

CLINICAL PROBLEM SET # 8

Patient
Male, 62 years old
Chief Complaint
"My son is your patient, Doctor. I am from Libya and came to visit him and his family. Just before I left for this trip, my family dentist told me he could not save this tooth (<i>the patient is pointing to the right side of the mandible</i>). My son really trusts you and wanted me to wait with the extraction until you see the tooth. But now the tooth started hurting really badly... I have only emergency medical insurance, but my son will pay for the treatment – whatever you decide is best for me. I trust you..."
Background and/or Patient History
Truck driver; Smoker, 40-pack-years; A head trauma 20 years ago with one episode of generalized seizures.
Medications:
Valproic Acid (1000 mg daily)
Current Findings
Non-restorable tooth #29; Caries of tooth #30. Temp: 98.4 F BP: 125/85 mmHg HR: 85 bpm Height: 5'4", Weight: 125 lb The extraction of tooth #29 under local anesthesia went well and was unremarkable. The dentist prescribed Tylenol with Codeine #3 tablets (300 mg Tylenol with 30 mg Codeine; three times a day) to relieve the post-surgical pain.

Four Days Later:

The patient's consciousness rapidly deteriorated and he became unresponsive. His son called 911. The patient was taken to the hospital, where they measured arterial blood gases. A partial pressure of oxygen was 56 mmHg (a fraction of inspired oxygen 0.5) and carbon dioxide 80 mmHg. The patient was treated with noninvasive ventilation and transferred to the ICU. The neurological exam revealed a score of 6 on the Glasgow Coma Scale (the patient did not open eyes, and responded neither verbally nor by limb withdrawal to pain stimulation). The pupils were miotic.

After two hours of assisted ventilation, the partial pressures of oxygen and carbon dioxide were 72 mmHg and 54 mmHg, respectively, but no improvement of the neurological status. The serum urea nitrogen and creatinine levels were elevated, but subsequently normalized with hydration. The blood level of ammonia was normal. The serum level of Valproic Acid was within the therapeutic range.

1. What is the likely mechanism of the patient's current condition? How could it be related to the dental treatment he received four days earlier?
2. How should the patient be treated in the ICU besides the assisted ventilation? Please justify your answer.
3. If his son needed a similar dental treatment, what approach would you take? Would there be a need for a modification to your standard protocol?
4. Have you discussed before a case with a similar dental treatment strategy? If so, what was the outcome?

Phenytoin (oral). Ther. Cp 20 mg/L ASAP. What is the initial dose? F 90%; Prot. Binding 90%; CL 0.2 L/kg/day; Vd 0.8 L/kg; Patient's b.w. 50 kg, Plasma

Vol. 2 L.

40 mg	A
44.4 mg	B
444 mg	C
200 mg	D
222 mg	E
2.2 g	F
800 mg	G
889 mg	H
8.9 g	I
Impossible to calculate because Phenytoin follows capacity-limited metabolism	
J	

This was an epilepsy case, that she was taking Phenytoin.
We are calculating initial dose.

Answer: H

We are looking for loading dose, we want fast action.

J: capacity-limited meaning first-order until saturated and then zero-order, but half life is what you cannot calculate after that, it depends on the concentration, but we are looking for dose. So you need the volume.

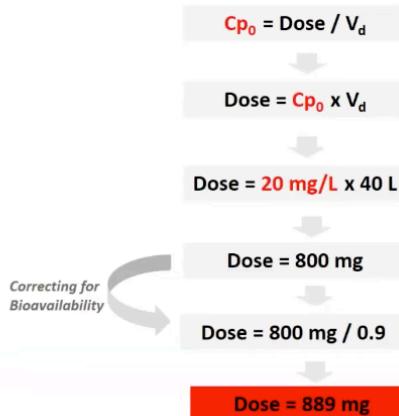
Tx Idiopathic Epilepsy: Phenytoin (oral). Therapeutic plasma concentration **20 mg/L** ASAP.

What is the initial dose of Phenytoin?

