

CASE REPORT

Rare case of norethisterone-induced hepatitis: A case report

Eiman A. Arafa¹ | Vasumathi Dhayabaran² | Nabil E. Omar³  | Ahmed Awaisu⁴ 

¹Pharmacy Department, Alkhor Hospital, Hamad Medical Corporation, Doha, Qatar

²Department of Obstetrics and Gynecology, Alkhor Hospital, Hamad Medical Corporation, Doha, Qatar

³Pharmacy Department, National Center for Cancer Care & Research, Hamad Medical Corporation, Doha, Qatar

⁴Department of Clinical Pharmacy and Practice, College of Pharmacy, QU Health, Qatar University, Doha, Qatar

Correspondence

Ahmed Awaisu, Department of Clinical Pharmacy and Practice, College of Pharmacy, QU Health, Qatar University, P.O.Box 2713, Doha, Qatar.
Email: aawaisu@qu.edu.qa

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Abstract

We report a case of probable norethisterone-related liver injury, manifesting as a significant rise in liver transaminases in a 62-year-old woman. Upon discontinuation of norethisterone, liver transaminases decreased to normal level within two weeks. Knowledge of rare adverse effects of drugs such as norethisterone is necessary for rapid identification and management, especially in patients with risk factors such as non-alcoholic liver disease and obesity.

KEYWORDS

adverse drug reaction, drug-induced hepatitis, liver injury, liver transaminases, norethisterone, progesterone

1 | BACKGROUND

Norethisterone is a progesterone commonly used for contraception and in the treatment of some gynecological disorders including menorrhagia, delaying menstruation, abnormal uterine bleeding, and breast cancer.¹ Estrogen has been more associated with liver injuries than progesterone. However, a few cases of progesterone-induced liver injury have been reported in the literature. The plausibility of the association and the mechanism of progesterone-induced hepatic injury are not well understood. One study reported the effect of sex hormones on the development of halothane-induced hepatic injury in mice.² In this study, pre-treatment of mice with estradiol

diminished the effects of the liver injury, while progesterone intensified it.²

In this case report, we present a case of a patient who developed abdominal pain and vomiting associated with elevation of liver transaminases following the initiation of norethisterone tablets for the treatment of excessive vaginal bleeding. The Roussel Uclaf Causality Assessment Method (RUCAM), a causality assessment tool that is used specifically for suspected cases of drug-induced liver injury,² was applied to determine causality in this case. RUCAM includes the time of onset of the liver injury in relation to initiation of the drug, use of concomitant medications with a potential for liver injury, exclusion of non-drug causes of liver injury, response to drug withdrawal

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(subsequent course of injury), response to re-challenge, and specific risk factors (alcohol, age, pregnancy). Cases are assigned a score from -9 to $+14$ with ≤ 3 indicating unlikely, $4-5$ possible, $6-8$ probable, and >8 indicating highly probable drug-induced hepatotoxicity.² In our case, the RUCAM score was $+10$, indicating highly probable drug-induced liver injury. Similarly, using the Naranjo Adverse Drug Reaction Probability Scale, a score of 7 was obtained, indicating a probable drug-induced hepatotoxicity.³

2 | CASE DESCRIPTION

A 62-year-old woman (BMI: 36.3 kg/m^2) with a chief complaint of vaginal bleeding for two weeks attended a primary health center and was diagnosed with post-menopausal bleeding secondary to multiple fibroid uterus. She was started on norethisterone 5 mg per oral twice daily. Three weeks later, she presented to the emergency department of a secondary-level hospital with chief complaints of heavy bleeding, nausea, vomiting, and abdominal pain for two days. A previous record indicated that her baseline liver function test was normal [normal range of ALT ($0-30$), AST ($0-31$)]. At the time of presentation (i.e., about three weeks after starting the norethisterone), ALT and AST levels were elevated >20 times and >15 times above the baseline, respectively (see Table 1). Other liver function test parameters and coagulation profile were unremarkable (Table 2).

In addition, bilirubin, lipase, and amylase levels were within normal limit. However, abdominal ultrasound scan revealed fatty changes in the liver (suspected to be mild steatohepatitis due to non-alcoholic fatty liver disease), while transvaginal scan showed multiple fibroid uterus. The patient denied any use of herbal medications or use of alcohol. Her viral workup was negative for HBsAg, anti-HCV, IgM anti-HAV, and IgM anti-HEV, while autoimmune workup was negative for anti-nuclear antibody,

TABLE 1 Trend in liver transaminases fluctuation in a patient who received norethisterone 5 mg twice daily per oral for the treatment of abnormal uterine bleeding

Time/parameter (normal range)	ALT ($0-30 \text{ U/L}$)	AST ($0-31 \text{ U/L}$)
Baseline	25 U/L	23 U/L
3 weeks after initiation of norethisterone	731 U/L	487 U/L
3 weeks after discontinuation of norethisterone	20.1 U/L	17 U/L

anti-LKM, anti-mitochondrial antibody, and smooth muscle antibody. The liver transaminases progressively decreased and returned to normal levels over $2-3$ weeks upon discontinuation of norethisterone. A thorough medication reconciliation was conducted through interviewing the patient and checking our electronic medical record system (CERNER). It was confirmed that she was not taking any chronic or acute medications (either prescribed or over-the-counter) before starting norethisterone.

