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CASE REPORT

Iron and acetaminophen a fatal combination?

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Summary

Intentional iron overdose in adults is uncommon. Clinical consequences are variable and depend on the quantity of iron ingested and the delay to treatment. Severe iron overdose can lead to multi-organ failure and acute hepatic necrosis. Here, we report three cases of polypharmacy overdose including iron resulting in acute liver failure. Despite maximum supportive care including liver transplantation in two cases, all patients died. Iron poisoning may have an additive toxic effect in drug-induced acute liver failure and worsen outcome.

Introduction

Accidental iron toxicity is not uncommon in the paediatric setting, whereas among adults iron ingestion in the majority is with suicidal intent and is rarely seen. The incidence of iron poisoning among children <5 years of age has been reported to be as high as 30%; however, this number seems to be in decline following the introduction of unit dose packaging of iron supplements [1–3]. In its most severe form, iron toxicity can lead to acute liver and multi-organ failure. Initial treatment includes gut decontamination, chelation therapy with desferrioxamine and organ supportive measures [4]. Liver transplantation in patients presenting with acute liver failure (ALF) is a treatment option but conclusive evidence regarding its efficacy is lacking. Here we present three cases of ALF resulting from acetaminophen and diclofenac overdose complicated by concomitant iron intoxication. All patients fulfilled transplant criteria for ALF and two were transplanted, none survived. We postulate that iron poisoning had a significant impact on the ultimately fatal disease course of these patients.

Case 1

An 18-year-old woman was admitted to her referring hospital having ingested approximately 60 mg of diazepam, 600 mg of diclofenac and ferrous sulphate, possible more than 6 g, 24–48 h prior to admission. Her admission liver function tests were compatible with a diagnosis of hyper acute hepatic necrosis [aspartate transaminase (AST) 13374 IU/L, prothrombin time (PT) 90 s, lactate (lac) 18 mmol/L] and she was clinically encephalopathic. Admission and pre- transplantation iron serum levels were 67 mmol/L (374 μg/dL) and 34.6 mmol/L (193 μg/dL) respectively (normal range 14–30 mmol/L). She was commenced on intravenous N-acetylcysteine and desferrioxamine.

Within the first 24 h following transfer, she developed acute respiratory distress syndrome, P/F < 100 mmHg and vasoplegic shock. Desferrioxamine was discontinued given concerns regarding respiratory toxicity [5]. Transthoracic echocardiogram revealed right heart dysfunction and pulmonary hypertension. Over the next 12 h both her oxygen and inotropic/vasopressor requirements

decreased significantly with aggressive multi organ support. An intracranial pressure (ICP) monitoring device was inserted (right fronto-parietal region) and the opening ICP measured 28 mmHg; Intracranial hypertension responded to hypertonic saline and mannitol therapy.

Seventy-two hours after admission, she underwent liver transplantation. Histology of the explant showed massive liver cell loss consistent with drug-induced injury. Postoperatively, there was continuing improvement in respiratory function but she developed progressive cholestatic graft dysfunction [bilirubin (Bil) 217 μmol/l] with no clear cause found either on the remainder of her blood tests or on imaging studies. Cytomegalovirus (CMV) titre was not elevated and there was no evidence of rejection on liver biopsy.

Over the course of the next 3 weeks, she remained severely jaundiced (Bil 466 μmol/l) and a repeat CT demonstrated a patent hepatic artery with new areas of graft ischaemia. She underwent a laparotomy to refashion a perforated bile duct. A repeat liver biopsy did not demonstrate evidence of acute cellular rejection.

The postoperative course was complicated by recurrent sepsis and development of new cavitating lung lesions compatible with a diagnosis of invasive aspergillosis, which was treated with liposomal amphotericin Fig. 1. The following 6-week period was characterized by an undulating disease course, with persistent graft dysfunction, renal failure and episodes of septic shock. By the end of this time period, her clinical condition worsened with new onset neurological signs: CT brain showed bleeding into an abscess cavity, which was evacuated Fig. 2. Voriconazole was added as culture confirmed invasive aspergillosis.

Her clinical condition continued to deteriorate finally progressing to brain stem death approximately 12 weeks after her initial admission.

