London Health Sciences Centre
Southwest Ontario Regional Base Hospital Program

Medication Overdoses

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Pharmacology Review

First, some terms:

- Affinity – the tendency of a drug to combine with its receptor
- Efficacy – the drugs ability to initiate biological activity once bound
- Half life – time required for the body to eliminate 50% of the drug
- Agonist – drugs which bind to receptors and produce a response

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More terms…

- Antagonist – drugs which bind to receptors to produce a blocking effect

- Synergism – the combined action of two drugs that is greater than the sum of each individual agent acting independently (1+1=3)

- Potentiation – the enhancement effect cause by concurrent administration of two drugs in which one drug increases the effect of the other drug (a+b=A)

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Routes of administration

- Enteral – administration by mouth; oral or sublingual
- Parenteral – introduces drugs directly across the bodies barrier defense into the systemic circulation; IV, IM, SQ

First pass metabolism:

- Most drugs via oral route are absorbed in the GI tract
- When this occurs, the drug then enters the portal circulation and encounter the liver before they are distributed into the general circulation.
- In the liver, the drug undergoes biotransformation, making some it more readily available for use, or ready to be eliminated in urine or bile.

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Therapeutic Index:

- "is the ratio of the dose that produces toxicity to the dose that produces a clinically desired or effective response in a population of individuals"

Therapeutic index = TD50/ED50

- TD50= drug dose that produces a toxic effect in half the population
- ED50= drug dose that produces a desired response in half the population
- The therapeutic index is a measure of a drug's safety, a larger value indicated a wide margin between doses that are effective and doses that are toxic

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- Pharmacokinetics examines the movement of a drug over time through the body.

- The speed of onset of drug action, intensity of the drugs effect and the duration of drug action are controlled by four pathways of drug movement and modification in the body:
    1. Absorption
    2. Distribution
    3. Metabolism
    4. Elimination

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The Dose Response

Assumptions:

- Response is due to chemical administered
- The response is related to the dose
- There is a receptor site with which the chemical interacts
- The degree of response is related to the concentration at the site
- The concentration at the site is related to the dose administered

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Spectrum of undesired effects:

- Allergic reactions
- Idiosyncratic reactions
- Immediate vs. delayed toxicity
- Reversible vs. irreversible toxicity
- Local vs. systemic toxicity

So what are some commonly seen overdoses?

2008 Annual Report of the American Association Poison Control Centers' National Poison Data System (NPDS)

Common Overdoses

Categories associated with largest number of fatalities
1. Sedative/Hypnotic/Antipsychotic
2. Opioids
3. Antidepressants
4. Cardiovascular Drugs
5. Acetaminophen Combinations
6. Alcohols
7. Stimulants/Street Drugs
8. Acetaminophen Alone
9. Antihistamines
10. Anticonvulsants

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- Benzodiazepines
- High therapeutic index
- Severe toxicity can lead to a comatose patient with respiratory depression and hypotension
- Potentiation caused with alcohol/other CNS depressants

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- Fentanyl, morphine, oxycodone
- Heroin
- Methadone
- Clinical triad:
  - CNS depression
  - Respiratory depression
  - Pupillary miosis
- Other possible findings:
  - Ventricular arrhythmias
  - Seizures
- Combined with sedative/hypnotics = increased CNS depression, particularly respirations

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- Cyclic antidepressants
- Narrow therapeutic index
- Ingestion of more than 1 g is potentially lethal
- Can cause cardiac toxicity resulting in arrhythmias such as blocked ventricular conduction and ventricular tachycardia
- Use to be the most common cause of overdose-related deaths
- New number 1?

