Marijuana and Cocaine: Implications for Anesthetist
The oldest known written record on cannabis use comes from the Chinese Emperor Shen Nung in 2727 B.C.
History

- In India it was used recreationally.
- Muslims introduced hashish, whose popularity spread quickly throughout 12th century Persia and North Africa.
- 1545 the Spanish brought marijuana to the New World.
- Marijuana was listed in the United States Pharmacopeia from 1850 until 1942.
- Prescribed for various conditions including labor pains, nausea, and rheumatism.
PISO'S CURE

A MEDICINE FOR
Coughs, Colds, etc

Each fluid ounce contains
1/4 grain Cannabis Indica, 6 minims Chloroform and other valuable ingredients.

Shake the Bottle until all the sediment is mixed.
Marijuana composition.

- Marijuana (pot, hash, grass, cannabis, weed, THC) - obtained from the plant Cannabis sativa.

- Cannabis contains more than 200 different chemicals.

- **THC** (or delta-9-tetrahydrocannabinol) - primary ingredient in marijuana, main psychoactive constituent. It is the chemical that causes marijuana users to feel “high”.

- **Cannabidiol** (CBD) does not activate pathways in the brain that cause a high. It has some therapeutic properties (reduced pain, anxiety, nausea).
- Cannabinol (CBN). Can be helpful in glaucoma and is a potent COX inhibitor.

- **Elimination half-life** in occasional users is ≈ 56 h, while it is ≈ 28 h in chronic users. Complete elimination of a single dose may require up to 30 days.

- Metabolism of cannabinoids occurs in the liver, into more than 20 metabolites, most with psychoactive properties.

- In urine metabolites can be detected for several weeks, hair – 90 days after past use.
Endocannabinoid system (ECS)

- The balance between inhibition and excitation, blood sugar, BP, hormone levels; regulation of sleep and mood;
- This system is involved in maintaining nearly every biological process in all humans.
- ECS comprises:
  - a) two G-protein-coupled receptors (cannabinoid receptors) CB1 and CB2: THC binds and activates them;
  - b) endogenous ligands for these two receptors (endocannabinoids).
Endocannabinoid system (ECS)

- ECS discovered in the mid-1990s by Israeli researcher Dr. Ralph Mechoulam who also identified THC as the main active ingredient in cannabis.
  - Our bodies actually produce the ECs similar to how our body produces narcotic-like endorphins.
  - Contrary to popular belief, endocannabinoids are more strongly linked to ‘runner’s high’ than endorphins.
Dopamine (DA)
- Like caffeine, alcohol, tobacco, amphetamine and cocaine, use of marijuana is associated with a release of dopamine => euphoria
  - directly or indirectly, all addictive drugs work by triggering increases in extracellular DA in a key region of the reward (limbic) system, specifically, in the nucleus accumbens (brain reward center).
  - DA neurons are highly concentrated in nucleus accumbens.
Dopamine

- GABA ↓ the amount of DA released from dopaminergic neurons in the nucleus accumbens.
- GABA is blocked by marijuana compounds (THC) and endocannabinoids => ↑ in the amount of DA released.
Inhibitory drugs decrease post-synaptic transmission

Examples:
- Alcohol, benzodiazepines, THC

What is the effect of tetrahydrocannabinol (THC)?
Normal:
- Dopamine release is moderated (inhibited) by GABA

With THC:
- THC mimics cannabinoids and inhibits GABA release by binding to cannabinoid receptors
- GABA cannot inhibit dopamine release
- More dopamine is released

Effects on mood:
- Dopamine is involved in reward pathways, enhancing feelings of pleasure
- Not as extreme release of dopamine as with cocaine, but still higher than normal

Effects on behaviour:
- intoxication
- hunger
- memory impairment
- potential dependency

http://is.gd/Jellinek
Marijuana receptors

The cannabinoid receptor system has two kinds of receptors:

- **CB1** receptors – found mostly in the brain (cerebellum, basal ganglia, hippocampus) => cannabinoids influence memory processing, pain regulation and motor control.

- Endocannabinoids released by a depolarized neuron bind to CB1 receptors on either pre-synaptic glutamatergic or GABAergic neurons.
Marijuana receptors

- **CB2 receptors** – found mostly on cells of the immune system (spleen, tonsils, T-cells, B-cells and macrophages).

- Selective CB2 receptor agonists have become increasingly popular subjects of research for their potential anti-inflammatory and anti-cancer effects.
Marijuana and anesthetics/drugs

- Limiting glutamate (brain’s main excitatory neurotransmitter) release causes reduced excitation, while limiting GABA release suppresses inhibition.
- Marijuana combined with drugs like alcohol or benzodiazepines and other sedative hypnotic drugs may enhance depression of the central nervous system.
- Increased sleeping time of barbiturates by cannabidiol.
Marijuana and anesthetics/drugs

- Any drug which causes respiratory or cardiac depression may have its effect augmented by cannabis.

