physostigmine (median dose 1 mg)

- 19 had purely antimuscarinic toxicity
- 12 did not have antimuscarinic toxicity
- 4 with mixed toxicity
- 4 patients had unknown cause for AMS

22 patients had full reversal of their delirium

- 19/19 pure antimuscarinic
- 3/4 unknown cause for AMS

Complications of Diagnostic Physostigmine Administration to Emergency Department

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- 19/19 pure antimuscarinic
- 3/4 unknown cause for AMS

Complications

- one patient with antimuscarinic poisoning had brief seizure without adverse sequelae*
- one patient with a mixed ingestion had hypoxia*
- no dysrhythmias reported
- no cases of cholinergic excess
- no patients required atropine
Phystostigmine

0.5 – 2 mg slow IVP
* 0.02 mg/kg (max 0.5 mg) in pediatric patients

Give at rate up to 1 mg/min
* my preference: dilute in 20 mL and give over 5 minutes

Repeat q 10 – 60 min PRN

Some medications don’t play nice with others

A 34 y/o female with a h/o depression is admitted to the trauma service with multiple extremity fractures s/p MVC. Imaging was otherwise normal.

No other PMH. No h/o tobacco, alcohol, or drug use.

Her pain is being controlled with scheduled tramadol and PRN fentanyl.

Sixteen hours after admission she is noted to be tachycardic, diaphoretic, and confused. Exam is notable for bilateral ankle clonus and patellar hyperreflexia. She also has a tremor at rest.

What’s going on here?
Syndrome of excessive stimulation of specific serotonin (5-HT) receptors in CNS and PNS

5-HT\textsubscript{1A} and 5-HT\textsubscript{2A}

Typically due to interaction of multiple serotonergic agents, usually with different mechanisms

- Increased production
- Direct agonism
- Enhanced 5-HT release
- Reuptake inhibition
- Decreased metabolism

A. Coincident with the addition of or increase in a known serotonergic agent to an established medication regimen, at least three of the following clinical features are present:

1. Mental status changes
2. Agitation
3. Myoclonus
4. Hyperreflexia
5. Diaphoresis
6. Shivering
7. Tremor
8. Diarrhea
9. Incoordination
10. Fever

B. Other etiologies (e.g., infectious, metabolic, substance abuse or withdrawal) have been ruled out

C. A neuroleptic had not been started or increased in dosage prior to the onset of the signs and symptoms listed above


1. Has a serotonergic agent been administered in the past 5 weeks?
   - If no, it’s not serotonin syndrome

2. Are any of the following symptoms present?
   - Tremor and hyperreflexia
   - Spontaneous clonus
   - Muscle rigidity, temperature > 38°C, & either ocular clonus or inducible clonus
   - Ocular clonus and either agitation or diaphoresis
   - Inducible clonus and either agitation or diaphoresis

Boyer E. NEJM 2003; 353:1113-1120
Antidepressants
- SSRIs
- SNRIs
- TCAs
- MAO-inhibitors
- SARIs
- lithium

Opioids
- fentanyl
- meperidine
- tramadol
- pentazocine
- dextromethorphan

Serotonergic xenobiotics

Cocaine
Amphetamines
Amphetamine-like compounds
- cathinone
- bath salts
- phenylethylamines
- tryptamines
- mescaline
LSD
Psilocybin-containing mushrooms

Serotonergic xenobiotics

Linezolid
Methylene blue
Chlorpheniramine
Tryptophan
Triptans
Dexfenfluramine
Fenfluramine
Sibutramine
St. John’s wort
Stop the exposure
Airway and breathing
Circulation
Chill out the patient, literally
Chill out the patient, figuratively
• benzodiazepines
• cyproheptadine

Indication
• serotonin toxicity refractory to benzodiazepines

Dose
• 4 - 12 mg PO/PT then 4 mg q 1 - 4 hours PRN, max 32 mg daily
• Peds: 0.25 mg/kg/d divided q 6 hours, max 12 mg daily

Contraindications
• angle-closure glaucoma
• bladder neck obstruction or prostatic hypertrophy
May cause antimuscarinic side effects

Key points
Consider what medical conditions may have led to the trauma you are treating.

Do not worship the urine drug screen – it’s a false idol.

Know what lab tests may needed to diagnose or exclude concomitant toxicological conditions in the trauma patient.

Diazepam is the ideal benzodiazepine to treat alcohol withdrawal.

When diazepam is not an option, consider phenobarbital.

Key Points

There are many substances with serotonergic effects. Concomitant use can lead to serotonin syndrome.

In the patient with undifferentiated agitation, benzodiazepines are your best, safest option.

Midazolam has a much faster onset of action than lorazepam.

Physostigmine is the specific antidote for antimuscarinic toxicity.