Fatal poisoning by isoniazid and rifampicin

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ABSTRACT

Isoniazid and rifampicin are used for management of tuberculosis. Acute poisoning due to isoniazid overdose is associated with repetitive generalized tonic-clonic seizures and severe metabolic acidosis. In toxic doses, rifampicin is known to produce hepatic, renal, hematological disorders, and convulsions. Sometimes, it may produce red man syndrome. We report a case of fatal poisoning with isoniazid and rifampicin. The case was characterized by late presentation, lactic acidosis, and renal failure.

Key words: Fatal poisoning, isoniazid, rifampicin

Introduction

Acute poisoning due to isoniazid and rifampicin overdose is often associated with generalized tonic-clonic seizures, altered sensorium, renal, hepatic dysfunctions, and severe metabolic acidosis. Sometimes with rifampicin ingestion, typical red man syndrome is also described. The prognosis and outcome depends on rapid diagnosis and timely management of complications. We herein report a fatal poisoning due to isoniazid and rifampicin.

Case Report

A 31-year-old male was brought with a history of vomiting, altered sensorium, and generalized tonic-clonic seizures, following ingestion of tablets of Isoniazid (9 gm) and rifampicin (6.75 gm). He was initially managed elsewhere and reached our emergency 32 h after ingestion. At presentation, patient was in shock, respiratory distress, and comatosed. He was immediately intubated and intravenous fluids and vasopressors support for shock was administered. Evaluation revealed orange and red color urine (no other features of red man syndrome), high anion gap metabolic acidosis due to lactic acidosis, rhabdomyolysis, renal, and hepatic dysfunction. Investigative work-up was tabulated [Table 1]. We could not measure blood levels of Isoniazid and rifampicin because of non-availability and the diagnosis of poisoning was considered depending on history, used labeled drug strips, and clinical features. Initially, patient received acute peritoneal dialysis support for 28 h as he was in shock, and subsequently when his blood pressure improved he was changed over to sustained low efficiency dialysis (SLED) support. Patient also received oral pyridoxine (as intravenous preparation is not available) in almost equal quantity to the quantity of isoniazid ingested. Despite all efforts, patient succumbed after 4 days.

Discussion

Accidental or intentional isoniazid poisoning manifests as generalized tonic-clonic seizures metabolic seizures and coma. Isoniazid is a hydrazid derivative of isonicotinic acid, and is absorbed rapidly from gastrointestinal tract reaching peak levels in 1-2 h. The distribution volume is 0.6-0.7 L/kg. It is excreted in 24 h in subjects with a normal renal function. Metabolism takes place by enzymatic acetylation and hydrolysis is in liver. The plasma half-life is 0.5-1.6 h by fast acetylation and 2.5 h by slow acetylation.[1] Isoniazid toxicity occurs with doses as low as 10 to 30 mg/kg. The manifestation being nausea, vomiting, blurred vision, and slurred speech. A dose over 20 mg/kg may be associated with hallucination, recurrent seizures, metabolic acidosis hypotension, and coma. Death may occur at doses of over 50 mg/kg.[1] The metabolite of isoniazid, isoniazid

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Table 1: The values of various parameters in the patient blood and urine samples at admission

Haematology	
Hb (gms/dL)	14.2
PCV %	44.8
Platelet count lakhs/cumm	4.4
TC/cumm	15 900
ESR (mm/first hour)	4
RBS/FBS (mgs/dl)	156/ 96
BT	4 min
CT	7 min
PT	P 21.6 S C 12.9 S
APTT	P 38.6 S C 33.4 S
Hepatic	
Bilirubin total /conj (mg/dl)	2.1/0.7
AST/ALP (units/L)	820/107
Total protein/albumin (gm/dl)	6/3.2
Renal	
Blood Urea/ S. creatinine (mg/dL)	108/5.6
S Sodium/S potassium (mEq/L)	138/5.0
Metabolic	
Calcium (mg/dL)	5.5
Phosphate (mg/dL)	23
Uric acid (mg/dL)	20.8
Other tests	
CPK (units/L)	115 950 <
LDH (units/L)	16 520 <
Amylase (units/L)	325
ABG	PH 7.094, HCO3 9.3 mEq/L PCO_2 18 mmHg
S. Lactic Acid (mg/dL)	53 (normal less than 18)
Anti Retroviral, HBsAg, HCV	Negative

