Methanol and Isopropanol Toxicology with Clinical Applications

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Learning Objectives

After reviewing this material the participant should be able to:

1. List the sources and trends in poisoning from methanol and isopropanol

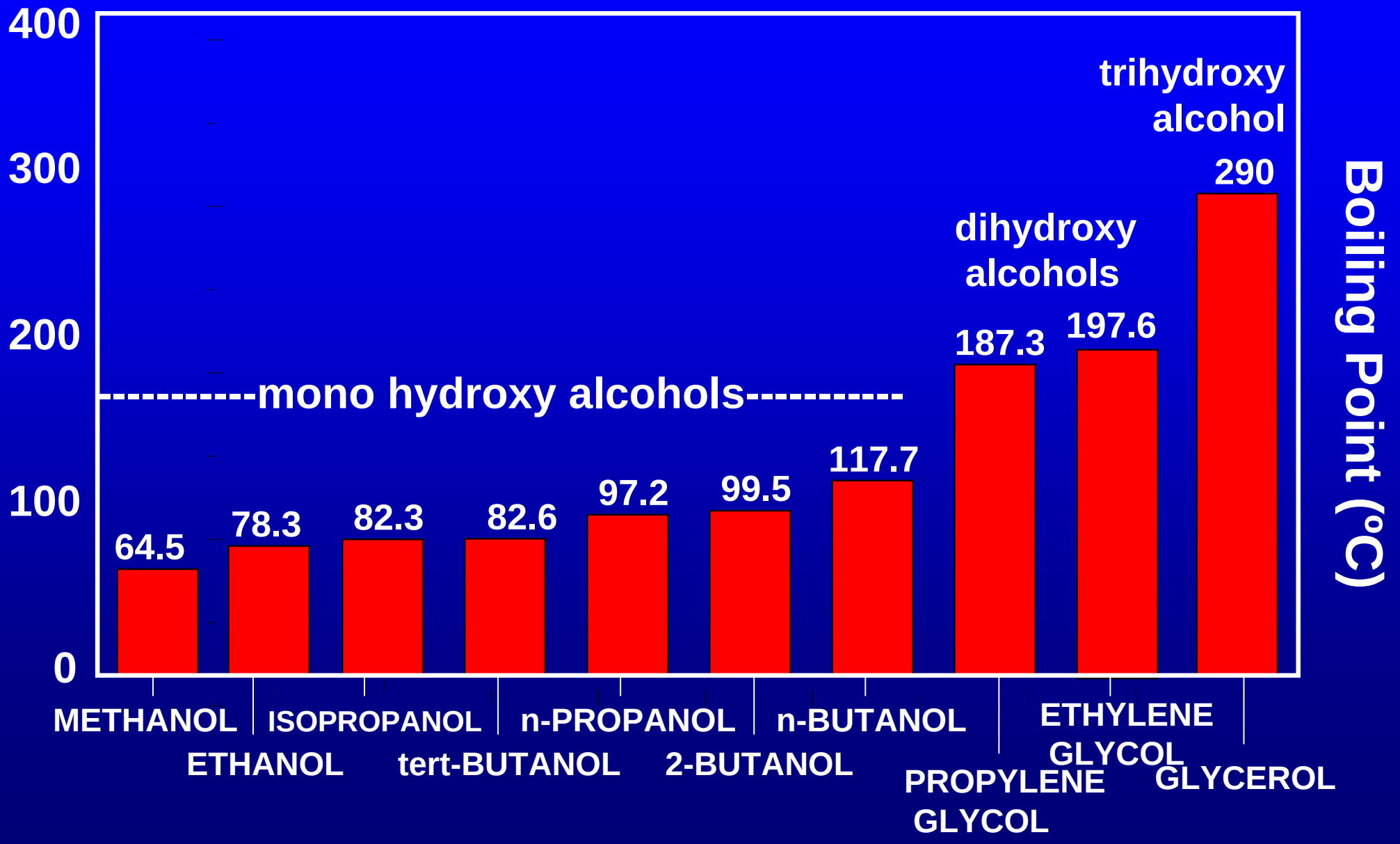
2. Describe methanol and isopropanol pharmacodynamics and the clinical findings in acute poisonings