- The inhalational anesthetics which sensitize the myocardium to the catecholamines may have a more profound response.
Marijuana and anesthetics/drugs
- Potentiation of the nondepolarizing muscle relaxants (THC possesses muscle relaxant and antispastic properties).
- Combined with amphetamines or cocaine increases the stimulatory effects.
Cannabinoids and anesthetic agents:
- Additive effects in the acutely intoxicated patient (↓ MAC).
- Development of cross-tolerance in the chronic user (↑ MAC).
  - Propofol requires substantially higher doses for the patient who routinely uses marijuana.
    - Cytochrome P-450 2B6 is predominantly involved in the oxidation of propofol by human liver microsomes.
    - Cytochrome P-450 enzyme induction is caused by chronic marijuana smoking.
Cardiovascular effects

- ↓ blood pressure, ↑ heart rate, often by as much as 30%.
- Acute doses of cannabis cause marked tachycardia (can last up to 3 hours) = increased cardiac work and oxygen demand and decreased oxygen delivery; myocardial depression.
  - In acute marijuana use ketamine, pancuronium, atropine and epinephrine should be avoided: ↑ HR
  - Beta-blockers can be beneficial.
Cardiovascular effects

- Tachycardia is most likely related to the anti-cholinergic effects of cannabis.

- Marijuana is a rare trigger for AMI.

- In a constricted vessel, activation of peripheral CB1 receptors with CBD caused the vessels to relax and dilate (cannabinoid attachment to CB1 = ↓cAMP production = vasodilation) => ↓BP
Temperature
- THC depresses the body's temperature regulatory mechanism.
- Cannabinoid administration decreases heat production by altering hypothalamic neurotransmitter production.
- Tylenol works partially by breaking down into a cannabinoid reuptake inhibitor, and therefore shares a pathway with marijuana.
- A drop in body temperature could result if the subject is exposed to a cold environment after smoking.
Non Smoker

Smoker
Respiratory effects

- Deep inhalations and long inspiratory times adopted by cannabis smokers = carboxyHgb concentration per cigarette is approximately five times greater than with a tobacco cigarette.

- Smoke from a cannabis joint contains the same constituents (apart from nicotine) as tobacco smoke including bronchial irritants and carcinogens.

- Possibility of airway hyper reactivity in the marijuana smoker is similar to that of the tobacco smoker.
Respiratory effects

- Upper-airway irritability and impairment of airway epithelial function and damage to bronchial tissue = chronic cough, bronchitis, emphysema and bronchospasm.

- Development of hyper-reactive airways in the chronic marijuana smoker - major cause of intraoperative complications.

- Marijuana smokers can be exquisitely sensitive, even if they have no past medical history significant for reactive airway disease.
Bronchospasm

- Tightened muscle
- Excess mucus
- Inflamed bronchial tube lining
- Alveoli filled with trapped air
Respiratory effects

- Histamine-releasing agents should be avoided.
- Dexamethasone is recommended as prophylaxis for cannabis smokers undergoing general anesthesia.
- Increased frequency of goblet cell hyperplasia (= increased mucus production) and loss of cilia = ↓ capacity to clear airways of the excess mucus.
  => Albuterol, steroids, potent inhalational agents (no Des for induction), LTA
Pregnancy and marijuana

- Readily crosses placenta.

- Acute use: cardiovascular stimulation at moderate doses and myocardial depression at higher doses

- Chronic use: ↑ maternal bronchitis, ↑ respiratory complications with GA

- ↓ uteroplacental perfusion => fetal intrauterine growth restriction (IUGR)

- Low birth weight, preterm labor, ↑ risk of complications during labor, delayed cognitive development in infants.
COCAINE

- Cocaine is a natural product extracted from the leaves of Erythroxylon coca Lam (coca leaves).
- Cultivated widely in South America; the only known natural source of cocaine.
- Normally produced as the hydrochloride salt, it has limited medical use as an ester topical anesthetic.
- The free base (crack) is a smokable form of cocaine.
- Coca leaves have been used as a stimulant by some indigenous people of South America since historical times.
- Purified cocaine has been misused as a central nervous system (CNS) *stimulant* since the early years of the twentieth century.
- Powerful *sympathomimetic* drug.
- Cocaine is highly "reinforcing": when it is given to animals, they will give it to themselves.
- If animals are given the choice, they will put up with electrical shocks and give up food and water if they can get cocaine.
- **Monoamines**: class of chemicals characterized by a single amine group; includes neurotransmitters:
  - **norepinephrine** (noradrenaline) – outside brain – “fight or flight” response, inside brain – hunger, alertness, arousal;
  - **dopamine** (coordinated movement and reward),
  - **serotonin** (sleep and mood).
Without Cocaine

nerve impulse

• dopamine

Vesicle with dopamine

dopamine transporter

Pre-synaptic neuron

Synaptic cleft

Post-synaptic neuron

dopamine receptors

nerve impulse
- Cocaine blocks reuptake of dopamine, norepinephrine, and serotonin.