3 | DISCUSSION

Different types of liver injuries including cholestatic injury, hepatitis, benign neoplasms, peliosis hepatitis, sinusoidal obstruction syndrome, and increase in size of pre-existing hemangioma's have been associated with female sex hormones or oral contraceptives. High doses of progestins can lead to elevation of liver enzymes usually within one to two weeks of treatment initiation, and typically manifest as serum aminotransferase (ALT and AST) elevations without elevations in alkaline phosphatase (ALP) or bilirubin. With dose modification or discontinuation of therapy, these abnormalities usually resolve rapidly. There are few published case reports showing symptoms such as nausea, vomiting, and abdominal pain with rise in serum aminotransferases and jaundice during progesterone therapy, but there was no clear relationship to progesterone therapy. The mechanisms of progesterone-induced hepatic injury are not fully understood. One reported mechanism is that the cholestatic jaundice reported with progesterone-only therapy may be due to estrogenic compounds that might be the metabolites of semi-synthetic progesterone.⁴ Another mechanism is based on a study in animal models, which indicates that progesterone can increase the production of proinflammatory cytokines which may have a role in progesterone-induced hepatic injury.⁵

One case series involving three cases of norethisterone-related liver injury was published in the literature.⁶ In these cases, ALT and AST levels were elevated to >10 times the upper limit of normal (ULN). In addition, the liver transaminases levels returned to near-normal range within two weeks of the drug discontinuation, reflecting the trend in our case report.⁶ In the current case report, the patient's history and laboratory investigations excluded any other drug and non-drug causes for hepatitis, particularly the use of any other drugs or herbs. The symptoms, laboratory findings, clinical presentations, and resolutions were strongly associated with norethisterone use and discontinuation. While the patient's underlying non-alcoholic fatty liver disease could result in mild steatohepatitis which might have coincided with the increase in liver enzymes, the acute and high rise in the

TABLE 2 Trend in other liver function test parameters and coagulation profile in a patient who received norethisterone 5 mg twice daily per oral for the treatment of abnormal uterine bleeding

Time/parameter (normal range)	INR (critical high >4.9)	aPPT (24.6–31.2 s)	Bilirubin (0–21 µmol/L)	Albumin (35–50 g/L)
Baseline	1	24	7	35
3 weeks after initiation of norethisterone	1.1	19.8	9	31
3 weeks after discontinuation of norethisterone	1	23.9	7.1	33.4

liver enzyme suggests that the episode is more likely to be drug-induced. Nevertheless, non-alcoholic fatty liver disease maybe a potential risk factor for drug-induced liver injury and potentially more severe injury.^{7–9} Studies have reported several drugs that may induce liver injury in the context of obesity and non-alcoholic fatty liver disease.⁹ Therefore, this patient has at least two underlying risk factors for drug-induced liver injury (i.e., obesity and non-alcoholic fatty liver disease). However, after gastroenterology consultation, it was deemed that biopsy was not required for definitive diagnosis since the patient was on norethisterone which can cause hepatitis or cholestasis, coupled with the chronological improvement in liver function test post-discontinuation of norethisterone.

In the previously published literature, there are some case reports describing hepatic effect of norethisterone represented as cholestasis^{10,11} or jaundice,^{12,13} but very few reports about isolated elevated liver transaminases.^{6,13} It is very important for clinicians to collect more information to help in identifying drug-induced hepatic disturbances, so the offending drugs can be discontinued, and appropriate treatment and follow-up initiated. In addition, before initiation of oral contraceptive pills, clinicians should recognize and advise patients who are at risk for the development of complications such as individuals with alcohol use disorder or those with advanced age. FDA guidelines for industry on drug-induced liver injury recommend treatment discontinuation in the presence of transaminases >8 times the ULN or >5xULN for more than 2 weeks.¹⁴

4 | SUMMARY

We report a case of probable norethisterone-related liver injury, manifesting as a significant rise in liver transaminases in a 62-year-old woman who received norethisterone for the treatment of excessive vaginal bleeding due to a large uterine fibroid. Approximately, two weeks after the initiation of norethisterone, liver function test showed marked elevation of liver transaminases, suggesting norethisterone-induced liver injury. Upon discontinuation of norethisterone, the levels of the liver transaminases decreased to near normal

within two weeks. Adverse drug reaction (ADR) probability was assessed using two different tools. Roussel Uclaf Causality Assessment Method (RUCAM) for drug-induced liver injury indicated “highly probable” ADR with a score of +10, while Naranjo Probability Scale indicated “probable” ADR with a score of 7.