4. Utilize pharmacokinetic principles and calculations for interpretation of laboratory findings

5. Describe the role of the clinical toxicology laboratory in the identification and monitoring of acute poisoning

6. Apply toxicology principles to clinical case studies

"Volatile Alcohols" - A Relative Term



Properties of Ethanol, Methanol and Isopropanol

	Ethanol	Methanol	Isopropanol
Formula	C_2H_5OH	CH_3OH	C_3H_7OH
Mol wt, daltons	46.07	32.04	60.10
CAS #	64-17-5	67-56-1	67-63-0
Physical Properties:			
b.p. at 1 atm (ºC)	78.3	64.5 ºC	82.3 ºC
Spec. grav. at 20 ºC	0.790	0.792	0.785
Vapor pres. at 20 ºC	43 mmHg	96 mmHg	
Thresholds:			
Odor	10 ppm	100 ppm	90mg/m^3
Inhalation toxicity, ppm	1000	200	400
Lethal oral dose, g/Kg	5-8 (3 peds)	1-5	3-4
Lethal blood level, mg/dL	350-500	150-200	130-200

Clinical and Toxicological Properties

	Ethanol	Methanol	Isopropanol
Odor	+	-	+ (acetone)
CNS depression	+	+	+
Convulsions	+	+	+
Time to peak blood level without a meal	15-90 min	similar to ethanol	similar to ethanol
Half-life in Blood $T_{1/2}$	2-14 hr(zero order)	2-24hr (zero order)	3-6.6hr (first-order)
V_d in blood	0.6 (approx.)	0.6 (approx.)	0.6 (approx.)
Metabolic acidosis	- to mild lactic acid or ketoacidosis	severe acidosis from formic acid	- to mild lactic acid acidosis
Major metabolite	acetaldehyde	formic acid	acetone (also CNS depressant
Anion gap	-/+	+	-/+
Osmolal gap	+	+	+
Osmolal equivalent of 1mg/dL alcohol	0.23 mOsmol/Kg	0.34 mOsmol/Kg	0.17 mOsmol/Kg

Case 1: Methanol Poisoning

History and Physical Exam

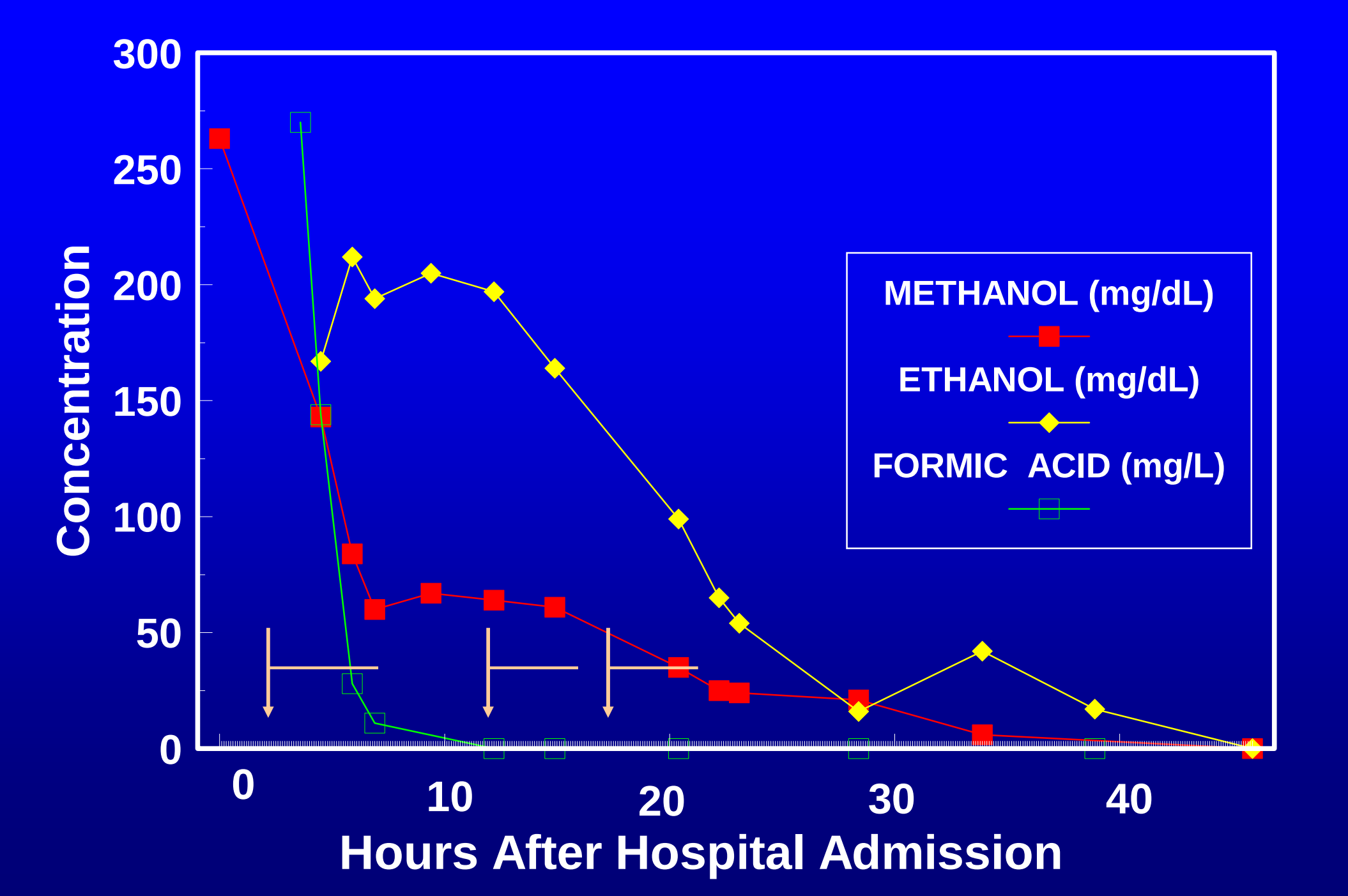
45-year-old white male (80 kg wt)
ingested 2/3 gallon windshield solvent (30% v/v methanol)
unconscious, hypothermic, dilated pupils, mild papilledema

