A rare case of norethisterone-related drug-induced liver injury

Introduction

Drug-induced liver injury is hepatic dysfunction following initiation of a drug or herb. In most cases, discontinuation of the agent reverses the liver injury, but other outcomes include acute liver failure, transplant and death (Chalasani et al 2017).

Discussion

Norethisterone is a progesterone, licensed for contraception, menorrhagia, dysfunctional uterine bleeding, breast cancer and postponement of menstruation (Joint Formulary Committee, 2018). Although progesterones have been less associated with hepatic injuries than oestrogens, there have been sporadic reports of drug-induced liver injury caused by progesterones. The mechanism of progesterone-related drug-induced liver injury is not fully understood – mouse models indicate that progesterone can increase extracellular signal-regulated kinase phosphorylation and affect Kupffer cells, which may have a role in drug-induced liver injury as a result of production of pro-inflammatory cytokines (Toyoda et al, 2012).

A literature search was undertaken on EMBASE using 'norethisterone' and terms related to liver injury using a thesaurus – one report of three cases of norethisterone-related drug-induced liver injury was identified (Choudhary et al, 2017). In these cases, alanine aminotransferase and aspartate aminotransferase levels were elevated to >10x upper limit of normal and in two cases returned to near-normal range within 2 weeks of norethisterone withdrawal, mirroring the trends in the current case. All four cases were incidentally identified as the patients were asymptomatic; the cases are further described in *Table 1*.

The Roussel Uclaf Causality Assessment Method is a validated tool used to establish causality in cases of possible drug-induced liver injury. Data included in the Roussel Uclaf Causality Assessment Method score include time of onset, concomitant medication, non-drug causes of liver injury, response to drug withdrawal and rechallenge. Cases are assigned a score from -9 to +14 with

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CASE REPORT

A 51-year-old HIV-positive African woman was noted to have elevated transaminase levels on routine bloods. Previously in the normal range, her aspartate aminotransferase and alanine aminotransferase levels were 700 IU/litre and 1017 u/litre respectively. Her alkaline phosphatase level was minimally elevated at 111 IU/litre and bilirubin was within the normal range at 5 umol/litre. HIV was well controlled with a CD4 count of 370 mm^3 and an undetectable viral load (<50 copies/litre). In addition to HIV, she had a past medical history of *Pneumocystis jirovecii* pneumonia, tuberculosis adenitis and postmenopausal bleeding secondary to uterine fibroids. Regular medication included Atripla (efavirenz, emtricitabine, tenofovir disoproxil fumarate) and norethisterone. No medication changes had been made in the past 2 months. There was no history consistent with hepatic ischaemia.

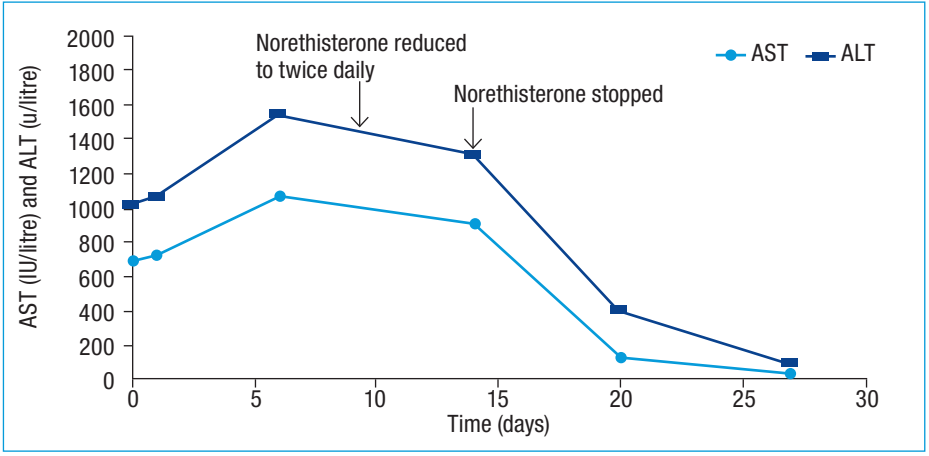
The patient reported a 2-week history of coryzal symptoms, dry cough and lethargy. She had been taking an over the counter cold and flu remedy (paracetamol, diphenhydramine hydrochloride, pseudoephedrine), but did not use more than the recommended dose of paracetamol (4 g per day). Minimal alcohol consumption was reported and illicit drug use denied. She was a health-care worker, but had never received a needle-stick injury. She had travelled to her birth country 7 months earlier, but had not been unwell during or after this trip. There was no history of diarrhoea, vomiting or abdominal pain. On examination, the abdomen was soft and non-tender with no evidence of hepatomegaly.

