Correction to: Mifepristone: An Uncommon Cause of Drug-Induced Liver Injury

Ishani Shaha, f, Tyler Putnam, Evan Daughertyb, Neil Vyasc, Keng-Yu Chuangd, e, f

This is to correct the published article, Gastroenterology Research, 2019;12(3):181-184. DOI: 10.14740/gr1188.

After the publication of our initial article [1], we were made aware by the patient’s treating endocrinologist that the patient was also on ethinyl estradiol and norethindrone (Loestrin), an oral contraceptive. The patient failed to provide us with this information when she was admitted. We were also given access to more detailed information regarding the patient’s mifepristone dosing history (Fig. 1). These are essential data to be included in our case report as two potential mechanisms could be used to explain the patient’s development of jaundice while taking mifepristone.

Drug-induced intrahepatic cholestasis has long been observed in patients on oral contraceptives and during the latter stages of pregnancy [2]. In hepatocytes, the bile salt export pump constitutes the predominant bile salt efflux system and mediates the cellular excretion of conjugated bile salts into the bile canalculus [3]. In vitro, inhibition of the bile salt export pump by exogenous estrogen has been proposed as the pathophysiological mechanism behind estrogen-exposure-inducing inhibition of bile acid secretion and transportation [4]. This mechanism is consistent with the liver biopsy findings of this patient, demonstrating intrahepatic cholestasis.

Loestrin is metabolized in the liver via cytochrome P450 3A4 (CYP3A4), whereas mifepristone is a strong inhibitor of CYP3A4. We postulate that the gradual escalation of mifepristone increased liver exposure to Loestrin, resulting in the development of hepatic cholestasis that reversed upon discontinuation of both drugs. Although it could be questioned why Loestrin and mifepristone were prescribed concurrently, the patient’s endocrinologist deemed it essential as Loestrin provided estrogen replacement and contraception that is required for women of reproductive age while taking mifepristone.

An alternative mechanism that could have caused the patient’s symptoms could be mifepristone-induced direct cholestatic liver injury similar to that caused by anabolic steroids because mifepristone has a classic 17-carbon steroid ring structure typical of steroids [5]. Funke et al [6] reported a similar case of a patient with Cushing’s syndrome on increasing doses of mifepristone up to 900 mg once daily, who then developed a cholestatic liver injury. This patient, in contrast to our patient, was not on any other medications known to induce cholestatic injury. Upon cessation of mifepristone, the patient’s hyperbilirubinemia and elevated alkaline phosphatase returned to normal [5].

Anabolic steroids are characterized by the substitution of a phenyl-amino-dimethyl group at the 11P-position of the steroid ring as well as radicals located at the C17 position. Cholestasis due to the C17 variable androgens was observed in some animal models where the possible mechanism of action could have been reduced bile salt transporter proteins and disruption of the intrahepatic microfilaments [4]. In this setting, cholestatic injury is typically reversible upon discontinuation of the glucocorticoid. The similar clinical phenotype reported by Funke et al [6] and our patient’s case support this mechanism as an underlying pathological process.

In summary, there are two possible mechanisms to explain our patient’s cholestatic injury. Mifepristone could have inhibited the metabolism of estrogen when the mifepristone dose was escalated, which could have precipitated hepatic cholestasis. Alternatively, mifepristone could have acted like an anabolic steroid to cause liver injury. Therefore, our case report highlights the importance of the knowledge of concomitant drug use, particularly those that behave as CYP3A4 substrates or inhibitors, when considering mifepristone therapy. Close liver function monitoring when patients start mifepristone treatment and during dose escalation is advisable, especially when the patient is on other drugs that may act as CYP3A4 substrates or inhibitors.

Ishani Shaha, f, Tyler Putnam, Evan Daughertyb, Neil Vyasc, Keng-Yu Chuangd, e, f

Department of Internal Medicine, Creighton University at St. Joseph’s Hospital and Medical Center, Phoenix, AZ, USA. Email: keng-yu.chuang@dmgaz.org; Ishani Shah, Department of Internal Medicine, Creighton University at St. Joseph’s Hospital and Medical Center, Phoenix, AZ, USA. Email: ishani1991@gmail.com

doi: https://doi.org/10.14740/gr1188c1
Acknowledgments

Portions of this case were presented as a poster at the 101st Annual Meeting and Expo of the Endocrine Society, March 23 - 26, 2019, New Orleans, Louisiana; and an abstract was published in the Journal of the Endocrine Society ENDO 2019 Abstracts Volume 3, Issue Supplement 1, April - May, 2019.

References

1. Shah I, Putnam T, Daugherty E, Vyas N, Chuang KY. Mifepristone: an uncommon cause of drug-induced liver injury. Gastroenterology Res. 2019;12(3):181-184.
2. Anand V, Gorard DA. Norethisterone-induced cholestasis. QJM. 2005;98(3):232-234.
3. Meier Y, Zodan T, Lang C, Zimmermann R, Kullak-Ublick GA, Meier PJ, Stieger B, et al. Increased susceptibility for intrahepatic cholestasis of pregnancy and contraceptive-induced cholestasis in carriers of the 1331T>C polymorphism in the bile salt export pump. World J Gastroenterol. 2008;14(1):38-45.
4. Lang C, Meier Y, Stieger B, Beuers U, Lang T, Kerb R, Kullak-Ublick GA, et al. Mutations and polymorphisms in the bile salt export pump and the multidrug resistance protein 3 associated with drug-induced liver injury. Pharmacogenet Genomics. 2007;17(1):47-60.
5. Bond P, Llewellyn W, Van Mol P. Anabolic androgenic steroid-induced hepatotoxicity. Med Hypotheses. 2016;93:150-153.
6. Funke K, Rockey DC. Cholestatic drug-induced liver injury caused by mifepristone. Hepatology. 2019;69(6):2704-2706.