- Binds to the monoamine transporters (which are located in presynaptic terminals) that normally remove the excess of these neurotransmitters from the synaptic gap =>

- Prevents neurotransmitters from being reabsorbed by the neurons that released them = ↑ their concentration in the synapses.
- DA reuptake blockade accounts for most of the drug’s reinforcing, stimulating effects. Cocaine activates the **mesolimbic** system - a system of dopaminergic neurons.

- Snorting cocaine produces a relatively slow onset of the high, but it may last from 15 to 30 minutes.

- High from smoking is more immediate but may last only 5 to 10 minutes.
- The “crash” occurs because after the initial “high” normal levels of dopamine are undershot: neurons run out of DA neurotransmitters.

- The receptors for DA then disappear as a response mechanism to the high availability of the neurotransmitter.

- ↑↑ DA during cocaine high -> production of less DA, downregulation of DA receptors, reduced number of DA neurons =》

  - anhedonia, need for larger dose
  - tolerance, addiction
Exogenous pyrogens (infectious agents, toxins, tumors)

Monocytes, macrophages, endothelial cells, other immune cells

FGE 2

Antipyretics

Heat production (involuntary muscle contractions)

Heat conservation (vasoconstriction, behavior changes)

NSAIDs

Anterior Hypothalamus

Elevated Thermoregulatory set-point
Effects of cocaine on brain

- Euphoria (cocaine high), psychomotor agitation
- hyperthermia
- intracerebral hemorrhage
- ischemic stroke (cerebral vasoconstriction) or hemorrhagic stroke
- seizures secondary to acute hyperthermia (severe vasoconstriction hinders dissipation of body heat)
- rupture of an aneurysm
- acute intoxication $\uparrow$ MAC of volatile anesthetics
- chronic use $\downarrow$ dose of agents (catecholamine depletion)
Cardiovascular effects of cocaine.

- Stimulates the sympathetic NS: inhibition of catecholamine uptake into postganglionic sympathetic nerve terminals.
- Stimulates release of endothelin-1, a potent vasoconstrictor, from endothelial cells and inhibits nitric oxide production, the principal vasodilator produced by endothelial cells.
- Increases myocardial oxygen demand by increasing both heart rate and blood pressure.
- ↓ oxygen supply via coronary vasoconstriction (→ ischemia)
Cardiovascular effects of cocaine.

- Higher incidence of MI and the risk of MI increases by 24-fold in the first hour after cocaine use.

- Sodium channel blockade = QRS and QTc prolongation => cocaine-induced arrhythmias, especially torsades de pointes.
Lungs and respiratory system

- Snorting cocaine damages the nose and sinuses.
- Regular use can cause nasal perforation.
- Smoking crack cocaine irritates the lungs and can cause permanent lung damage.
- Direct irritant of the airways.
- Damages bronchial epithelial cells, stimulating and exposing vagal receptors, causing severe *bronchospasm*, and exacerbating asthma.
Beta-2 adrenoceptor agonists

1. Terbutaline
2. Clenbuterol
3. Salbutamol
4. Salmeterol
5. Pirbuterol
6. Isoetarine
7. Orciprenaline

β-2 receptors

- Bronchial smooth muscle
  - Bronchodilation
- Uterine muscle
  - Uterine relaxation (tocolysis)
Bronchospasm treatment

- Deepen level of anesthesia: volatile agent, propofol (ketamine, lidocaine)
- 100% O2
- B-2 agonist
- Epinephrine
- Corticosteroids
- Aminophylline IV
Lungs and respiratory system

- “Crack lung” is a more severe condition that develops in individuals with heavy crack cocaine use.
  - Characterized by severe inflammation and scarring of lung tissue.
  - Positive pressure ventilation may precipitate alveolar hemorrhaging.
  - Plateau pressures $<$ than 30 cmH2O to avoid barotrauma.
The **diaphragm** is a muscle below the lungs. It flattens to draw air in as you inhale, then rises as you exhale.

Alveoli are air sacs at the ends of the bronchioles. Bronchioles are the smallest airways.

Blood vessels surround the alveoli.

Damaged alveoli supply less oxygen to the body.

