Nitrofurantoin Induced Liver Injury

David McCracken*
South West Acute Hospital, UK

Abstract

Drug induced liver injury is a recognised cause of acute liver failure. A wide range of drugs have been implicated, of which the most common are Paracetamol and antibiotics. Nitrofurantoin is a commonly prescribed antimicrobial which may cause liver injury from either acute or chronic exposure. This complication was thought to occur with an extremely low incidence; however recent data suggests that it may be significantly more common.

We present a case of Nitrofurantoin induced liver injury in a 78 year old lady due to prophylactic use for 12 months with full resolution following withdrawal of the offending agent.

Discussion and review of the literature includes the low incidence and how this may be a substantially more regular occurrence than previously described, treatment by withdrawal of the causative agent and prognosis which is generally good, however cirrhosis and death have both been reported. The pattern of injury and clinical features are also reviewed, both of which are extremely variable but may be defined in relation to acute or chronic features.

CASE REPORT

A 78 year old lady was admitted to hospital with a three week history of painless jaundice, lethargy and anorexia associated with several episodes of intermittent confusion. Her past medical history consisted of hypertension, ischaemic heart disease, osteoporosis and recurrent urinary tract infections for which she was on Aspirin, Atorvastatin, Bendroflumethiazide, Bisoprolol, Calichew, Escitalopram, Lactulose, Nitrofurantoin, Omeprazole, Risedronate and Solifenacin. She gave no history of alcohol excess, vomiting and diarrhoea, recent foreign travel or contact with anyone else who was jaundiced.

Her routine blood tests on admission to hospital showed a Bilirubin of 153, AST 930, ALT 492, GGT 166 and ALP 131, although examination of previous liver function testing demonstrated progressive derangement over the past twelve months. A mixed hepatitic and cholestatic picture was observed, however transaminase predominance was noted as AST peaked at 1018. Coagulation screen showed mild derangement with a Prothrombin Time of 14.6, an Activated Partial Thromboplastin Time of 32.2 and Fibrinogen concentration of 1.4. A liver screen showed that the patient was Cytomegalovirus, Epstein-Barr, Herpes Simplex, Hepatitis B and C negative. Immunoglobulins were normal while anti-mitochondrial, anti-nuclear; smooth muscle and anti-liver kidney microsomal antibodies were all negative. An ultrasound was performed of the patient’s abdomen which showed irregularity of the surface of the liver suggestive of focal fatty change with moderate volume ascites. The gallbladder was unremarkable, as was the rest of the abdomen.

Following adequate resolution of the ascites with diuretic treatment, a liver biopsy was obtained which showed a mixed hepatitic picture. The pathologist described marked portal inflammation associated with cholangio-metaplasia indicating a degree of cholestatic injury. This was evidenced by CK7 immuno histochemical staining. Hepatocyte loss was also seen with early bridging fibrosis between portal triads and central veins.

As the biochemical and serological liver screen did not reveal any abnormalities and the ultrasound and liver biopsy were suggestive of mixed hepatitic inflammation, it was felt that this lady’s jaundice was most likely due to Nitrofurantoin which she had been taking at a dose of 100 milligrams, once daily as long term prophylaxis against recurrent urinary tract infections for the preceding twelve months. This was felt to be the most likely causative agent as derangement in liver function tests appears to have been present for approximately a year, peaking prior to admission, and corresponds with the duration of treatment with Nitrofurantoin.

Limitations of this case are however evident, as the patient was taking several medications which are documented to cause hepatotoxicity.

Treatment included withdrawal of the presumed causative agent along with withdrawal of all potential hepatotoxic agents and diuretic therapy for ascites. RUCAM scoring suggested that
Nitrofurantoin was highly probable to be the causative agent and based on this, all other potential agents have been reintroduced following normalisation of hepatic function with no ill effects.

The patient made a good recovery and eight months later is asymptomatic, with no evidence of coagulopathy or ongoing liver dysfunction.