F 90%; Protein Binding 90%; pKa = 3.98; LogP 3.4; t_{1/2} 8-60 hrs (capacity-limited metabolism); CL 0.2 L/kg/day; Vd 0.8 L/kg; Tmax 3-12 hrs. Patient's b.w. 50 kg, plasma volume 2 L.

$$V_d = 0.8 \text{ L/kg} \times 50 \text{ kg} \quad V_d = 40 \text{ L}$$

- A. 40 mg
- B. 44.4 mg
- C. 444 mg
- D. 200 mg
- E. 222 mg
- F. 2.2 g
- G. 800 mg
- H. 889 mg
- I. 8.9 g
- J. Impossible to calculate because Phenytoin follows capacity-limited metabolism



If you have a question about drug that stays completely in circulation and you are not given Vd, plasma volume is the same thing.

A drug is eliminated according to first-order kinetics. Its Cp at time 0 is 60 mg/L. After 8 h., Cp drops to 15 mg/L. The elimination half-life is:

2 hours	A
2.67 hours	B
4 hours	C
32 hours	D
impossible to deduce from these data since the drug's elimination follows first-order kinetics	E

Answer: C

A lipophilic drug (F 20%, first-pass hepatic) is inactivated in the liver and excreted through bile and kidney. Cp of Active Drug will be INCREASED in the following conditions, EXCEPT:

An advanced age	A
Congestive heart failure	B
Liver disease	C
Obstruction of bile ducts	D
Kidney disease	E
Conditions resulting in Pharmacokinetic Tolerance	F
Inhibition of the enzyme metabolizing the drug	G

Answer: F

B:

Drug Action Modifiers (Cont'd)

6. Pathological States:

A. Gastrointestinal Diseases: Decreased absorption of orally-administered drugs (e.g., achlorhydria, diarrhea, coeliac disease, other malabsorption syndromes).

B. Liver Dysfunction (specific hepatic disease, infection, reduced blood flow to the liver, etc):

- i) ↓ hepatocellular function ⇒ ↑ bioavailability of drugs with high first-pass metabolism,
- ii) ↓ serum albumin ⇒ ↓ protein binding of drugs (e.g., Diclofenac, Warfarin) ⇒ ↑ drug in free form,
- iii) ↓ drug metabolism and elimination (e.g., Lidocaine, Morphine) ⇒ ↑ plasma drug concentration & ↑ duration of drug action (⇒ ↑ drug half-life),
- iv) Prodrugs with hepatic metabolism for activation (e.g., Bacampicillin) may become less effective,
- v) ↓ biliary excretion of drugs
- vi) Insidious effects of drugs that are potentially toxic to their primary organs of elimination (e.g., Acetaminophen accumulation ⇒ hepatic necrosis ⇒ further impairment of drug metabolism)

C. Kidney Disease:

- i) ↓ clearance of drugs that are primarily excreted unchanged ⇒ ↑ drug half-life (⇒ ↑ dosage interval),
- ii) ↓ serum albumin ⇒ ↓ protein binding of acidic drugs ⇒ ↑ drug in free form,
- iii) ↓ excretion of inactive metabolites ⇒ ↑ risk of untoward reactions,
- iv) renal failure ⇒ ↑ permeability of blood-brain barrier ⇒ ↑ effectiveness of centrally-acting drugs (e.g. opiates, barbiturates, benzodiazepines): GFR ↓↓⇒ loop and thiazide diuretics ineffective.

D. Congestive Heart Failure:

- i) mucosal edema, vasoconstriction ⇒ ↓ drug absorption from the GI tract,
- ii) ↓ perfusion ⇒ ↓ Vd (but ↑ Vd for some drugs due to ↑ extracellular fluid),
- iii) ↓ liver perfusion, ↓ GFR/↑ tubular reabsorption ⇒ ↓ drug elimination ⇒ ↑ drug half-life

E. Thyroid Disease (non-pharmacokinetic effects): Hypothyroidism ⇒ ↓ sensitivity to CNS depressants; Hyperthyroidism ⇒ ↑ systemic effects of Epinephrine; ↓ potency of morphine

As long as absorption is several times faster than elimination, it will not have much effect on drug effectiveness, so even though absorption is decreased on CHF it is not a major issue