Admission Labs

Na+ 154 mEq/L, K+ 4.4 mEq/L, Cl- 106 mEq/L, CO2 6 mmol/L, anion gap 46 mEq/L, osmolality 465 mOsm/L, BUN 14 mg/dL, creatinine 1.6 mg/dL, glucose 225 mg/dL, CK 4662 IU/L, arterial pH 6.76, PCO2 38 mmHg and PO2 180 mmHg (50% O2), serum methanol 260 mg/dL (82 mmol/L) formate 27 mg/dL (5.9 mmol/L)

Treatment

intravenous ethanol and hemodialysis started 2 hrs after admission for an initial duration of 5.5 hrs and two subsequent 4 hour dialysis


300
250
200
150
100
50
0
Concentration
0
10
20
30
40
Hours After Hospital Admission
METHANOL (mg/dL)
ETHANOL (mg/dL)
FORMIC ACID (mg/L)

Methanol in Consumer Products

gas-line antifreezes (99-100% v/v)
windshield washer fluids (17-95%)
windshield deicers (4-89%)
duplicating fluids (60-90%)
paint removers (3-50%)
model airplane fuels (43-77%)
carburator fluids (1-38%)
ethanol denaturants (2-5%)
solid can fuels (<4%)
glass cleaners (1-40%)

