A SUICIDAL CASE OF ISONIAZID TOXICITY

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Abstract

Background: Isoniazid remains a mainstay for the treatment of tuberculosis despite the fact that it can cause toxicity. **Case presentation:** The authors present a fatal case with a 39-year-old female, found dead at home. The woman had no history of tuberculosis and as far as could be determined had never been prescribed the drug. At the crime scene she appeared to have vomited. The pills were also discovered next to body. The autopsy findings were unremarkable, except for multivisceral congestion, steatosis, laceration of the tongue, urinary incontinence and a piece of a plastic blister pack in the stomach. Histological examination of the liver confirmed the presence of isoniazid-related hepatic injury. The concentration of isoniazid in the admission blood sample was grossly raised (92.8 mg/L). **Conclusion:** Drug effects and poisoning must be considered when trying to identify the cause of bizarre or unexplained death. Accurate, timely and confident identification of an agent poses a challenge to the forensic pathologist and may carry medico-legal implications. We discussed the approach to the problems of identifying this toxic agent such as an external and internal examination of body, toxicological and histopathological analysis.

Keywords: *Forensic Science, Forensic Pathology, Isoniazid, Suicide, Hepatocellular Necrosis*

Introduction- Isoniazid (INH) is the drug of choice for treatment of latent Tuberculosis despite the fact that it can cause severe toxicity. Chronic isoniazid toxicity has been reported in patients taking this drug for therapeutic purposes [1]. However, acute isoniazid poisoning as a result of attempted suicide is extremely rare [2]. The acute ingestion of large quantities of isoniazid is known to cause

severe toxicity and death as a result of recurrent seizures [3] or disseminated intravascular coagulation [4]. Hepatotoxicity is also a major adverse reaction of INH. However, severe liver injury is seen up to 1% of the patients [5,6]. Histological characteristics of severe INH – induced liver injury include hepatocellular damage with multilobular necrosis and a mononuclear cell infiltrate, which is generally indistinguishable from viral hepatitis [5]. These hallmarks can play a key role in identifying INH toxicity in a case of suspected poisoning.

Case report

History

A 39-year-old female, who was of the Roma ethnic group, was found dead at home. She had no history of serious diseases and as far as could be determined had never been prescribed the drug. The presence of vomitus and pills were detected at the crime scene.

Investigations and outcomes

Post-mortem examination revealed no focus of an obvious cause of death. The autopsy findings were unremarkable, except for multivisceral congestion, steatosis, laceration of the tongue, urinary incontinence and a piece of a plastic blister pack in the stomach. There was no evidence of the stress ulcerations of the gastric mucosa.

The blood sample obtained for analysis at the autopsy was taken from the left femoral vein three hours after death. Plasma was separated and stored at -80°C immediately until transport on dry ice to the Laboratory for bioanalysis. Isoniazid concentrations were measured with a validated method comprising liquid-liquid extraction, followed by ultraperformance liquid chromatography with UV detection (Waters Associates, Milford, MA, USA, 1525 multisolvent delivery system, a Rheodyne 7725 injector with 20-µL loop, and a Waters 2487 variable-wavelength UV–visible detector). Accuracy was between 97.8 and 106.7% for isoniazid dependent on the concentration level. The intra- and inter-assay coefficients of variation were <13.4 and <3.2% (dependent on the concentration) over the range of 0.05 to15.1 mg/L for isoniazid. Lower limits of quantification were 0.05 mg/L for isoniazid. The value of isoniazid in our case showed lethal concentration 92.8 mg/L in the blood sample.

The liver samples showed a hepatocellular necrosis, involving all zones of some lobules. The inflammatory response consisted mainly of lymphocytes and plasma cells. (Figure 1 and Figure 2).

