New Drugs of Abuse

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Khat

- Shrub whose leaves are chewed for their effects
- Native to E. Africa & Arabian Peninsula
- Contains *cathinone*, a natural alkaloid
  - Primary psychostimulant in the plant
  - Present in the leaves

Image from: http://en.wikipedia.org/wiki/Khat

Objectives

- Become familiar with the clinical presentation of newer street drugs
- Become familiar with management of patients presenting with intoxication from newer drugs of abuse
- Become familiar with substances commonly found as street drug adulterants

Khat

- Use dates back to ~ 640 A.D.
  - Religious ceremonies
  - Social pasttime
- Emerged in the West in 1980's
- Highly perishable

POISON HELP 1-800-222-1222

Image from: http://en.wikipedia.org/wiki/Khat

Clinical Effects: Acute

- Typical sympathomimetic presentation
- Tachycardia, Hypertension, Tachypnea
- Diaphoresis
- Agitation
- Psychosis
- Death

Coronary Vasospasm & Myocardial Infarction

- Observational studies in Yemen
- Peak daily incidence of MI parallels peak "chewing times"
- MI presents at a younger age in khat users
- Independent risk factor for in-hospital mortality in patients with ACS

Clinical Effects: Chronic Use

- Thromboembolic events
- Cardiac rhythm disturbances
- Dilated cardiomyopathy
- Hepatotoxicity
- Withdrawal syndrome
- Death
- Cancer?

Treatment

- Supportive
  - Benzodiazepines
- Admission for:
  - Serious symptoms
  - Suicidal patients

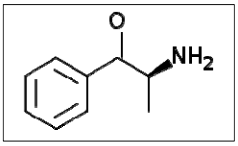

Image from: http://en.wikipedia.org/wiki/File:S-Cathinone.svg

Status

- 1993: Cathinone made Schedule I according to the U.S. Controlled Substance Act

Image from: http://en.wikipedia.org/wiki/Khat

Bath Salts

- No legitimate use for bathing!
- No legitimate medicinal use!
- Labeled, "not for human consumption"
  - Intended for substance abuse
- Widely available
- Looks like baby powder or flour

"Bath Salts"

- Synthetic designer drug
  - Cathinone derivative
- Primary ingredients:
  - "MDPV": inhibits NE and dopamine reuptake
  - Mephedrone: unknown MOA; likely MAOI, similar to MDMA

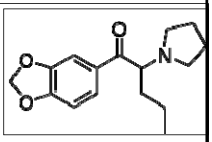

Image from: http://en.wikipedia.org/wiki/Methylenedioxypyrovalerone

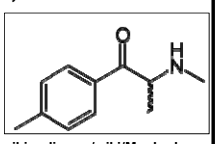

Image from: http://en.wikipedia.org/wiki/Mephedrone

Marketing Tricks

- Legal high
- "Legal cocaine"
- Enhances alertness
- Facilitates relaxation
- Aphrodisiac
- Plant food
- Insect repellent

Brand Names

- Ivory Wave
- Vanilla Sky
- White Rush
- Charge Plus
- Ocean Snow
- Red Dove
- Cloud Nine

Adverse Effects: Acute

- Hypertension, tachycardia, hyperthermia
- Diaphoresis
- Altered mental status
  - Paranoia, panic attacks, psychosis
  - Violence, aggression
- Insomnia
- Extreme psychomotor agitation
- Seizure

Route of Abuse

- Oral ingestion
- Intranasal
- Smoked
- Intravenous
  - Less common
  - Bath salts less effective in solution
- Rectal

Adverse Effects: Subacute - Chronic

- Long term use leads to tolerance
- Compulsive, repetitive use
  - Intense craving
  - Withdrawal
- Long standing depression and paranoia
  - Resembles schizophrenia
- Suicide and homicide

Laboratory Evaluation

- Routine drugs of abuse tests do not detect
  - Can trigger positive amphetamine result
  - Most do not
- Can obtain MDPV and mephedrone levels
  - Send out test to specialized labs
  - Quantitative level using GC/MS

Treatment is Supportive

- Quiet room, low lighting
- Benzodiazepines for agitation, hypertension and tachycardia
  - Dexmedetomidine: anecdotal success
- Intravascular volume repletion

Other laboratory testing

- Liver function tests
  - MDPV is metabolized in liver
- Renal function tests
- CPK
  - Rhabdomyolysis not uncommon

Aggressive Cooling

- Usual maneuvers
- May need intubation and paralysis
- Succinylcholine contraindicated
  - Rhabdomyolysis & hyperkalemia
  - Use nondepolarizing agents
- Continuous EEG monitoring if paralyzed

