

CASE REPORT**Three cases of intentional isoniazid overdose – a life-threatening condition**

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Currently, isoniazid (INH) overdose seems to be a growing and life-threatening problem, partly due to the recent national roll-out of INH preventive therapy (IPT) for HIV-positive adults. We present three cases, two of which were fatal, seen at Frere and Cecilia Makiwane hospitals, East London, South Africa over the past 16 months.

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Case 1

A 21-year-old HIV-infected woman with a CD4 count of 215 cells/ μ L, who was on unidentified antiretroviral (ARV) treatment, presented to her local district hospital, having ingested 70 rifampicin (150 mg)/isoniazid (INH) (75 mg) combination tablets for continuation-phase treatment of tuberculosis (TB). No specific therapy was given. She was fully conscious on days 1 and 2, but had a Glasgow coma scale (GCS) score of 7/15 on day 3. No seizures were observed. On the day of her arrival at our institution, her GCS score was 6/15 and she was intubated and ventilated in the intensive care unit (ICU). The patient had a compensated metabolic acidosis on analysis of arterial blood (standard bicarbonate 18 mmol/L), but the lactate level was not measured. On admission, her serum creatinine was 254 μ mol/L, but it normalised within 3 days. Pyridoxine 5 g was administered via a nasogastric tube (NGT), but with no response in her level of consciousness. She spent almost 4 months in the ICU, without any neurological recovery, and died shortly after transfer to a general ward.

Case 2

A 32-year-old HIV-infected woman, who was receiving tenofovir/emtricitabine/efavirenz fixed-dose combination ARVs, and 300 mg INH daily as INH preventive therapy (IPT), was found unconscious with two empty bottles of each of the abovementioned agents. She suffered multiple seizures while being transferred to our hospital, was assessed as being in status epilepticus on arrival, and required 60 mg diazepam and a phenytoin loading dose to terminate her seizures. She suffered a cardiorespiratory arrest, and was resuscitated, intubated and ventilated in the ICU. Once the INH ingestion was recognised, 5 g pyridoxine was administered via an NGT. Her arterial blood lactate level was 15.3 mmol/L, and her serum creatinine 220 μ mol/L, both of which normalised with supportive care. A computed tomography (CT) scan of her brain was normal. Her GCS improved from 3/15 to 7/15 by day 10, but failed to recover further. On day 31 she was transferred to a general ward and died.

Case 3

A 52-year-old HIV-infected woman, with a CD4 count of 274 cells/ μ L, was found unconscious with empty tenofovir/emtricitabine/efavirenz fixed-dose combination ARVs and IPT containers. She was also heavily intoxicated with ethanol. She arrived at the hospital in

status epilepticus, her seizures were refractory to clonazepam and a phenytoin loading dose infusion, but her convulsions decreased during a propofol infusion in the ICU. There was a 48-hour delay before INH toxicity was recognised as the possible cause of her seizures; 5 g pyridoxine was then administered via an NGT, after which she experienced no further seizures. Her arterial lactate was 16.6 mmol/L and serum creatine kinase 41 015 U/L. She developed acute renal failure, requiring 7 days of haemodialysis, after which her renal function recovered fully. A CT scan of her brain was normal. She was extubated after 11 days, and continued to full recovery after almost 4 weeks.

Discussion

INH, the hydrazide of isonicotinic acid, has been the mainstay of TB treatment and prevention since the 1950s. Most clinicians are familiar with the common side-effects of peripheral neuropathy and hepatotoxicity, but lesser known, severe INH toxicity is characterised by recurrent seizures, lactic acidosis, coma and death. As little as 1.5 g INH has been reported to cause mild toxicity, doses of 6 - 10 g may result in severe toxicity, while doses >15 g may be fatal.^[1]

INH is rapidly absorbed, reaching peak levels in 1 - 2 hours, with minimal protein binding. It is metabolised in the liver by polymorphic acetylation, with a half-life of between 1 and 4 hours, varying between fast and slow acetylators. INH exerts toxicity by inhibiting pyridoxine kinase, the enzyme responsible for the production of pyridoxal phosphate, the active form of pyridoxine. Pyridoxal phosphate is a co-factor in the synthesis of gamma-aminobutyric acid (GABA), a major inhibitory neurotransmitter.^[1] Consequently, INH toxicity leads to reduced GABA, which can induce seizures. Lactic acidosis is thought to occur by INH inhibition of lactate dehydrogenase via its effect on the co-enzyme nicotinamide adenine dinucleotide. This is exacerbated by increased lactate production during seizures.

For the management of an INH overdose, after initial stabilisation, gastric lavage is indicated within 1 hour of INH ingestion. This can be followed by charcoal administration, which can be given with sorbitol,^[2] concurrently with the prompt administration of high doses of pyridoxine, preferably as an intravenous preparation, but as crushed tablets via an NGT if the former is unavailable. Most authors recommend a mass equivalent dose according to the amount of INH ingested, if known. This was shown to have superior seizure control in a case series of five patients compared with 41 cases reported in

the literature, where other approaches were used.^[3] If the ingested dose is unknown, 70 mg/kg pyridoxine is recommended, up to a total of 5 g.^[1] This alone may be enough to terminate seizures, but if not, benzodiazepines are the preferred anticonvulsant. Animal studies have demonstrated synergy between pyridoxine and diazepam (a GABA_A benzodiazepine-site agonist) in reducing INH-induced seizures, but not with phenytoin (a sodium channel antagonist).^[1] Haemodialysis will eliminate INH, but it is generally not required, except in the most severe cases that do not respond to pyridoxine. Based on the half-life of INH, it should be used early to obtain an optimal effect.^[1]

Notably, all three of our patients developed acute renal failure, one requiring dialysis, but renal function recovered in all. This has only been described in one other INH toxicity case report, where INH was combined with rifampicin.^[4] Two, and possibly all three patients, co-ingested unknown amounts of tenofovir-containing fixed-dose combination tablets. Even though tenofovir is known to cause nephrotoxicity over time in therapeutic doses, no cases of acute renal failure have been reported with an overdose.^[5] Case 3 had a high creatine kinase level, presumably caused by seizure-induced rhabdomyolysis, which may have contributed to acute tubular necrosis.

From a public health perspective, our concern is that severe INH overdose cases are likely to become more frequent following the recent roll-out of IPT for HIV-positive adults in South Africa (SA). INH is now available as a 300 mg tablet (previously 100 mg or a maximum of 150 mg in combination with rifampicin), giving a total dose of 8.4 g in a month's supply (well into the range of severe toxicity). IPT is administered for long periods (6 - 36 months), and potentially most of SA's estimated 6.5 million HIV-infected adults qualify to

receive it.^[6] While the benefits of IPT in preventing TB are clear, we believe clinicians need to be aware of the risk of INH overdose, and be cautious when considering IPT for patients with suicidal risks. HIV-positive patients have a high level of suicidal ideation (up to 83% in a recent post-voluntary testing and counselling study in KwaZulu-Natal^[7]), and there is evidence that efavirenz may further increase the risk of suicidality.^[8]

Emergency clinicians need to have a high index of suspicion for INH overdose in patients presenting with resistant status epilepticus or unexplained lactic acidosis, and be familiar with the emergency management, as discussed above. The registration and supply of intravenous pyridoxine, and the availability of laboratories determining INH levels, would also assist in better managing suspected cases.

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