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Top three:

- Calcium channel blockers
  - Decreased AV node conduction
  - Reduced CO and BP
- Cardiac glycosides
  - Acute or accumulative
  - Sinus bradycardia, ventricular arrhythmias
- Beta-blockers
  - Most toxic = propranolol
  - 2-3 X the therapeutic dose can cause serious toxicity
  - Bradycardia & hypotension

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- Analgesic (salicylate, ibuprofen)
- Toxic metabolite formed in liver
- Hepatic encephalopathy; renal failure may occur
- Hepatic toxicity = 7.5 – 10g
- Fatalities can result with 15g

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- Potentiates the effects of various drugs when taken in combination
- Ethanol – leads to trauma/illness
- Ethylene glycol and methanol – more lethal alcohols
- Listerine: alcohol content?
- Phenolic compounds
- Lethal dose?

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- Diphenhydramine/ Dimenhydrinate
- H1 receptors
- Hallucinogenic
- Anticholinergic

Treatments

Examples of medications we carry that also serve as antidotes:

- Atropine ⇒ anticholinesterases; organophosphates, carbamates
- Glucagon ⇒ calcium channel blockers; beta-blockers
- Sodium bicarbonate ⇒ membrane-depressant cardiotoxic drugs (tricyclic antidepressants; quinidine)

Examples of specific antidotes:

- Flumazenil ⇒ benzodiazepines
- Digoxin Immune Fab (Digibind) ⇒ digitalis toxicity
- N-acetylcysteine ⇒ acetaminophen

Enhanced Elimination Methods

Hemodialysis

- "is especially useful in overdose cases in which the precipitating drug can be removed and fluid and electrolyte imbalances are present and can be corrected"
- Toxic alcohols (ethylene glycol & methanol) are good examples of dialyzable toxins

Forced Diuresis

- Osmotic diuresis with mannitol may prevent the reabsorption of certain toxins
- Alkalinization of urine to help facilitate excretion of weak acid drugs (salicylates) and long-acting barbiturates

Problems with Initiating Treatments in the Field

Problem #1:

Antidote may need to be given over certain length of time.

- Patient has overdosed on a beta-blocker
- Antidote: Glucagon
- Initial dose: 0.05 mg/kg (up to 10 mg) over 1 minute
- Continued treatment: Infusion of 2-5 mg/hr in 5% dextrose

Problems with initiating treatments in the field:

<u>Problem #2</u>: Antidote dosage may be specific to serum levels.

- **Patient presenting with digitalis toxicity**
- **Antidote: Digibind**
- **Amount of Digibind to administer is based on either exact amount of digoxin tablets ingested, or serum levels (which take 6-8 hours post-ingestion to be accurate)**

Problems with initiating treatments in the field:

<u>Problem #3</u>: The antidote itself may have adverse reactions.

- **Patient has ingested a very large amount of a benzodiazepine.**
- **Antidote: Flumazenil**
- **Flumazenil runs the risk of causing seizures in patients with:**
  - **seizure history**
  - **benzodiazepine dependence**
  - **also overdosed on TCAs**

Example scenario:

You are responding code 4 for a semi-conscious patient, possible overdose. You arrive to find a 45 year old female lying on the sofa clutching her abdomen, in obvious discomfort, and slightly lethargic. Her husband states she has a history of depression but has been trying to "wean herself off her meds", and so hasn't taken her Zoloft for quite some time. She has been particularly upset over a recent death in the family and when husband arrived home for work, he found patient as is with two empty bottles of extra-strength Tylenol and and empty bottle of vodka on the end table. Patient has a history of past suicide attempts, also by ingesting Tylenol. Husband isn't sure how many tablets were remaining in the bottle, but is pretty sure one of them was near full.

Acetaminophen overdose management:

Antidote: N-acetylcysteine (NAC)

Best results occur if given within 8-10 hours of overdose.

Serum levels of acetaminophen must be acquired (minimum 4 hours post-ingestion).

NAC can be given orally or intravenously, but both require multiple repeat dosages over several hours.

Can produce fever (rare), hypotension, and bronchospasms (particularly with asthmatics).

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What can we do?

Start with the basics!

BLS Standards:

1. **Initiate cardiac monitoring.**
2. **Elicit history. Attempt to identify/determine:**
   - **agent(s), quantity, time and route of administration or ingestion;**
   - **if a prescription drug – date of prescription; route of administration; compliance with same (e.g. number of pills left in the bottle prior to overdose);**
   - **patient's degree of danger to self/others (conscious patient).**

Start with the basics!