Supportive Care

- Counseling for depression and paranoia
- Drug treatment programs
- Case reports: resolution of paranoia and delirium with antipsychotics
  - After resolution of acute intoxication
  - Low doses used

Levamisole

- Veterinary antihelminthic
- No longer available for human use
- Cocaine adulterant
  - As much as 70% of cocaine in US
- Problem thought to have began in 2003
  - South American cartels

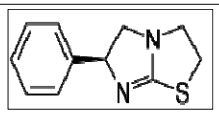

Image from: http://en.wikipedia.org/wiki/File:Levamisole2.svg

Legal Status

- DEA emergency ban announced Sept 7, 2011
- Ohio State Law banning bath salts went into effect on October 17, 2011

Clinical Effects

- Vasculopathic purpura
  - Characteristic skin lesions
  - Skin necrosis (digits, ears)
- Neutropenia
- Agranulocytosis
- Hyponatremia
  - Mechanism unknown

Treatment

- Supportive
- Cessation of levamisole exposure

Clenbuterol

- Potent, long acting β-adrenergic agonist
- Used outside US for treatment of reactive airway disease in humans and animals
- Used by body builders for sympathomimetic, lipolytic and anabolic effects
- Used as an adulterant in heroin and other drugs

Status

- Withdrawn from US Market in 2000
- Banned in US

January 28, 2005

21 year old New Jersey man hospitalized with an atypical reaction to heroin.

Patient reported chest pain, palpitations and shortness of breath that began soon after intranasal exposure.

Presentation

- Hypotension, Tachycardia
- Pale, diaphoretic skin and mydriatic pupils
- Laboratory testing
  - AGMA
  - Hypokalemia
  - Hyperglycemia
- Patient recovered with supportive care

Clenbuterol Toxicity

- Tachycardia, hypotension
- Palpitations
- Vomiting
- Muscle spasm
- Hyperreflexia
- Hyperglycemia
- Hypokalemia

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Following Three Months

- Poison Center reporting led to identification of 25 similar cases
  - 5 different states
- Samples collected and analyzed
  - State and local law enforcement and CDC involved
  - Presence of clenbuterol was identified

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Treatment

- Supportive Care
- Admission if
  - Serious symptoms
  - Suicidal

Synthetic Cannabinoids

- Appeared on the Internet in 2006
- Agonize endogenous cannabinoid receptors
  - JWH-018, JWH-073, JWH-175, CP-47,497
  - CB_1 and CB_2 receptors
  - More potent than Δ^9-tetrahydrocannabinol

Synthetic Cannabinoids

- Ingredients listed as plant or herbal material
  - Accuracy unknown
  - Product dipped in or sprayed with synthetic cannabinoids
- Labeled, "not for human consumption"
  - Marketed as incense

Synthetic Cannabinoids

- Many different products
  - "Spice", "K2", "Yucatan Fire", "Black Mamba", "Solar Flare"
- $25 - $40 per packet
  - More expensive than marijuana

The Appeal

- Novelty
- "Legal" high
- Generally not detected on drug screen

Clinical Effects

- Hypokalemia
- Anxiety, Agitation
- Tachycardia
- Vomiting
- Xerostomia
- Psychosis, Paranoia, Hallucinations
- Seizures
- Possible withdrawal syndrome

Treatment

- Supportive
- Benzodiazepines
  - Agitation
  - Tachycardia
  - Hypertension

Laboratory Evaluation

- Most products not detected on routine urine drugs of abuse screen
- Some companies report capability to detect JWH-018 and JWH-073 for up to 72 hours in urine
- Testing as dictated by clinical scenario

Status

- DEA's emergency scheduling authority used to temporarily classify 5 synthetic cannabinoids as Schedule I
  - November 24, 2010
  - JWH-018, JWH-073, JWH-200, CP-47,497 and cannabicyclohexanol

Summary

- Use of bath salts, khat, synthetic cannabinoids is currently illegal
- Replacement designer drugs already surfacing
- Toxicology screening not reliable
- Intoxication can be life threatening
- Withdrawal syndromes do exist

Objectives

- high dose insulin/euglycemia
- intravenous lipid infusion
- poison control center consultation

New Antidotes

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Antidote

1. noun, a substance which counteracts the effects of a toxicant

Drug Induced Cardiogenic Shock

- 35 y o woman overdosed on verapamil and propranolol in suicide attempt
- Unresponsive, BP 60/30, HR 70, RR 10, T 97
- Treatments:

intubation	IV fluid bolus x 2
atropine	calcium chloride x 4
glucagon bolus & infusion	dopamine

- BP 48/30: what's next?