Case 2

A 24-year-old man presented following a polypharmacy overdose including acetaminophen [100 tablets (50 g)], aspirin, ibuprofen, ketamine and iron tablets 24 h prior to admission. His acetaminophen and iron plasma levels were 267 mmol/l and 36.2 mmol/l (202 μg/dl) respectively. He was managed as per our standards of care for ALF [6] and was commenced on desferrioxamine. He was transplanted on day 9 following his admission. Histology of the explant showed centrilobular and mid-zonal hepatocyte loss with marked hepatocellular anisocytosis in the periportal regions, patchy hepatocellular steatosis, ductular reaction, and cholestasis.

His initial postoperative course was uncomplicated but there were concerns regarding low grade graft rejection for which he received empirical pulse steroid therapy on day 8 post-transplantation. On the following day, he deteriorated clinically with new onset neurological signs. A whole-body CT scan was consistent with features of disseminated septic emboli. Given concerns of invasive fungal infection, he was started on liposomal Amphotericin and later Voriconazole. A transesophageal echocardiogram revealed a suspicious mobile lesion in the right ventricular outflow tract Fig. 3.

He unfortunately continued to deteriorate and, progressed to brain stem death on day 13 post-liver transplantation. Post-mortem examination was consistent with disseminated aspergillus infection.

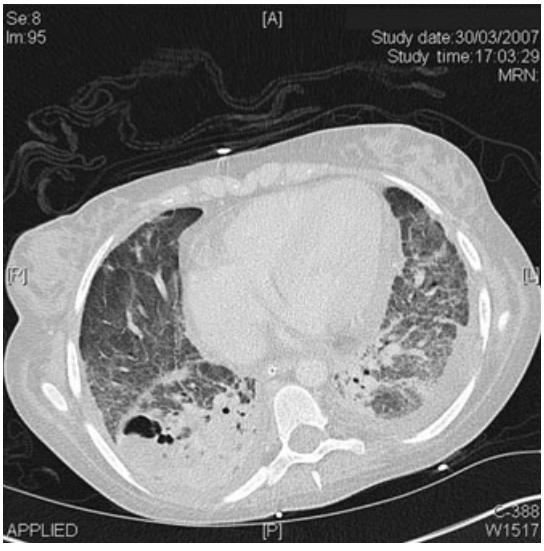

Figure 1 CT scan demonstrating cavitating lung lesions.

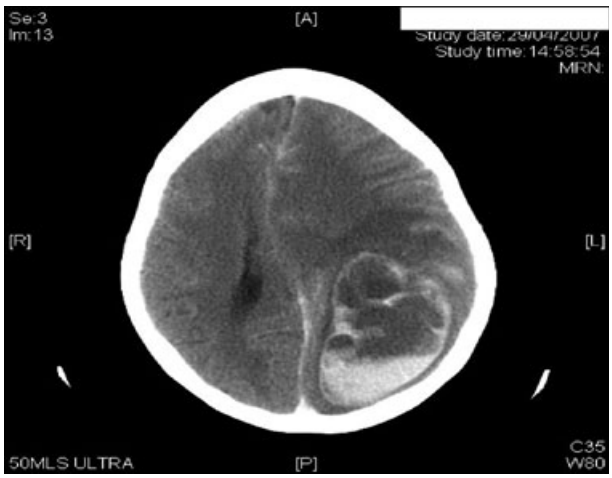

Figure 2 Abscess cavity with bleeding in the left cerebral hemisphere.

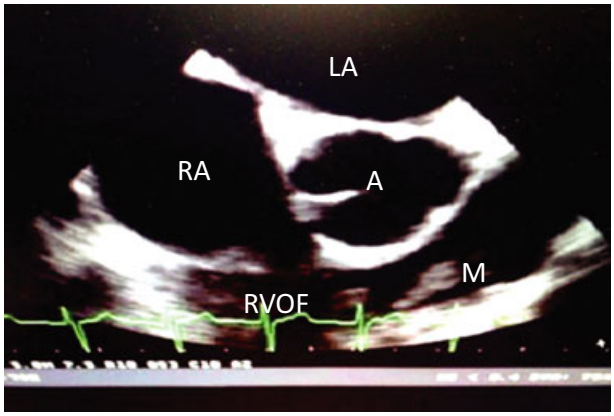

Figure 3 Mobile mass (M) in the right ventricular outflow (RVOF) tract on echocardiogram. LA, Left atrium; RA, Right atrium; A, Aortic valve. Modified RV inflow/outflow view.