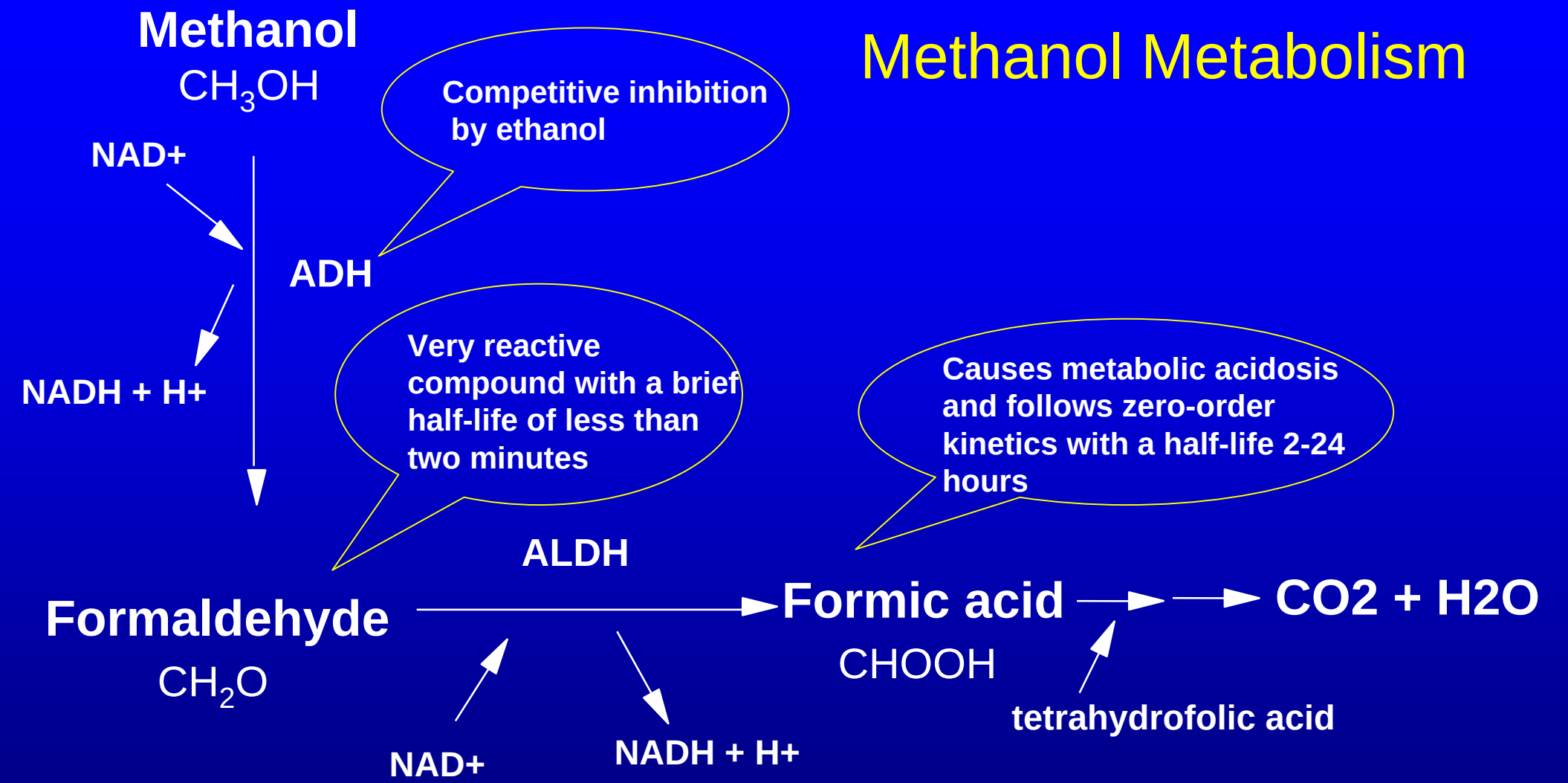
Methanol Toxicodynamics

- Initially methanol poisoning causes nausea, abdominal pain, lethargy, confusion
- Severe poisoning progresses to anion-gap metabolic acidosis, coma, seizure, and respiratory/circulatory failure
- Metabolic acidosis and optic neuropathy are due to formic acid
- Lactic acid accumulation is sometimes found in methanol poisoned patients due to methanol-induced hypotension

Methanol Toxicokinetics

- Rapid absorbtion (oral, respiratory or dermal)
- Rapid distributed (approx. Vd 0.6 L/kg)
- Peak blood level: 15-90 minutes post-ingestion
- Elimination: metabolism (90-95%), urination (<5%) and respiration (limited route in humans)
- Blood clearance rate zero order
  - mild intoxication: half-life 14-20 hrs
  - severe intoxication: half-life 24-30 hours
- Methanol half-life prolonged by ethanol to >30 hours and reduced by dialysis to <3.5 hours

Methanol Metabolism



Dialysis of Methanol and Formic Acid

- Half-life without dialysis or methanol
  - formate 2-24 hrs
  - methanol 14-30 hrs
- Half-life without dialysis
  - formate 0.8-2.8 hrs
  - methanol <3.5 hrs