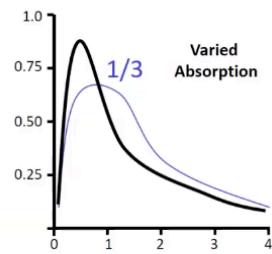
But Vd is decreased

CHF affects all four of ADME

Outcomes are increased drug action/duration

Congestive Heart Failure & Drug Action

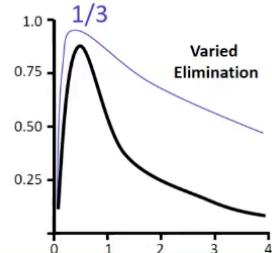
- i) Mucosal Edema / Vasoconstriction ⇒
↓ Drug Absorption from the GI Tract



- ii) ↓ perfusion ⇒ ↓ Vd
↑ Vd for some drugs
due to ↑ extracellular fluid

$$C_{p_0} = \frac{D}{V_d}$$

- iii) ↓ Liver Perfusion ⇒
↓ Drug Elimination
⇒ ↑ Drug Half-Life



- iv) ↓ GFR / ↑ Tubular Reabsorption ⇒
↓ Drug Elimination
⇒ ↑ Drug Half-Life

Question about Tardive Dyskinesia:

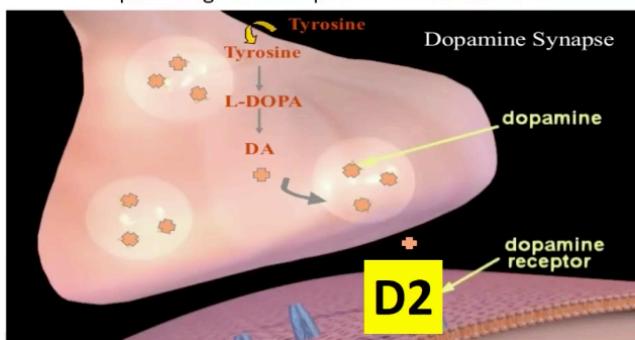
"...genetic polymorphisms of dopaminergic and antipsychotic drug receptor targets (...) explain tardive dyskinésias and how polymorphisms in receptors may lead to these episodes of undesirable side-effects..."

Kunal Mansukhani

PSYCHOSES

The Dopamine Hypothesis

The underlying pathophysiologic basis of psychoses is hyperactivity of dopaminergic D2 receptor neurotransmission.



There is enhanced dopaminergic transmission and the mechanism is through D2 receptors and street drugs all act through enhancing dopaminergic transmission

This is a slide from our future lecture:

Typical Antipsychotics

Mechanism of Action:
Blockade of Dopamine D2 receptors \Rightarrow ↓ DA transmission in mesolimbic dopamine pathways.

Blockade of histamine (H1)* and muscarinic (M1)* receptors \Rightarrow sedation (at times desirable).
*except Haloperidol - low H1/M1 affinity.

Indications:

- The positive symptoms of psychosis seen in most psychotic disorders

Side effects:

Neurological (extrapyramidal syndrome): Acute dystonia (spasm of muscles of tongue, face, neck, back), Parkinsonism, Perioral tremor ("rabbit syndrome"), Tardive dyskinesia (involuntary, tic-like movements of the face, eyelids, mouth), Neuroleptic malignant syndrome (extreme rigidity, fever, unstable BP; fatal!).

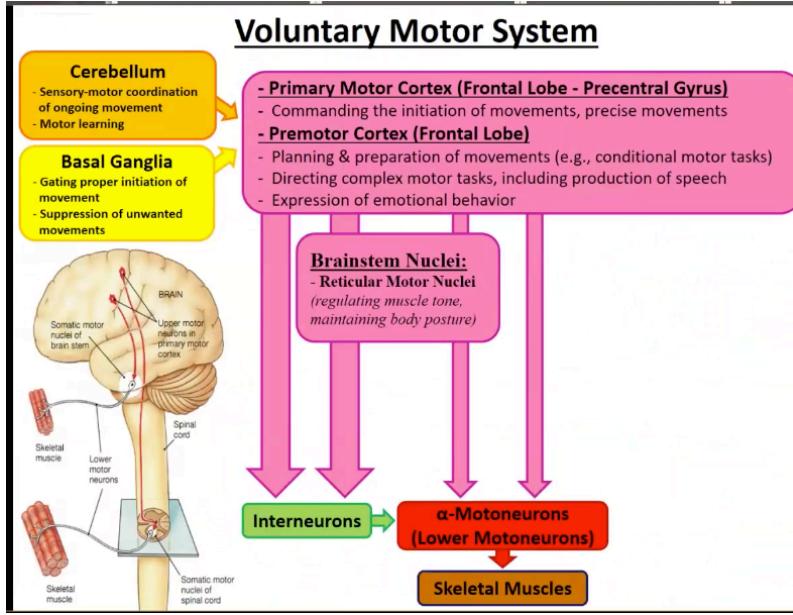
Cardiac: ventricular arrhythmias and sudden cardiac death!