BLS Standards:

3. **Attempt to perform at minimum:**
   - **CNS: pupillary size, equality, reactivity;**
   - **Baseline GCS;**
   - **Skin: colour, condition; note needle track marks, open skin lessions, unusual breath odours e.g. turpentine, acetone**
   - **Vital signs**
   - **Collect all medication and chemical containers, drug paraphernalia, plants, mushrooms etc. for transport to the receiving facility. (Note: If police are at scene, they may prohibit removal of evidence – document this on ACR)**

Start with the basics!

BLS Standards:

4. **If indicated – high concentration oxygen; initiate rapid transport**
5. ***Specific to overdose/poisoning:***

   b) Dilution of the ingested agent:

   - **Dilute the agent only if advice is available regarding recommended dilution procedures e.g. product information label and/or poison control center or base hospital physician and the patient meets all of the following criteria:**
     - **Fully conscious and understands instructions (GCS of 15)**
     - **Is cooperative**
     - **Has not seized or vomited spontaneously**
     - **Is not exhibiting periods of instability with respect to the ABCs, LOC (not fluctuating b/w wakefulness and drowsiness)**

CTAS

Level I resuscitation – conditions that are threats to life or limb requiring aggressive interventions

- Time to physician immediate

Level II Emergent – conditions that are a potential threat to life limb or function, requiring rapid medical intervention or delegated acts.

- Time to physician assessment <15 min

Level III Urgent – conditions that could potentially progress to a serious problem requiring emergency intervention.

- Time to physician assessment <30 min

CTAS

- **II - Emergent**
- "**Overdose:** Intentional overdoses are particularly unreliable when trying to determine which agents have been ingested and the actual quantity. These patients require early physician assessment, or advice, with regard to the need for toxic screening, monitoring or methods of preventing absorption, enhancing elimination or administration of antidotes. Patients with any signs of toxicity (altered mental state, abnormal vital signs) should be seen very quickly (£5 minutes)."
- Note: Unconscious patients from overdose are CTAS I

Code and CTAS?

- **The patient's presenting complaints remains the primary determinant of the CTAS acuity level**
- **But symptoms of overdose may require time to present**

Code and CTAS?

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So is there anything else we could potentially be doing for these patients?

Gastrointestinal Decontamination:

Methods of "Gut Emptying"
Emesis
Gastric Lavage
Cathartics
Activated Charcoal

Gastrointestinal Decontamination:

Methods of "Gut Emptying"
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- Laxative agents to hasten GI toxin removal
- Whole bowel irrigation (polyethylene glycol electrolyte, or PEG-ES)
- Possibly beneficial for sustained-release or entericcoated drugs, metals, illicit drug packets

Gastrointestinal Decontamination:

Methods of "Gut Emptying"
Emesis
Gastric Lavage
Cathartics
Activated Charcoal

- Possibly useful in pre-hospital setting?

What about activated charcoal?

- Activated charcoal absorbs the toxin, thereby preventing its absorption as it moves through the GI tract.
- Activated charcoal is not absorbed or metabolized and is eliminated unchanged in the feces along with any bound drug.
- The effectiveness of activated charcoal in preventing the absorption of ingested substances decreases with time; the greatest benefit is seen when it is administered within 1 hour of the toxic ingestion.

What about activated charcoal?

- **Activated charcoal is contraindicated if a patient has an unprotected airway (e.g. decreased level of consciousness without endotracheal intubation).**
- **It is relatively contraindicated for use in a caustic ingestion.**
- **Because activated charcoal can cause vomiting, it is also contraindicated for use in ingestions of pure petroleum distillates that are not well absorbed and carry a high risk of aspiration.**
- **Activated charcoal is generally well tolerated. The most common adverse effects are nausea, vomiting (15%) and constipation.**

What about activated charcoal?