Standard Pharmacokinetic Equation

$$Cp(g/L) = \frac{D(g)}{Vd(L/Kg) \times W(Kg)}$$

where Cp = plasma or serum concentration in grams per liter
D(g) = total ethanol content of body in grams
Vd(L/Kg) = volume of distribution in liters per kilogram
W (Kg) = body weight in kilograms

Rearranged Pharmacokinetic Formula

$$D(g) = Cp(g/L) \times Vd(L/Kg) \times W(Kg)$$

CLINICAL CASE DISCUSSION

Re-Cap of Case 1: Methanol Poisoning

History and Physical Exam

45-year-old white male (80 kg wt)
ingested 2/3 gallon windshield solvent (30% v/v methanol)
unconscious, hypothermic, dilated pupils, mild papilledema

Admission Labs

Na+ 154 mEq/L, K+ 4.4 mEq/L, Cl- 106 mEq/L, CO2 6 mmol/L, anion gap 46 mEq/L, osmolality 465 mOsm/L, BUN 14 mg/dL, creatinine 1.6 mg/dL, glucose 225 mg/dL, CK 4662 IU/L, arterial pH 6.76, PCO2 38 mmHg and PO2 180 mmHg (50% O2), serum methanol 260 mg/dL (82 mmol/L) formate 27 mg/dL (5.9 mmol/L)

Treatment

intravenous ethanol and hemodialysis (started 2 hrs after admission for an initial duration of 5.5 hrs and two subsequent 4 hour dialysis)

Case 1: Questions

1. What is the severity and cause of acidosis in this patient?

2. What was the osmolal gap when the patient initially presented in the emergency department and is the gap consistent with the concentration of methanol?

3. What is the total amount of methanol in the body when the serum methanol level was 260 mg/dL, assuming V_d of 0 .6 L/Kg?

4. What is the affect of ethanol on methanol clearance from the body and what is the relative clearance rate of methanol and formic acid during dialysis?

5. Assuming a V_d of 0.6, how many grams of ethanol should given to the patient as a loading dose to achieve a serum concentration of 100 mg/dL?

Case 1

1. What is the severity and cause of acidosis in the patient?

Case 1

2. What is the osmolal gap when the patient initially presented in the emergency department and is the gap consistent with the concentration of methanol?

Case 1

Serum Measurements:
Na 154 mEq/L, Cl 106 mEq/L, CO2 6 mmol/L, BUN 14 mg/dL, gluc 225 mg/dL, Osmolality 465 mOsm/kg, methanol 260 mg/dL

Calc. Osmolality: 2Na + glucose/18 + BUN/2.8 = 326 mOsm/kg

Osmol gap: 465 mOsm/kg - 326 mOsm/kg = 139 mOsm/kg

Osmol Equivalent of 260 mg/dL of Methanol:

$$260 \text{ mg/dL} \times \frac{0.34 \text{mOsm/kg}}{1 \text{ mg/dL methanol}} = 88 \text{ mOsm/kg}$$

Case 1

3. What is the total amount of methanol in the body when the serum methanol level was 260 mg/dL, assuming a V_d of 0.6 L/Kg?

formula: $D(g) = Cp(g/L) \times Vd(L/Kg) \times W(Kg)$

$D(g) = 2.6\ g/L \times 0.6\ L/Kg \times 80\ Kg = 125\ g$

where D(g) = total ethanol content of body in grams
Cp = plasma or serum concentration in grams per liter
Vd(L/Kg) = volume of distribution in liters per kilogram
W (Kg) = body weight in kilograms

Case 1

4. What is the affect of ethanol on methanol clearance from the body and what is the relative clearance rate of methanol and formic acid during dialysis?