PCV =Packed Cell Volume; ESR = Erythrocyte Sediment Rate; RBS = Random Blood Sugar; FBS = Fasting Blood Sugar; TC = Total Count; BT = Bleeding Time; PT = Prothrombin Time; APTT = Activated Partial Thromboplastin Time; CPK = Creatinine Phosphokinase; LDH = Lactate Dehydrogenase; ABG = Arterial Blood Gas; HCV = Hepatitis C Virus; HbsAg = Hepatits B Surface antigen

hydrazone is produced by dehydrazination that inhibits formation of pyridoxal-5 phosphate from pyridoxine by inhibiting pyridoxine phosphokinase competitively. The other metabolite of isoniazid such as hydrazines and hydrazides formed by acetylation and hydrolysis also inhibits pyridoxal-5 phosphate. Pyridoxal-5 phosphate is a cofactor in gamma amino butyric acid (GABA) synthesis from glutamic acid by decarboxylation. Thus, the metabolite of isoniazid inhibits formation of pyridoxal-5 phosphate and ultimately decreases GABA production. The decrease in GABA is associated with seizures and other central nervous manifestation.[1-3] Isoniazid inhibits conversion of lactate to pyruvate which in turn results in lactic acidosis. The seizures activity further aggravates lactate accumulation and increase lactic acidosis. Acetyl hydrazine metabolite of isoniazid is hepatotoxic. Sometimes, isoniazid (INH) also causes hyperglycemia by blocking specific steps in Krebs cycle that requires nicotinamide adenine dinucleotide and also from stimulating glucagon secretion. Thus, isoniazid toxicity manifests with central nervous dysfunction and hepatic dysfunction with metabolic abnormalities such as lactic acidosis, hyperglycemia, and hyperkalemia.[1-3] Despite the reported efficacy of hemodialysis and peritoneal dialysis in isoniazid poisoning, closer scrutiny revealed that only 9.2% of dose is dialyzable and the rest is handled through hepatic metabolism. However, metabolites of isoniazid are rapidly cleared through normal kidney, and hence forced diuresis is preferred to accelerate isoniazid clearance.[4]

Rifampicin in toxic doses is known to produce gastrointestinal, hepatic, renal dysfunction, hematological, and central nervous system manifestation. It often presents with metabolic acidosis, convulsions, thrombocytopenia, cholestatic jaundice, oliguric renal failure, and redman syndrome. The typical features of red man syndrome are glowing red discoloration of skin, facial, and periorbital odema. The toxicology findings are attributed to high concentration of rifampicin and two major metabolites 25-desacetyl rifampicin and 3-formylrifamycin. The toxic effects have been described with ingestion of 9-12 g and 14-15 g of rifampicin in various situation.[5,6] About 70-80% of rifampicin is bound to protein and is distributed throughout body. The diacetyl metabolite is less toxic and its aqueous solubility results in better elimination in bile. In general, rifampicin is well tolerated by man even in very high doses and intoxication, with fatal outcomes being exceptional. However, when there is a liver disease with inadequate liver function, the enzyme capacity of liver becomes inadequate for complete metabolism of rifampicin to its desacetyl form. This results in accumulation of unchanged rifampicin that is more toxic and results in fatal poisoning.[5,6] rifampicin is not significantly removed by hemodialysis in view of large molecular weight, wide distribution in tissue, and high (80%) protein binding. However, rifampicin has rapid hepatic clearance.[7]

In certain situations, toxic over-dosage of Isoniazid and rifampicin in combination has been recorded. In such situations, patients presented with variety of manifestation such as convulsions, altered sensoruim, coma, metabolic acidosis, rhabdomyolysis, renal failure, and variable hepatotoxicity. In terms of management, apart from general measures such as providing airway by intubation, gastric lavage with activated charcoal, correction of metabolic acidosis by soda bicarb, and measures to correct hypotension and hyperkelemia.

Pyridoxine supplementation has been found to be useful in the management of neurological complication of isoniazid. In general, pyridoxine is given in doses equal to the amount of isoniazid ingested, and is given intravenous over 30-60 min for patients without

seizures and over 3-5 min in patients with seizures. The dose can be repeated at 5-20 min interval until seizures cease.[4,8]

Conclusion

In conclusion, we report a case of fatal poisoning from Isoniazid and rifampicin combination, with detailed literature review. With increasing usage of antituberculosis drugs, and in view of increasing prevalence of various forms of tuberculosis in community, it may be prudent to educate health-care providers and immediate relatives to bring the patient in case of accidental or suicidal poisoning at the earliest for timely management, and also to ensure the availability of intravenous preparation of pyridoxine in all centers and availability of monitoring blood levels of isoniazid and rifampicin in selected centers. The late referral, shock, severe lactic acidosis, and renal failure would have been contributory for fatal outcome in our patient. Isoniazid poisoning should be suspected in all patients where symptoms are coma and seizures especially in those who have access to isoniazid.

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