**DISCUSSION**

Drug induced liver injury is a common cause of acute liver failure in adults and comes with a significant mortality. Figures in the United States suggest that drugs are the likely causality in up to 13% of all acute liver failure cases [1].

Causality is often difficult to identify and even when a drug is suspected this is often difficult to confirm. Thousands of drugs have been associated with causing liver injury and a comprehensive database has been initiated in the United States by the National Institute of Health [2]. The most common agents implicated in drug induced liver injury are Paracetamol followed by Co-Amoxiclav [3,4]. New clinical guidelines have been published in July 2014 by the American College of Gastroenterology regarding the diagnosis and management of idiosyncratic drug induced liver injury. It includes an algorithm to allow systematic investigation and assessment of abnormal liver function tests in order to help implicate a drug when it is suspected to be the causative agent [5].

Nitrofurantoin is a commonly prescribed oral antimicrobial frequently used in the acute treatment of urinary tract infections and also as chronic long term prophylaxis. Figures from the Health and Social Care Information Centre show that there were almost 2 million community prescriptions of Nitrofurantoin in 2013 in England alone [6].

As with any drug, Nitrofurantoin has a long list of recognised adverse effects, however significant sequelae are said to occur in less than 1% of cases. The most common of these is lung injury in the form of interstitial pneumonitis which may in turn cause pulmonary fibrosis. This is followed by Nitrofurantoin induced liver injury and other recognised significant sequelae include peripheral neuropathy and blood disorders such as thrombocytopenia, agranulocytosis and a plastic anaemia [7].

Historically, data would suggest that Nitrofurantoin induced liver injury is an extremely uncommon event with incidence reported as 2.4 cases per 100,000 in the United Kingdom [8] and 13.9 +/- 2.4 cases per 100,000 in France [9]. A recent population study performed in Iceland, however, suggests that this may be much more common following chronic exposure to specific drugs, including Nitrofurantoin, and patients will often have raised gamma globulins, positive anti-nuclear antibodies or positive anti-smooth muscles antibodies on serological testing [16,17].

Outcomes in these patients can be extremely variable and unpredictable, particularly as severity and prognosis appear to be unrelated to the dose prescribed or the duration of administration [5]. Prognosis does appear to be much worse in patients with jaundice and hepatocellular injury where mortality may be as high as 14% as reported by Hyman Zimmerman [18]. Cases of cirrhosis have been reported; however it would appear that the majority of cases carry a good prognosis with many acute drug induced liver injury cases resolving rapidly following withdrawal of the offending drug and period of washout, and gradual improvement in cases following chronic exposure [18].

The mainstay of treatment involves withdrawal of the offending agent with further avoidance in the future including clear documentation of an adverse drug reaction to prevent inadvertent, inappropriate prescription by other health professionals. The benefit of corticosteroids is unclear and evidence is scarce, however they are recommended if the patient has features in keeping with an autoimmune-like hepatitis as they have been shown to have significant morbidity and mortality benefits within this group [20]. As with all patients with acute
liver failure, referral for consideration of liver transplantation should be considered early in the disease course [21].

Further treatment of recurrent urinary tract infections should be introduced with caution as many of the common antibiotics used in these circumstances, such as Trimethoprim, Co-Amoxiclav and Ciprofloxacin have also been documented to cause hepatotoxicity with similar risk factors to those already discussed [2].

CONCLUSIONS

Nitrofurantoin is a commonly prescribed antimicrobial, both for short term treatment and long term prophylaxis against urinary tract infections and has well recognised adverse effects including liver injury, the incidence of which may be significantly higher than first thought. The pattern of injury is extremely variable as are the clinical features. Treatment involves withdrawal of the causative agent, in this case Nitrofurantoin, though corticosteroids may be useful if autoimmune features are present. Prognosis is generally good; however cirrhosis and death have both been reported.

REFERENCES

2. Livertox.nih.gov