Case 1

5. Assuming a V_d of 0.6, how many grams of ethanol should given to the patient as a loading dose to achieve a serum concentration of 100 mg/dL?

formula: $D(g) = Cp(g/L) \times Vd(L/Kg) \times W(Kg)$

$D(g) = 1.0\ g/L \times 0.6\ L/Kg \times 80\ Kg = 48g$

where D(g) = total ethanol content of body in grams
Cp = plasma or serum concentration in grams per liter
Vd(L/Kg) = volume of distribution in liters per kilogram
W (Kg) = body weight in kilograms

ISOPROPANOL INTOXICATION

Case 2: Isopropanol Poisoning and Treatment

History and Physical Exam

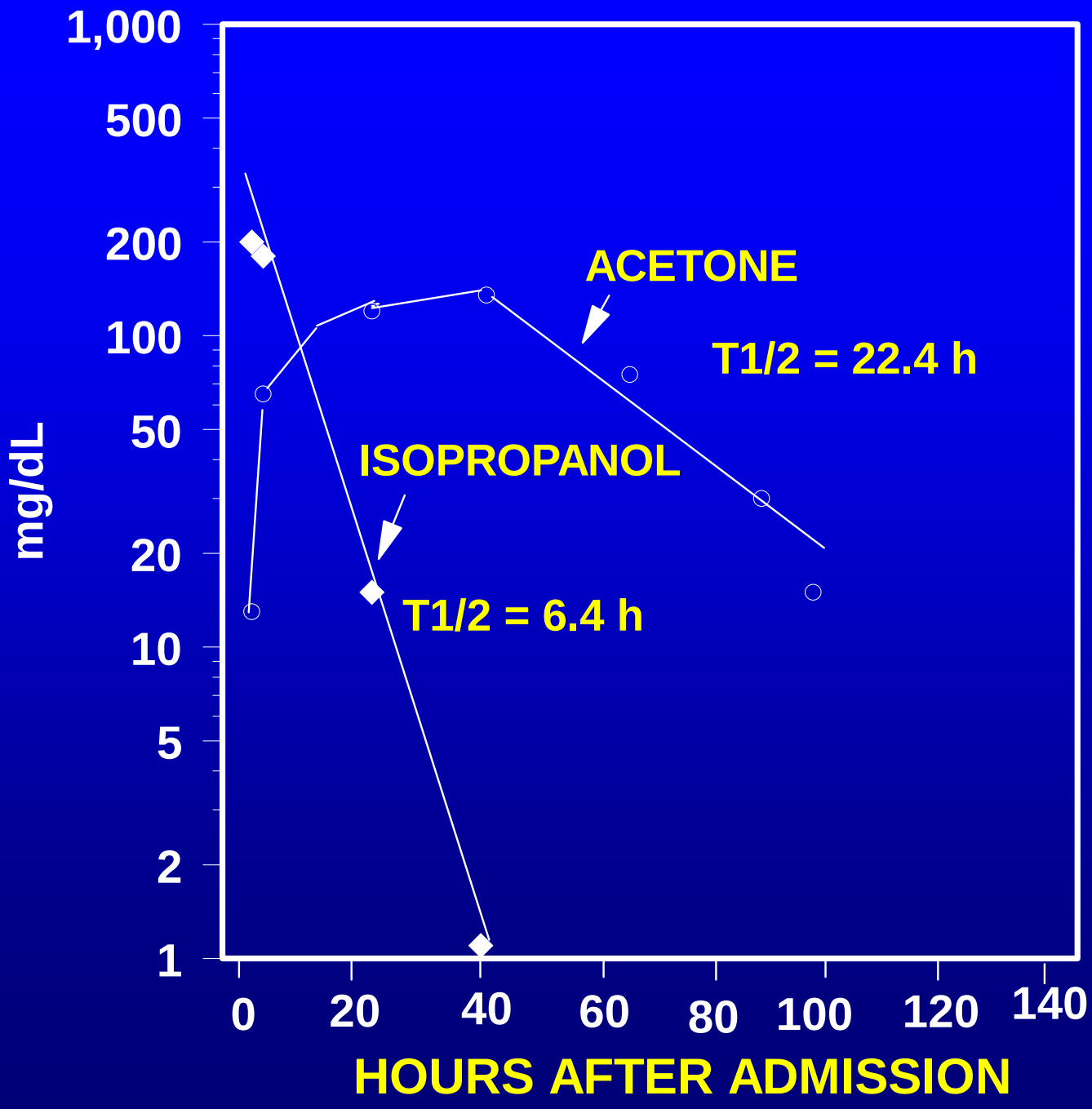
A 46-year-old black woman was brought to the emergency room in Grade V coma without a prior medical history. Patient had fruity breath, no signs of trauma, temperature 35 ºC, pulse rate 100 beats/min, 24 respiration/min, and b.p. 100/80 mmHg. Neurological exam revealed equal, slowly reactive 2-mm diameter pupils, flaccid extremities, no pain response, symmetrically diminished deep tendon reflexes, and flexed toes.