Case 3

A 20-year old man was transferred 48 h after polypharmacy overdose including a significant amount of iron, acetaminophen, amoxicillin, erythromycin, loperamide and tricyclic antidepressants. The total quantity of the drugs ingested was not entirely clear from the presenting history. Initial blood tests were consistent with acute severe liver injury [AST 11555 IU/L, PT 154 s, lactate 18 mmol/l, ammonia 156 μmol/l]. Admission and pre-transplant listing iron levels were 128 mmol/l (715 μg/dl) and 23.7 mmol/l respectively. He was managed as per our fulminant care pathway and was commenced on desferrioxamine. He was initially listed for a liver transplant but later temporarily suspended from the transplant list 72 h post admission as there was improvement in both his metabolic and neurological state (lactate 1 mmol/l, ammonia 100 μmol/l).

Over the next 10 days, there was evidence of progressively worsening cholestasis (Bil 341 μmol/l) and rising ammonia levels without evidence of raised intracranial hypertension. This was thought to be driven by sepsis although cultures remained negative. At that stage, transplantation was not thought to offer a survival benefit over medical therapy.

Over the following week, he developed pupillary abnormalities; CT demonstrated evidence of cerebral oedema with cerebellar and transtentorial herniation. Post-mortem examination of the liver demonstrated sub-massive liver necrosis secondary to drug toxicity.

Discussion

Acute iron overdose frequently leads to gastrointestinal disturbances. Intracellular iron exerts its toxic effect on mitochondria; this leads to anaerobic metabolism and thus metabolic acidosis [7]. Myocardial failure, caused by ROS-induced myocardial damage results in profound shock observed in the later stages of illness [8]. Once hepatotoxicity has developed the mortality rate can be 50% or more [9]. Liver transplantation as rescue therapy has been reported but primarily in the paediatric setting [9,10].

A clinically useful classification of the effects of iron poisoning into four progressive stages has been proposed: Stage-I (Stage of gastrointestinal toxicity): Stage-II (Stage of apparent stabilization or quiescent phase): Stage-III (Stage of mitochondrial toxicity): Stage-IV (Stage of gastric scarring) [11].

Although all three of our reported cases were caused by polypharmacy overdose including acetaminophen in two, we feel that concomitant iron ingestion played an important role in the pathogenesis and eventually resulted in the fatal outcome of these patients. The rapid progression to ALF is hypothesis generating in terms of a double-hit mechanism. Acetaminophen or drug-induced centrilobular necrosis in combination with a more periportal distribution of necrosis caused by iron could have led to rapid and irreversible liver damage, leaving no room for hepatic regeneration [12]. Hepatic iron concentration was not analysed in this series although Pestaner *et al.* has described excess hepatic iron concentrations (range 1600–4182 μg/g of dry tissue) from autopsy specimens [13].

Previous case reports of iron overdose, suggest a dose-related hepatotoxic effect with a serum toxicity threshold of 1700 μg/dl [7]. However, this is not universally accepted as there is a possibility of idiosyncratic reaction to iron [14] in those with lower serum levels. As all patients in our series had overdosed with suicidal intent, it was impossible to get an accurate timing of drug (iron) overdose; hence serum iron levels may have been misleading. Regardless, all patients were commenced on chelation therapy at the referring hospital.

The risks of microbial and opportunistic infections are substantial in the setting of ALF [15]. Two patients succumbed to opportunistic infections in the form of disseminated aspergillosis. A higher incidence of invasive fungal sepsis in patients with evidence of hepatic iron overload in the explanted liver has been reported [15,16]. Excess iron in these patients may have been contributory in the pathogenesis via two possible mechanisms: the enhanced virulence of the micro-organisms in the presence of iron and the impact of iron on host immune responses.

All three patients in our series fulfilled King's College Hospital poor prognostic criteria for acetaminophen-induced liver failure [17,18]. Approximately 80 patients with ALF are currently admitted to our institution

annually, a third of whom will require urgent listing for liver transplantation. The overall 1 year survival of acetaminophen- or drug-induced ALF in the context of liver transplantation is ~80% [19]. Many patients present in MOF with injury severity not dissimilar to the cases presented.

