# Isoniazid toxicity

## CASE PRESENTATION

Dr Khalilzadeh

# patient

A17-years-old female patient with LOC , seizure referred to this center

She had taken 56 pills(izoniazid - rifampicin) an hour before admission

PMH: tuberculosis

PDH: isoniazid – rifampicin

BP: 140/86

HR:108

O2%:88

RR:28

Laboratory:

PH:6.76 PCO2:26.8 HCO3:3.6 BE: -0/4

# ISONIAZID
# Pharmacology

Isoniazid (INH) interacts with InhA
a mycobacterial enzyme that is required

for the synthesis of very-long-chain lipids (mycolic acids) that are important components of mycobacterial cell walls

Isoniazid itself does not directly interact
with the InhA enzyme

# Pharmacology

Instead, INH is a prodrug that undergoes metabolic

activation by a mycobacterial catalase-reductase known as KatG to produce

a highly reactive intermediate

This INH-derived species enters the

binding site of InhA where it is covalently linked to the reduced form of nicotinamide

adenine dinucleotide (NADH), irreversibly inhibiting this enzym

# Pharmacokinetics and Toxicokinetics

INH is rapidly absorbed

reaching peak plasma concentrations within 2 hours

volume of distribution of approximately 0.6 L/kg

negligible binding to serum proteins

# Mechanism of Toxicity

Isoniazid creates a functional deficiency of pyridoxine by at least two mechanisms:

- hydrazone INH metabolites inhibit pyridoxine phosphokinase, the enzyme that converts pyridoxine to its active form, pyridoxal-5-phosphate

- INH reacts with pyridoxal phosphate to produce an inactive hydrazone complex that is renally excreted. This interferes with the synthesis and metabolism of -aminobutyric acid (GABA), the primary inhibitory neurotransmitter in the CNS

# Clinical Manifestations of INH Toxicity
## *Acute Toxicity*

**Isoniazid produces the triad of :**

**seizures refractory to conventional therapy**

**severemetabolic acidosis**

**coma**

**These clinical manifestations may appear as soon as 30 minutes following ingestion**

**Vomiting**

**slurred speech**

**dizziness and tachycardia**

**may represent early manifestations of toxicity**

# Acute Toxicity

Seizures may occur following the ingestion of greater than 20 mg/kg of INH, and invariably occur with ingestions greater than 35-40 mg/kg

Protracted coma typically occurs with acute severe INH toxicity

Coma may last as long as 24-36 hours and persist beyond the termination of seizure activity, as well as the resolution of acidemia

sequelae from acute INH toxicity include:

- hypotension
- hyperpyrexia
- renal failure
- hyperglycemia

Glycosuria

and ketonuria

# *Chronic Toxicity*

Chronic therapeutic INH use is associated with a variety of adverse effects

The most disconcerting is hepatocellular necrosis

Asymptomatic elevation of aminotransferases is common in the first several months of treatment

laboratory testing may reveal the onset of hepatitis up to 1 year after starting INH therapy

Clinically relevant hepatitis occurs in only 0.1% of patients appropriately selected for therapy

The death rate from INH hepatotoxicity is only 0.001

# Diagnostic Testing

Acute INH toxicity is a clinical diagnosis that may be inferred by history and confirmed by measuring serum INH concentrations

Acute toxicity from INH has been defined as a serum INH concentration greater than 10 mg/L at 1 hour after ingestion

greater than 3.2 mg/L at 2 hours after ingestion

greater than 0.2 mg/L at 6 hours after ingestion

# Management
## *Acute Toxicity*

The initial management requires termination of :

seizure activity

fluid resuscitation

and stabilization and correction of vital signs with maintenance of a patent airway

Clinicians should consider the administration of sodium bicarbonate to treat severe acidemia with a pH <7.0

Gastrointestinal decontamination should be performed with activated charcoal when there are no contraindications

# Management
## *Acute Toxicity*

The antidote for INH-induced neurologic dysfunction**: pyridoxine**
Pyridoxine rapidly terminates seizures, corrects metabolic acidosis, and reverses coma

To treat acute toxicity, the intravenous pyridoxine dose in grams should equal the amount of INH ingested in grams with a first dose in an adult of up to 5 g

Unknown quantities of ingested INH warrant initial empiric treatment with a pyridoxine dose of no more than 5 g

pediatricdose: 70 mg/kg to a maximum of 5 g

# Management
## *Acute Toxicity*

Benzodiazepines

Asymptomatic patients who present to the emergency department within 2 hours of ingestion of toxic amounts of INH should receive prophylactic administration of 5 g pyridoxine

Asymptomatic patients may be observed for a 6-hour period for signs of toxicity

Although hemodialysis has been used to enhance elimination of INH in acute overdose, with clearance rates reported as high as 120 mL/min, hemodialysis is rarely indicated.