Other complications:

- **can create constipation**
- **can result in the formation of clumps of foreign material which may also lead to perforation of the bowel**
- **will also absorb specific antidote if it is given after charcoal**
- **contraindicated if ingested toxin is corrosive, a strong acid or alkali drug**

Conclusion

Poisonings represent one of the most common medical emergencies and account for a large portion of emergency department visits. Early recognition and management can save lives. Initial management should involve the traditional ABCs of airway securement and cardiorespiratory support. Subsequent management can then focus on identification of a specific toxin and consideration for decontamination, with determination of the extent of intoxication deciding the patient's ultimate disposition.

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Addendum to Rounds:

Adam Dukelow spoke briefly re: Trauma patients arriving at UH ER instead of Vic. Recent cases have been brought to his attention by ER physicians at UH.

Part of the problem is that all these patients were assigned CTAS 3 by the paramedics, and Vic was on time-consideration.

He presented and discussed these slides re: CTAS 2 for trauma, and there will be future direction re: transport directly to Vic rather than UH.

1. The **presenting complaint** is determined by the triage nurse early in the triage process. This automatically generates a complaint-specific minimum CTAS level.
2. **First-order modifiers** are then applied, where appropriate, starting with vital signs, which, based on defined alterations in hemodynamic stability, blood pressure, temperature, level of consciousness and degree of respiratory distress, may change the triage level.
3. **Pain severity** is then determined, differentiating central versus peripheral and acute versus chronic recurring pain. The CTAS level assigned is based upon the highest level identified by any of the modifiers. For example, a patient with normal vital signs may be assigned a CTAS Level of III, IV or V based on the presenting complaint. However, if they have central pain that is severe, then they would be assigned a CTAS Level II on the basis of their pain scale.
4. **Mechanism of injury** (i.e., high- or low-risk mechanism) is considered for all trauma patients. High-risk mechanisms translate to an immediate CTAS Level II.
5. **Second-order modifiers** are also important for specific complaints to help risk stratify patients, especially when first-order modifiers are not definitive.

Table 7. Mechanism of injury and CTAS level

Risk level	Mechanism of injury and examples	CTAS level
High	**General trauma** Auto accident: ejection from vehicle, rollover, extrication time >20 min, significant intrusion into passenger's space, death in the same passenger compartment, impact >40 km/h (unrestrained) or impact >60 km/h (restrained)	II
	Motorcycle accident where impact with a car >30 km/h, especially if rider is separated from bike	
	Pedestrian or bicyclist run over or struck by vehicle at >10 km/h	
	Fall of >6 m	
	Penetrating injury to head, neck, torso or extremities proximal to elbow and knee	
High	**Head trauma** Auto accident: ejection from vehicle, unrestrained passenger striking head on windshield	II
	Pedestrian struck by vehicle	
	Fall from >3 feet or 5 stairs	
	Assault with a blunt object other than fist or feet	
High	**Neck trauma** Auto accident: ejection from vehicle, roll-over, high-speed (esp. if driver unrestrained)	II
	Motorcycle accident	
	Fall from >3 feet or 5 stairs	
	Axial load to the head	

Mechanism of injury

The mechanism of injury can be used as a modifier, and it alone can determine the CTAS level as Level II when there is a high-risk mechanism. Abnormal vital signs associated with injury are used to define Level I and Level II, and in those cases the mechanism of injury would add nothing. The mechanism of injury is important for stable patients at risk for a serious injury. High-risk mechanism of injury victims are given a CTAS Level II (see Table 7, p. 426).

Low	**General trauma** Auto accident: car-on-car rear-end collision, while coming to a stop, or impact <30 km/h and driver restrained	Use other modifiers
Low	**Head trauma** Auto accident: low-impact (<30 km/h) and driver restrained	Use other modifiers
	Fall or trip while standing on the ground	
	Fist fight or blow to head (excluding with pointed or heavy object) with no loss of consciousness	
Low	**Neck trauma** Simple rear-end collision (car-on-car), driver ambulatory after injury (driver not intoxicated or confused due to head injury) or delayed onset of neck pain	Use other modifiers