Metabolic (greatest concern during long-term treatment): weight gain, dyslipidemia (elevated serum triglycerides) and impairments of glycemic control.

The slide includes images of three antipsychotic medications: Chlorpromazine Hydrochloride Tablets, USP (10 mg), Haloperidol Injection, USP (5 mg/mL), and Fluphenazine Hydrochloride Injection, USP (2.5 mg/mL). The text on the slide is organized into sections: Mechanism of Action, Indications, and Side effects. Several sections and specific text entries are circled in red.

Typical antipsychotics block dopamine D2 receptors.

Side effects are tremors



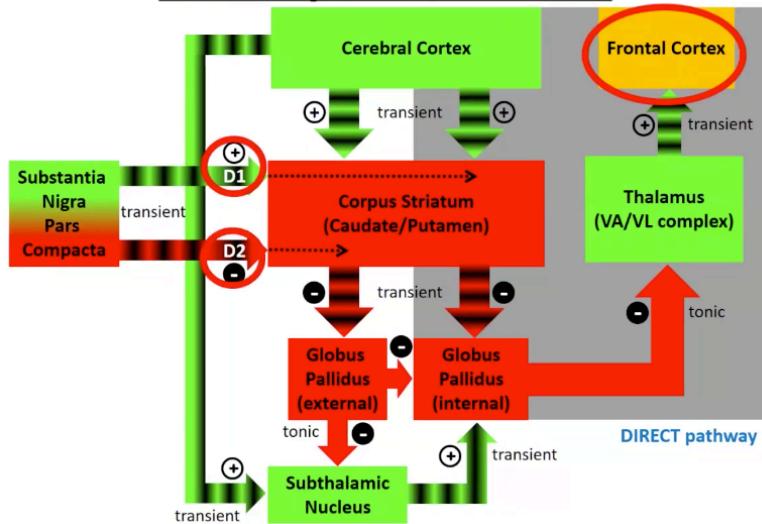
Voluntary movement controlled by primary motor cortex.

Two important structures in brain that control voluntary movement: cerebellum and basal ganglia

Cerebellar lesion causes intension tremor, for Parkinson's disease there is resting tremor.

Basal ganglia is for initiating movement and suppression of unwanted movement.

Basal Ganglia: Internal Circuits



Information comes from the frontal cortex but is under control of this circuit in basal ganglia and D1 and D2 dopaminergic receptors are critical.

Polymorphisms makes same drug act with different strength/efficacy for receptors

Polymorphisms change the receptors on which the anti-psychotic drugs act

Which adverse reaction is most likely to be genetically-determined?

Allergic reactions	A
Extension effects	B
Iatrogenic effects	C
Idiosyncrasies	D
Mutagenic effects	E

Answer: D

E: mutagenesis is drugs that affect the genes

Inhalation anesthesia with Isoflurane might lead to Malignant Hyperthermia if the patient carries a mutation in the gene encoding:

CYP2D6	A
Ryanodine Receptor 1	B
Dopaminergic Receptor	C
Beta-1-Adrenergic Receptor	D
Glucose-6-phosphate dehydrogenase (G6PD)	E

Answer: B

The 'Ultrarapid Metabolizer' phenotype is most likely to be a result of:

Gene deletion	A
Defective splicing	B
Missense SNPs	C
Gene duplication	D
A, B, and C are correct answers	E