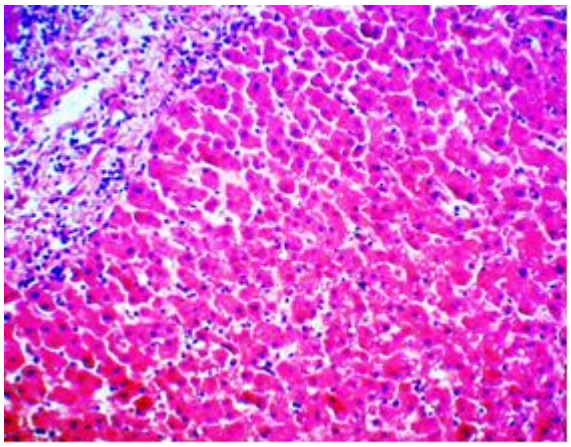

Figure 1

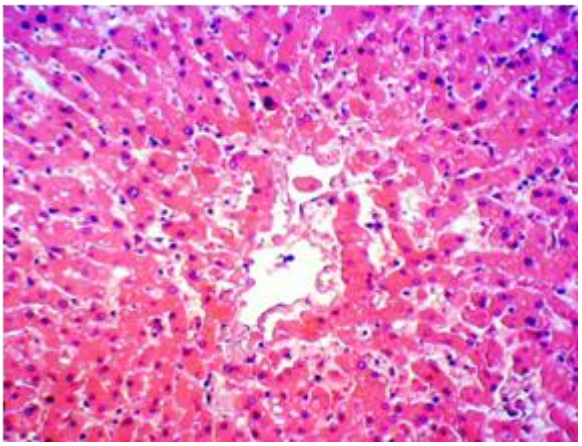

Figure 2

Figure 1. Acute hepatocellular injury. (Hematoxylin and eosin, magnification X 100). The photomicrograph shows a marked inflammatory response, which is consisted of lymphocytes and plasma cells, in the portal areas as well as in the zones of necrosis.
Figure 2. Acute hepatocellular injury. (Hematoxylin and eosin, magnification X 100). A lobular disarray, ballooning and acidophilic staining are seen.

Discussion - Isoniazid toxicity causes the clinical triad of recurrent seizures, a metabolic acidosis and coma [2]. Stewart et al (1995) described a case of fatal poisoning in which isoniazid directly led to Disseminated Intravascular Coagulation (DIC) [10]. Acute ingestion of 2-3 g of INH can cause acute toxicity whilst 80-150 mg/kg is associated with a high mortality rate [3]. Therapeutic doses produce plasma levels in the range 3-10 mg/L and fatalities have been reported with levels in the range 13-244 mg/L [7-9]. In the present case, the value of isoniazid showed lethal concentration 92.8 mg/L in the blood sample.

The drug forms hydrazones with pyridoxal phosphate, decreasing the coenzyme essential for the production of the inhibitory neurotransmitter, γ-aminobutyric acid (GABA) in the central nervous system. Hence INH can cause seizures in susceptible individuals even at therapeutic concentrations [11]. In our case, the presence of fresh bite marks of the tongue and a urinary incontinence are the useful signs for the assignment of death to an epileptic seizure and especially for death during acute convulsion [12]. Isoniazid also inhibits the conversion of lactate to pyruvate. This combination between the seizure-induced tissue hypoxia and an increased serum lactate level can cause a severe anion gap metabolic acidosis [2].

In our case, we found no evidence of DIC. Thus it excludes this diagnosis as a cause of death.

The mechanism of the INH- induced liver injury in humans remains unknown, however, there is increasing evidence that it is immune mediated [13]. The incidence of INH – induced liver damage appears to be higher in patients with slow acetylator phenotype [14, 15], because the slow acetylators have higher concentrations of the acetyl hydrazine – metabolite compared with rapid acetylators [16]. Studies have shown large variations of the slow acetylator phenotype among ethnic groups: e.g. 54.9 % of Hungarian Vlax Roma population [17]. Therefore, the presence of the hepatocellular damage with multilobular necrosis associated with a mononuclear cell infiltrate

suggests that the victim was a slow inactivator of INH, which is commonly seen in the Indian and Roma population.

Conclusion- This particular case brings to light the fact that all findings from the crime scene to the autopsy table must be used to identify the cause and the mechanism of death. Drug effects and poisoning must be considered when trying to determine the cause of bizarre or unexplained death. The forensic pathologist must not underestimate the facts, the crime scene investigation, the external and internal examination of body, the toxicological and histopathological analysis in a case of suspected poisoning.

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