High-dose insulin / euglycemia

- Bolus: 1 Unit/kg regular human insulin IV
- Drip: 1 - 10 Unit/kg/hr
- Dextrose: D_{50} bolus then D_{10} drip
- Bedside blood glucose checks
- Watch K^+, Mg^{++}, phosphate

Holger et al, Clin Toxicol 2011

Options

- More fluids
- Add vasopressors & titrate upward
- More calcium
- Call Poison Control: 800-222-1222
- High-dose insulin / euglycemia
- Intravenous lipid infusion
- Invasive support measures

High-dose insulin: disclosure

FDA has approved neither this dosing regimen nor this indication

High-dose insulin: evidence

- ✓ In vitro Studies & Animal Studies
- ✓ Case Reports
- ✓ Case Series
- ✓ Reviews
- ✓ Expert Opinion
- X Randomized or Controlled Trials

High Dose Insulin: Side Effects

- Hypoglycemia
- Hypokalemia
- Hypophosphatemia

- Delays & Calculation Errors

Engebretsen et al. Clin Toxicol 2011

High Dose Insulin: effects

- Inotropy, improved contractility, improved relaxation
- Vasodilation & capillary bed recruitment
- Overall: improved cardiac output, perfusion
- Often: improved HR & BP

Engebretsen et al. Clin Toxicol 2011

High Dose Insulin: Clinical Monitoring

- Mental status
- Skin warmth & color
- Pulses & capillary refill
- Urine output
- Cardiac output monitoring
- Vitals

Case One: Outcome

- 35 y o F verapamil & propranolol OD
- Failing despite aggressive treatments
- Poison Control recommends HDI / E
- 30 minutes after bolus insulin: 94/54
- Vasopressors stopped
- Insulin infusion 28 hours 1 unit/kg/hr
- Full Recovery

Vasopressors & HDI/E

- No evidence vasopressors work for drug-induced cardiogenic shock
- Higher insulin doses required with vasopressors
- Taper/stop vasopressors after HDI/E
- Use HDI/E before vasopressors

•Holger Clin Toxicol 2009, 2011; Engebretsen Clin Toxicol 2011

High Dose Insulin: Lab Monitoring

- Bedside [glucose]: Q 10 – 60 min
- [K+]: Q 1 – 4 hours
- Serum pH, lactate, phosphorus, Mg++

Drug Induced Cardiotoxicity

- 40 y o man in cardiac arrest after trigger points injections with bupivacaine
- Intubated, CPR in progress x 30 minutes
- Treatments:

intubation	epinephrine
amiodarone	vasopressin
defibrillation x multi	

- asystole: what's next?

Options

- Stop
- Call Poison Control: 800-222-1222
- High-dose insulin / euglycemia
- Intravenous lipid infusion
- Invasive support measures

IV lipid infusion: disclosure

FDA has approved neither this indication nor these doses

Intravenous Lipid 20% Infusion

- Bolus: 1.5 mL/kg
  - Repeat up to 3x for persistent shock
  - Continue repeat boluses if asystole
- Infusion: 0.25 - 0.5 mL/kg/min

Jamaty, Clin Toxicol 2010; Cave & Harvey, Acad Emerg Med 2009

IV Lipid infusion: evidence

- ✓ In vitro Studies & Animal Studies
- ✓ Case Reports & Case Series
- ✓ Reviews & Expert Opinion
- X Randomized or Controlled Trials

IV Lipid infusion: indications

Life-threatening cardiotoxicity from
- local anesthetics
- haloperidol
- tricyclic antidepressants
- lipophilic beta blockers and calcium channel blockers
- others

CNS tox, seizure, coma from lipid-soluble drugs

Jamaty, Clin Toxicol 2010
Cave, Acad Emerg Med 2009; Cave, Emerg Med Australas 2011

IV Lipid Infusion: Side Effects

- Hyperamylasemia
- Respiratory distress syndrome
- Hematuria

- Multi complications associated with TPN: not (yet) reported in rescue therapy

Cave, Crit Care Med 2011; Mirtallo et al, Annals Pharmacother 2010;
Cave, Emerg Med Australas 2011

IV Lipid Infusion: effects

- Lipid Sink: decreased free drug level
- Improve myocardial FFA uptake, use
- Improve myocardial Ca++

Jamaty, Clin Toxicol 2010; Cave & Harvey, Acad Emerg Med 2009

IV Lipid Infusion: Monitoring

Vitals & Perfusion

Case Two: Outcome

40 y o man, bupivacaine → cardiac arrest

45 min CPR → asystole

1.5 mL/kg 20% intravenous lipid →return of spontaneous circulation in 2 minutes

Conclusions

- High-dose insulin / euglycemia for drug-induced cardiogenic shock: can use early, and perhaps instead of vasopressors
- Intravenous Lipid Infusion for cardiotoxicity from selected drugs: can use before arrest
- Poison Control can help: 800-222-1222

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