Answer: D

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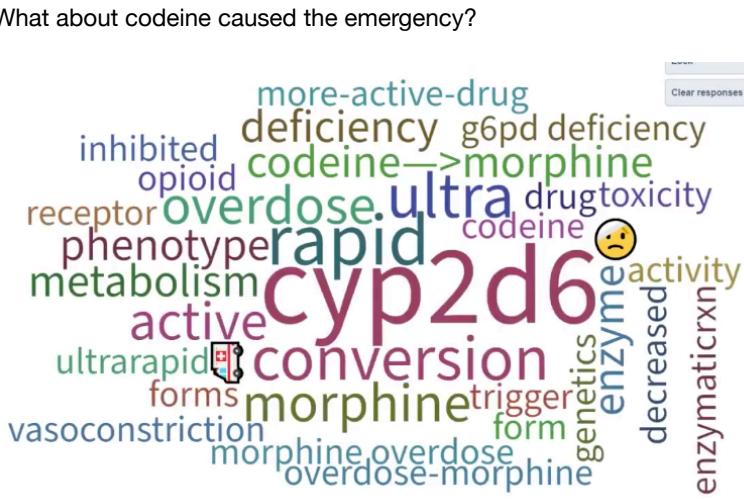
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3. If his son needed a similar dental treatment, what approach would you take? Would there be a need for a modification to your standard protocol?
4. Have you discussed before a case with a similar dental treatment strategy? If so, what was the outcome?

In ONE WORD: what part of the dental treatment could have precipitated the patient's condition?



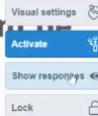
Codeine, tylenol, extraction, valproic acid, analgesics in general
Anesthesia blocks all types of sensation
Analgesia is just pain

In a SHORT PHRASE: what is the mechanism patient's emergency?



CYP2D6 metabolizes codeine to the more active substance morphine
This patient has mutation that makes him ultra rapid so there are higher concentrations of morphine
Those who are not interested in smoking have a slower metabolism, heavy smokers are ultra rapid metabolizers
Most critical side effect of morphine overdose is respiratory depression
So you need to give him oxygen

In a SHORT PHRASE: how should the patient be treated in the ICU?



You know the problem is high levels of morphine, how do you remove the effect of morphine? It acts on the respiratory

non-competitive. antagonist
non-competitive-antagonist
body competitive agent remove dialysis
naloxone
excretion increase antagonist
narcam reversal morphine flush norcan
antagonist narcancan ventilation

You need an antagonist of the morphine receptor

Would there be a need for a modification to a standard Tx protocol for the patient's son?

YES

A

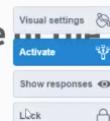
NO

B

YES

You can test the son for polymorphisms, but the simplest way is to avoid codeine
Its a genetic disorder so think about family members and how you would treat them

In a SHORT PHRASE: what was the outcome
case we discussed before?



(Lady who thought she got pregnant after dental treatment, she had tooth extracted, she also got codeine with tylenol)

enterohepatic cycling
called working codeine
decreased conversion
didn't work
 morphine
conversion medicine
idk cimetidine pain
patient

Drug did not work because her enzyme she was a poor metabolizer, a very large percentage of the population are low metabolizers, this means codeine is very ineffective as an analgesic

A man with poor CYP2C19 phenotype and acute
cardiac ischemia. Which of the following drugs
may cause unexpected results?

Clopidogrel	A
Codeine	B
Warfarin	C
Isoflurane	D
Ethanol	E

Answer: A

Clopidogrel is an anti-platelet agent, it is a prodrug so it needs to be converted to have anti-platelet effect

A student-volunteer's genome includes a gene polymorphism associated with an increased risk of hemolytic anemia. Which of the following proteins is it?

CYP2D6	A
CYP2C19	B
CYP2C9	C
Dopaminergic receptor	D
Glucose-6-phosphate dehydrogenase (G6PD)	E

Answer: E

A child is in coma with cyanosis. She was given codeine with acetaminophen. The child became unresponsive and "turned blue". Which allele might be responsible?

CYP2D6*1x3	A
CYP2C19*2	B
CYP2C9*3	C
UGT1A1*28	D
DYPD*2A	E

Answer: A