5 | CONCLUSION

This case report emphasizes the importance of having awareness about potentially serious effects, history assessment, and medical consequences of liver injury due to norethisterone which is commonly used for many gynecological disorders. Prompt withdrawal of drug can lead to predictable recovery and favorable clinical outcomes as seen in the reported case. It is important for clinicians to consider risk factors such as obesity and non-alcoholic fatty liver disease when initiating patients on norethisterone or other hepatotoxic drugs.

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CONFLICT OF INTEREST

The authors declare no conflict of interests.

AUTHORS' CONTRIBUTION

EAA and VD identified and conceived the case report idea. EAA and VD contributed in acquisition of relevant patient data. EAA, VD, NEO, and AA contributed equally in literature review, and writing the manuscript drafts. NEO and AA revised and edited the manuscript drafts. All authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

ETHICAL APPROVAL

The case report was approved by the Institutional Review Board of the Medical Research Centre at Hamad Medical Corporation (approval number MRC-04-20-101).

CONSENT

This case report does not contain any personal identifier of the patient [such as name and photograph]. A written patient informed consent of patient information, images, and publication was signed by the patient. Copy of the written consent is available for review by the editor of this journal.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

ORCID

Nabil E. Omar  <https://orcid.org/0000-0001-8291-7987>

Ahmed Awaisu  <https://orcid.org/0000-0002-9029-8925>

REFERENCES

1. Joint Formulary Committee. *British National Formulary: Guidance on intravenous Infusions*, 75th ed. BMJ Group and Pharmaceutical Press.
2. Danan G, Benichou C. Causality assessment of adverse reactions to drugs-I. A novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries. *J Clin Epidemiol*. 1993;46(11):1323-1330.
3. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30(2):239-245. Available from doi:10.1038/clpt.1981.154
4. Levin ER, Vitek WS, Hammes SR. Estrogens, progestins, and the female reproductive tract. In Brunton LL, Hilal-Dandan R, Knollmann BC, editors. *Goodman & Gilman's: The Pharmacological Basis of Therapeutics*, 13th ed. McGraw-Hill Education; 2017;1-53. Available from: <http://accessmedicine.mhmedical.com/content.aspx?aid=1162541991>
5. Toyoda Y, Endo S, Tsuneyama K, et al. Mechanism of exacerbative effect of progesterone on drug-induced liver injury. *Toxicol Sci*. 2012;126(1):16-27. Available from <https://pubmed.ncbi.nlm.nih.gov/22157104/>
6. Choudhary NS, Bodh V, Chaudhari S, Saraf N, Saigal S. Norethisterone related drug induced liver injury: a series of 3 cases. *J Clin Exp Hepatol*. 2017;7(3):266-268. Available from: [/ pmc/articles/PMC5620103/?report=abstract](http://pmc/articles/PMC5620103/?report=abstract).
7. Massart J, Begriche K, Moreau C, Fromenty B. Role of non-alcoholic fatty liver disease as risk factor for drug-induced hepatotoxicity. *J Clin Transl Res*. 2017;3(Suppl 1):212-232. doi:10.18053/jctres.03.2017S1.006
8. Bessone F, Dirchwolf M, Rodil MA, Razori MV, Roma MG. Review article: drug-induced liver injury in the context of non-alcoholic fatty liver disease – a physiopathological and clinical integrated view. *Aliment Pharmacol Ther*. 2018;48(9):892-913. doi:10.1111/apt.14952
9. Allard J, Le Guillou D, Begriche K, Fromenty B. Drug-induced liver injury in obesity and nonalcoholic fatty liver disease. *Adv Pharmacol*. 2019;85:75-107. doi:10.1016/bs.apha.2019.01.003
10. Anand V, Gorard DA. Norethisterone-induced cholestasis. *QJM*. 2005;98(3):232-234. Available from <https://academic.oup.com/qjmed/article-lookup/doi/10.1093/qjmed/hci031>
11. W D. Norethisterone-induced cholestasis: the hidden alarm. *Int J Pregnancy Child Birth*. 2019;5(3):126-127. doi:10.15406/ipcb.2019.05.00161
12. Somayaji BN, Paton A, Price JH, Harris AW, Flewett TH. Norethisterone jaundice in two sisters. *Br Med J*. 1968;2(5600):281-283. Available from <https://pubmed.ncbi.nlm.nih.gov/4296504/>
13. Baines GF. Jaundice in a patient taking norethisterone compound tablets. *Lancet*. 1965;285(7376):108-109. doi:10.1016/S0140-6736(65)91695-8
14. Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation Drug Safety Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation [Internet]; 2009 [cited 2020 Jun 5]. Available from: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm> or Tel:800-835-4709 or 301-827-1800 <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>

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