Norethisterone Related Drug Induced Liver Injury: A Series of 3 Cases

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Drug induced liver injury (DILI) is uncommon and severe forms are associated with significant morbidity and mortality. Female sex hormones (estrogens and progestogens) related DILI generally occur with estrogen component. Progesterone component related DILI are infrequently reported. Norethisterone is commonly used drug in gynecologic practice to prevent excess per vaginal bleeding. We report 3 cases of Norethisterone related DILI manifesting as significant rise of transaminases. All of these patients took Norethisterone for prolonged periods and improved completely after withdrawal of drug. (J Clin Exp Hepatol 2017;7:266–268)

CASES

Case 1

A 27-year old female presented with irregular and severe per vaginal (PV) bleeding. She was diagnosed as a case of uterine fibroid and was given Tablet Norethisterone 5 mg twice a day. She took this medication for 2 months, her pre-anesthetic work up revealed raised transaminases (AST 826 IU/L, ALT 1327 IU/L with normal bilirubin and alkaline phosphatase). She was asymptomatic despite raised transaminases >10 ULN (upper limit of normal). Her viral work up was negative for HBsAg, antiHCV, IgM anti HAV and IgM anti HEV. Her autoimmune work up was negative for anti-nuclear antibody, anti LKM, anti mitochondrial antibody and smooth muscle antibody. Her transaminases improved after discontinuation of Norethisterone. However, she was again started on tablet Norethisterone for 2 weeks after normalization of LFTs due to severe bleeding again leading to impaired quality of life. At this point, the patient came to our hospital, liver function tests showed raised transaminases (Table 1). A diagnosis of drug induced liver injury (DILI) was kept. Her RUCAM score was +10, which was suggestive of highly probable DILI. She was advised to stop Norethisterone. Her transaminases improved over next 2 weeks and she underwent uneventful removal of uterine leiomyoma.

Keywords: drug induced liver injury, Norethisterone, sex hormones, progestogens

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Abbreviations: ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; DILI: drug induced liver injury; ULN: upper limit of normal

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Case 2

A 43-year old female presented with PV bleed. She was diagnosed as having fibroid uterus. She had received Norethisterone 5 mg once a day for 2 months when preanesthetic work-up revealed raised transaminases as shown in Table 1. Her viral markers were negative for HBsAg, antiHCV, IgM anti HAV and IgM anti HEV and ultrasound abdomen revealed normal liver and biliary system. Her RUCAM score was 8 (probable DILI) without re-challenge. Her transaminases improved over 2 weeks period after withdrawal of drug as shown in Table 1. She underwent uneventful surgery and surgical specimen revealed fibroid uterus with thickened endometrium.

Case 3

A 52-year old female presented with continuous PV bleed for 2 weeks after a 3 year period of amenorrhea. She was diagnosed as abnormal uterine bleeding with adenomyosis. She received tablet Ormeloxifene 60 mg twice weekly for 1 month and then it was switched to Norethisterone 5 mg thrice a day for 1 week and twice a day for 2 weeks. At this point she presented to us with raised transaminases. Her viral markers were negative (HBsAg, antiHCV, IgM anti HAV and IgM anti HEV) and ultrasound abdomen showed normal liver. Her RUCAM score probable (+7) for DILI. Her transaminases improved considerably after one week of Norethisterone stoppage. She was lost to follow up after that.

All these patients received Ursodeoxycholic acid 300 mg twice a day.

DISCUSSION

We present 3 cases of hepatitic type DILI due to Norethisterone. Female sex hormones or oral contraceptives have been shown to be associated with multiple types of liver injuries; various manifestations include including

Table 1 Biochemical Profile Before and After Discontinuation of Drug.

Serial number	Bilirubin (mg/dl)	AST/ALT (U/L)	ALP (U/L)	AST/ALT after Norethisterone withdrawal[a]
Case 1	0.2	628/1122	90	24/37
Case 2	1	228/614	89	23/43
Case 3	0.6	788/1058	151	223/516

[a]Repeat liver function tests were available at 13 days (case 1), 15 days (case 2) and 9 days (case 3); ALT (alanine aminotransferase), AST (aspartate aminotransferase), ALP (alkaline phosphatase).

hepatitic type, cholestatic type injury, benign neoplsams (adenoma), peliosis hepatitis, sinusoidal obstruction syndrome and increase in size of pre-existing hemangiomas.[1] Intrahepatic cholestatic jaundice is well known and is due to estrogenic component of combined oral contraceptive medications.[2–4] Multiple case reports of oral contraceptive induced liver injury have been described in the literature.[2–5] Progestogens are usually not implicated in the process of cholestasis. Norethisterone is a synthetic progestogen which is used in women with abnormal uterine bleeding. The exact mechanism of progestogen related cholestasis is not known. However, case reports of high dose progestogen related intrahepatic cholestasis are available in literature with Norethisterone and megestrol acetate where they have been used to treat breast cancer.[6,7] Case reports of Norethisterone induced cholestatic hepatitis has also been reported in patients taking it for contraceptive use as well.[8] Norethisterone has both estrogenic (which can explain cholestasis) and androgenic effects.[9,10] There are reports of hepatitic type injury with androgens[11] and the possible mechanism of DILI in current series should be related to androgenic effect of norethisterone. Generally Norethisterone is used for short periods of time. The RUCAM score[12] was highly probable in first case as she started medication on her own and re-challenge point were added to her score; as other 2 patients did not get any points for re-challenge (which is not advisable) hence RUCAM category is probable for them. The case number 3 was taking Ormeloxifene; however, it was stopped 3 weeks before presentation, DILI has not been reported with it and she still comes in category of probable DILI even if we give negative points to Ormeloxifene. Our series raises important question of differentiating drug adaptation from DILI as cases 1–3 had asymptomatic elevation of transaminases without rise of bilirubin (thus not suggestive of serious form of DILI). Sometimes liver adapts to injury, which causes transient elevation of enzymes[1] followed by normalization despite ongoing exposure to drugs (phenomenon of adaptation). Identification of adaptation versus DILI may be difficult sometimes as stopping a drug at the earliest possibility of mild injury does not allow learning whether adaptation will occur. On contrary, continuing same drug is unacceptable as it may cause severe form of DILI. There is no clear consensus on how to differentiate adaptation or when to stop a drug in presence of enzyme abnormalities. The higher degree of enzyme elevation and prolonged exposure to drug favors DILI in current series. FDA guidance for industry on DILI recommends treatment discontinuation in presence of transaminases > 8 upper limit of normal (ULN) or >5ULN for more than 2 weeks.[13] Liver biopsies are not routinely indicated in such cases for diagnosis; biopsy may be considered in atypical cases/prolonged DILI. Ursodeoxycholic acid is commonly used drug although there is no strong evidence in hepatitic cases.[14] This case series highlights the importance of having high index of suspicion, history evaluation and clinical implications of DILI due to Norethisterone, a commonly prescribed drug for abnormal uterine bleeding. The appropriate timing of drug withdrawal can lead to an uneventful recovery as seen in all cases. It is important that both physicians and patients understand the phenomenon of adaptation so that rechallenge that can lead to liver injury as exemplified by case 1 can be prevented.

CONFLICTS OF INTEREST

The authors have none to declare.

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