Blood tests confirmed no evidence of viral hepatitis, Epstein–Barr virus, cytomegalovirus, adenovirus or leptospirosis, and throat swab was negative for influenza. Full blood count, renal function, autoimmune screen, international normalized ratio, alpha fetoprotein and alpha-1 antitrypsin levels were all within normal ranges. Chest radiograph was clear and ultrasound scan showed normal appearance of the liver. On repeat testing aspartate aminotransferase and alanine aminotransferase levels continued to rise; 1 week later aspartate aminotransferase was 1074 IU/litre and alanine aminotransferase 1546 u/litre.

Although efavirenz is a recognized cause of elevated transaminase levels, this was considered unlikely in this case as the patient had been exposed to efavirenz for over 5 years with normal liver function tests. In clinic, the patient asked if norethisterone could be causing the transaminitis, having read the package insert describing 'elevated liver function tests' as a possible side effect. Norethisterone had been commenced 5 months earlier. A literature search identified three cases of norethisterone-related drug-induced liver injury, supporting her enquiry. The patient's postmenopausal bleeding had previously been so heavy as to require transfusion, so an alternative agent was required before norethisterone withdrawal. Intramuscular leuprorelin acetate was then commenced and norethisterone stopped. Before this the patient elected to reduce the dose of norethisterone from 5 mg three times daily to twice daily, with some resultant spotting.

Over the next 2 weeks her aspartate aminotransferase and alanine aminotransferase levels rapidly declined (*Figure 1*) to 30 IU/litre and 88 u/litre. Roussel Uclaf Causality Assessment Method score in drug-induced liver injury was calculated at 8, consistent with probable norethisterone-related drug-induced liver injury (Danan and Benichou, 1993). The patient was able to undergo a hysterectomy as planned.

Figure 1. Trend in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels over time.



LEARNING POINTS

- A high index of suspicion is needed to identify drug-induced liver injury.
- Consider drugs that have been prescribed over the past year – initially norethisterone was not considered as a potential cause as the patient was established on this drug.
- Be open to suggestions from patients as to the cause of their illness, especially where side effects are rare.
- The Roussel Uclaf Causality Assessment Method score can be used to quantify the likelihood of drug-induced liver injury.

Table 1. Summary of cases

Reference	Patient details	Duration of norethisterone	AST/ALT before withdrawal of norethisterone (IU/litre/u/litre)	AST/ALT 2 weeks after withdrawal of norethisterone (IU/litre/u/litre)	RUCAM score
Choudhary et al (2017)	27-year-old woman	2 months	628/1122	24/37	10
	43-year-old woman	2 months	228/614	23/43	8
	52-year-old woman	3 weeks	788/1058	233/516 (results from 1 week post withdrawal, patient then lost to follow up)	7
Current case	51-year-old woman	5 months	1074/1546	30/88	8

ALT = alanine aminotransferase; AST = aspartate aminotransferase; RUCAM = Roussel Uclaf Causality Assessment Method

6–8 indicating probable and >8 indicating highly probable drug-induced liver injury (Danan and Benichou, 1993).

Ethnic differences have been observed with the use of particular drugs known to cause liver injury, for example antibiotics, but there is no evidence of a general predisposition to drug-induced liver injury in different ethnic groups (Baehr et al, 2015; Licata et al, 2017). The severity of drug-induced liver injury was greater in black patients compared to white patients, with increased hospitalizations, transplants and deaths (Chalasani et al 2017). No data were identified regarding the impact of ethnicity in norethisterone-related drug-induced liver injury.

The substantial degree of elevation of liver enzyme levels, rapid return to normal on drug withdrawal, and exclusion of other possible causes of liver injury support norethisterone drug-induced liver injury as the cause in this case. The initial decline in alanine aminotransferase and aspartate aminotransferase levels on reduction from three times daily to twice-daily dosing further supports this by providing evidence of an inverse dose–response relationship. **BJHM**

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