Reference: Natowicz M et al. Pharmacokinetic analysis of a case of isopropanol intoxication. Clin Chem 1985;31:326.

Case 2: Admission Labs and Imaging

Arterial blood pH 7.35, PCO2 41 mmHg and PO2 99 mmHg; WBC 11800/mm3; hematocrit 41%; Na+ 140 mEq/L, K+ 3.7 mEq/L, Cl+ 106 mEq/L, total CO2 24 mmol/L, anion gap 10 mEq/L, BUN 80 mg/dL, creatinine 10 mg/dL, glucose 141 mg/dL, and negative serum ketones. Admission ethanol, isopropanol and acetone concentrations in serum were 13 (2.8), 200 (33), and 12 (2.1) mg/dL (mmol/L), respectively.

A chest roentgenogram revealed atelectasis at the lung bases, and computer tomography of the head was normal.


1,000
500
200
100
50
20
10
5
2
1
mg/dL
ACETONE
T1/2 = 22.4 h
ISOPROPANOL
T1/2 = 6.4 h
0
20
40
60
80
100
120
140
HOURS AFTER ADMISSION

Isopropanol Intoxication Statistics and Sources

- Approximately 19,000 isopropanol exposures, including 5 fatalities, were reported to the AAPCC in 2000
- One half of the poisonings resulted from ingestion of rubbing alcohol
- Isopropanol is used in some rubbing alcohol (70-90 %v/v), ethanol denaturants (5%), deicers (70-80%), glass cleaners (1-14%), liquid detergents (5-12%), cements (5-20%), paint strippers (2-11%), paint thinners (5-10%) and some skin and hair products