Inside alveoli

**O₂**

Inside blood vessel

**CO₂**

**Interstitium**

**O₂**

**CO₂**

**Scarred interstitium**
- Physiologic effects of cocaine ingestion are shortlasting.
- Chronotropic effect of IV cocaine peaks at 5–15 min while the half-life of this effect is 24 min.
- After intranasal ingestion elimination half-life is 45–90 min.
- Metabolites can be detected in urine for 3–7 (16 days in chronic heavy users) so that a patient may test positive for cocaine while not being acutely toxic.
Cocaine metabolism

- Ingested cocaine is rapidly hydrolysed, primarily by plasma (pseudocholinesterase) and liver esterases, to ecgonine methyl ester (EME) and benzoylcegonine.

- These metabolites possess no cocaine-like stimulation effects, detected in urine and are responsible for positive urine testing after cocaine ingestion.
Anesthesia and cocaine

- Most frequent problem - **severe hypertension** (induction, laryngoscopy, and tracheal intubation).

- *Ketamine* increases levels of circulating catecholamines, and should be avoided.

- *Halothane* sensitizes myocardium to catecholamines; should be avoided.

- *Etomidate* should be used with caution: possible myoclonus, seizures and hyperreflexia.

- *Propofol, Benzodiazepines, Thiopental* – safe.
Nitrates

The major anti-ischemic mechanism

Low doses:

- ↓↓ Preload
- ↓ Myocardial O₂ demand

High doses:

- ↓ Afterload
- ↓ Myocardial O₂ demand

↑ O₂ supply by dilation of large Epicardial coronary arteries

Adapted From Chong & Michel (2012)
Management of hypertension

- **Nitroglycerin and nitroprusside** (nitric-oxide mediated vasodilators) - effective at lowering BP and reversing coronary arterial vasoconstriction, but not heart rate.

- **Nitroglycerin** - useful for cocaine-induced chest pain. Possibility of reflex tachycardia.

- **Phentolamine** (alpha-blocker) may be used to treat cocaine-induced hypertension and coronary arterial vasoconstriction, does not reduce heart rate.
Management of hypertension

- **Calcium channel blockers** may be used to treat hypertension and coronary arterial vasoconstriction, but fail to lower HR.

- **Non-dihydropyridine** calcium channels blockers (*diltiazem* and *verapamil*) are preferable, as dihydropyridine agents (nifedipine) have much higher risk of reflex tachycardia.

- **Labetalol** (alpha and beta-blocker), reverts hypertension and tachycardia caused by cocaine, but has no demonstrable effect on coronary vasoconstriction. The antagonism of beta-adrenergic receptors is greater than its effects on alpha-adrenergic receptors.

- Titration of *esmolol* and *nitroprusside*
Ephedrine Mechanism

- MAO metabolizes cytoplasmic NE
- NE = Norepinephrine
- Ephedrine
  - reverse transport
  - Direct effects on: α & β receptors, TAARs
- Cytoplasmic pool
  - The cytoplasmic "pool" is finite & can be depleted by repetitive doses of ephedrine
- NE, vesicles
- NE, NET
- Stimulates adrenergic receptors
Management of hypotension

- **Phenylephrine**, a selective alpha-1 adrenergic receptor agonist is the drug of choice for hypotensive patients.

- **Epinephrine** should be avoided

- **Ephedrine** (synthetic noncatecholamine sympathomimetic; indirect alpha- and beta- adrenergic stimulation via norepinephrine release at sympathetic nerve endings, direct stimulation of alpha- and beta- receptors)

  - should be avoided due to the excess of catecholamines from cocaine’s effects (in acute intoxication).
Chronic use of cocaine

- Can cause left ventricular hypertrophy, systolic dysfunction, dilated cardiomyopathy, and myocardial depression.

- Response to ephedrine is ↓ due to depletion of NE stores (analogous to tachyphylaxis after repeated doses of ephedrine).

- Low doses of phenylephrine usually restore BP to normal levels.
Chronic use of cocaine

- Prolonged response to **succinylcholine** with low levels of pseudocholinesterase.

- In acute intoxication cocaine competes with succinylcholine for metabolism by pseudocholinesterase, decreasing the metabolism of both.

- With additive effect of cocaine reducing seizure threshold, **lidocaine** should be avoided as a treatment for ventricular dysrhythmias.
Pregnancy and cocaine
- ↑ likelihood of *placental abruption* and emergent CS.
- Acute cocaine intoxication *can mimic preeclampsia, eclampsia and MH*.
  - Fetal complications: fetal anomalies (*1st trimester*), premature labor, IUGR, uteroplacental insufficiency, acidosis, hypoxia, fetal distress. Rapid transplacental diffusion and high fetal cocaine blood levels.
  - *Epidural preferred* to control catecholamine release associated with labor.
MAO-Is

- Monoamine Oxidase (MAO) is an enzyme that breaks down 5-HT, NE, & DA

(A) Presynaptic terminal
(B) Postsynaptic cell