The uniformly negative outcome of this admittedly small series of patients raises the question whether the co-ingestion of iron may have influenced the outcome negatively. All three patients ultimately succumbed to infectious complications, in two because of proven opportunistic pathogens and in the third case because of cerebral oedema triggered by sepsis. In the nontransplanted patient, lack of timely hepatic regeneration because of the above explained mechanisms could have contributed to the outcome.

Conclusion

We postulate that iron overdose in association with ALF carries a very poor prognosis. Where it is difficult to establish a clear link between iron co-ingestion and poor outcome, commonly applied risk models for ALF may lack diagnostic accuracy in this setting.

Authorship

VKA: Collected, analysed and wrote the article. JW, WB, NH, JO: Reviewed the article. GA: Designed the study; wrote and reviewed the article.

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References

1. Tenenbein M. Unit-dose packaging of iron supplements and reduction of iron poisoning in young children. *Arch Pediatr Adolesc Med* 2005; **159**(6): 557.
2. Litovitz T, Manoguerra A. Comparison of pediatric poisoning hazards. *Pediatrics* 1992; **89**: 999.
3. Department of Health and Human Services. Iron-containing supplements and drugs: label warning statements and unit dose packaging requirements; final rule. *Fed Regist* 1997; **62**: 2217.
4. Baranwal AK, Singhi SC. Acute iron poisoning: management guidelines. *Indian Pediatr* 2003; **40**: 534.
5. Tenenbein M, Kowalski S, Sienko A, *et al.* Pulmonary toxic effects of continuous desferrioxamine administration in acute iron poisoning. *Lancet* 1992; **339**(8795): 699.
6. Auzinger G, Wendon J. Intensive care management of acute liver failure. *Curr Opin Crit Care* 2008; **14**: 2.
7. Robotham JL, Lietman PS. Acute iron poisoning: a review. *Am J Dis Child* 1980; **134**: 875.
8. Link G, Saada A, Pinson A, *et al.* Mitochondrial respiratory enzymes are a major target of iron toxicity in rat heart cells. *J Lab Clin Med* 1998; **131**: 466.
9. Tenenbein M. Hepatotoxicity in acute iron poisoning. *Toxicol Clin Toxicol* 2001; **39**: 721.
10. Kozaki K, Egawa H, Garcia-Kennedy R, *et al.* Hepatic failure due to massive iron ingestion successfully treated with liver transplantation. *Clin Transplant* 1995; **9**: 85.
11. Covey TJ. Ferrous sulphate poisoning. A review, case summaries, and therapeutic regimen. *J Pediatr* 1964; **64**: 218.
12. Witzleben CL. An electron microscopic study of ferrous sulphate induced liver damage. *Am J Pathol* 1966; **49**: 1053.
13. Pestaner JP, Ishak KG, Mullick FG, Centeno JA. Ferrous sulfate toxicity: a review of autopsy findings. *Biol Trace Element Res* 1999; **69**: 191.
14. Sumanth R, Daram Hayashi PH. Acute liver failure due to iron overdose in an adult. *South Med J* 2005; **98**: 241.
15. Singh Nina, Sun Hsin-Yun. Iron overload and unique susceptibility of liver transplant recipients to disseminated disease due to opportunistic pathogens. *Liver Transpl* 2008; **24**: 1248.
16. Alexander J, Limaye AP, Ko CW, *et al.* Association of hepatic iron overload with invasive fungal infection in liver transplant recipients. *Liver Transpl* 2006; **12**: 1799.
17. O'Grady JG, Schalm SW, Williams R. Acute liver failure: redefining the syndromes. *Lancet* 1993; **342**: 273.
18. Bernal W, Donaldson N, Wyncoll D, *et al.* Blood lactate as an early indicator of outcome in paracetamol-induced acute liver failure. *Lancet* 2002; **359**: 558.
19. O'Grady JG, Alexander GJ, Thick M, *et al.* Outcome of orthotopic liver transplantation in the aetiological and clinical variants of acute liver failure. *Q J Med* 1988; **68**: 817.