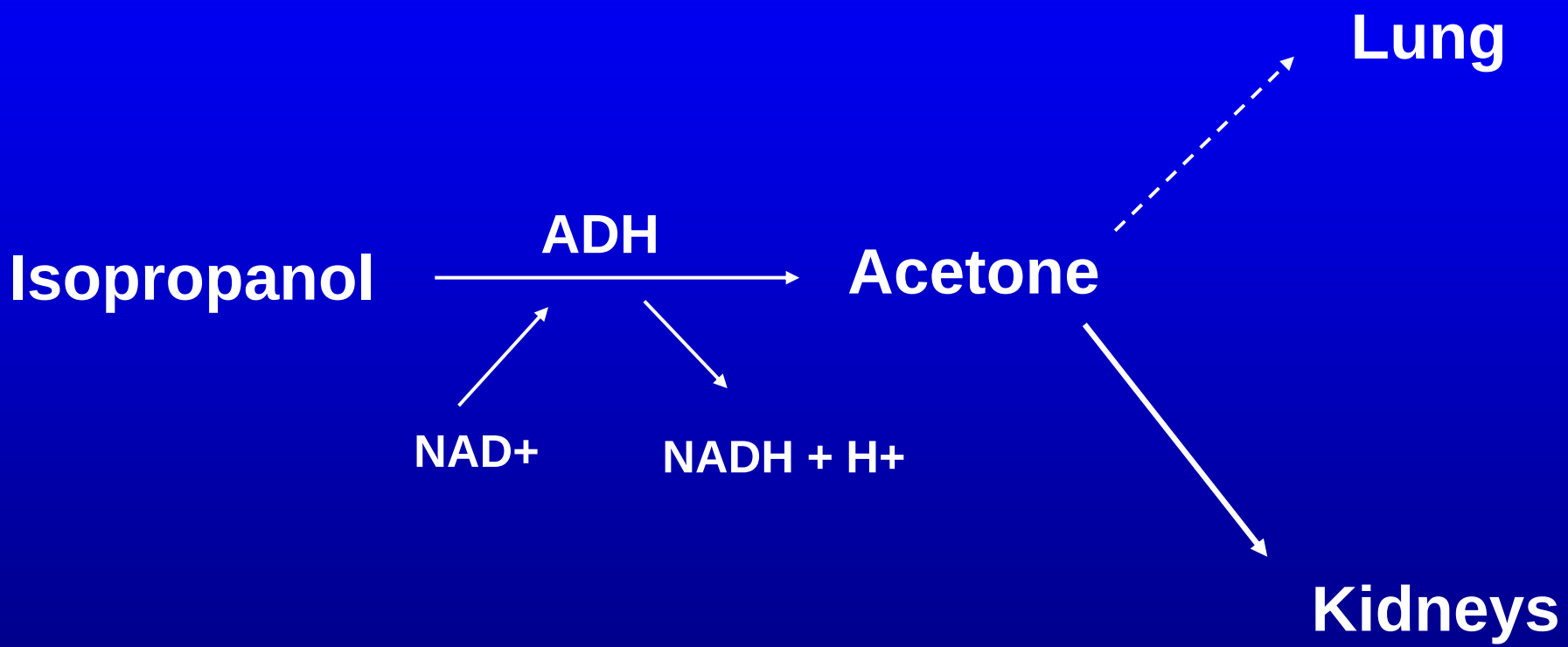
Isopropanol Toxicodynamics

- Gastrointestinal: pain, vomiting, gastritis with hematemesis
- Hepatic: fatty (triglyceride) infiltration
- Renal: hypotension may lead to renal failure
- Metabolic: ketosis and ketonuria without ketoacidosis
- Musculoskeletal: ataxia, rare myopathy
- Cardiovascular: arrythmia, hypotension
- Respiratory: depressed function in overdose
- CNS: dose-related depressant effect, headache, lethargy, ataxia, coma

Isopropanol Toxicokinetics

- Absorption: rapid from respiratory or gastrointestinal
- Peak Blood Levels: 30 to 60 minutes after ingestion
- Distribution: rapid (V_d 0.6-0.7 L/kg)
- Elimination: first-order (half-life 3-6.4 hours), approx. 80% metabolized with rest excreted in urine and saliva
- Metabolite: Acetone is major metabolite excreted primarily by the kidneys but also expired by lungs

Isopropanol Metabolism



Re-Cap of Case 2: Isopropanol Poisoning and Treatment

A 46-year-old black woman was brought to the emergency room in Grade V coma without a prior medical history. The arterial blood was pH 7.35 and serum chemistries included Na+ 140 mEq/L, K+ 3.7 mEq/L, Cl+ 106 mEq/L, total CO2 24 mmol/L, anion gap 10 mEq/L, BUN 80 mg/dL, creatinine 10 mg/dL, glucose 141 mg/dL, and negative ketones. Admission ethanol, isopropanol and acetone concentrations in serum were 13 (2.8), 200 (33), and 12 (2.1) mg/dL (mmol/L), respectively.

Case 2: Questions

1. How would the level of CNS depression in this case compare to an ethanol intoxication at the same alcohol concentration?

2. Assuming an isopropanol Vd of 0.6 and a patient weight of 70 kg, estimate the minimum dose of isopropanol taken by the patient in order to attain a serum isopropanol concentration of 200 mg/dL.

3. How do the elimination kinetics of isopropanol and acetone compare?

4. What affect would co-ingestion of ethanol have on isopropanol elimination and serum acetone concentrations?

Case 2

1. How would the level of CNS depression in this case compare to an ethanol intoxication at the same alcohol concentration?

Case 2

2. Assuming an isopropanol Vd of 0.6 and a patient weight of 70 kg, estimate the minimum dose of isopropanol taken by the patient in order to attain a serum isopropanol concentration of 200 mg/dL.

formula: $D(g) = Cp(g/L) \times Vd(L/Kg) \times W(Kg)$

$D(g) = 2.0\ g/L \times 0.6\ L/Kg \times 70\ Kg = 84\ g$

where D(g) = total ethanol content of body in grams
Cp = plasma or serum concentration in grams per liter
Vd(L/Kg) = volume of distribution in liters per kilogram
W (Kg) = body weight in kilograms

Case 2

3. How do the elimination kinetics of isopropanol and acetone compare?

Case 2

4. What affect would co-ingestion of ethanol have on isopropanol elimination and serum acetone concentrations?

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