Short Communication

Elagolix is porphyrogenic and may induce porphryic attacks in patients with the acute hepatic porphryias

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ABSTRACT

Elagolix is an FDA-approved treatment for moderate-to-severe pain associated with endometriosis but has been associated with increased acute porphryic attacks in women with the acute hepatic porphyrias (AHPs). A fluorescence-based screening assay for drug porphyrogenicity in LMH cells indicates that elagolix is porphyrogenic; thus, elagolix should be avoided or used with caution in patients with the AHPs.

1. Introduction

Endometriosis is a disease characterized by the presence of endometrial tissue outside the uterus, which can cause dysmenorrhea, pelvic pain and infertility [1]. In 2018, the FDA approved elagolix, the first oral GnRH receptor antagonist for moderate-to-severe pain associated with endometriosis, and it has shown promising result; however, it is not well known if it is contraindicated in other conditions [2,3]. The acute hepatic porphyrias (AHPs) are diseases caused by enzyme deficiencies in disease-specific steps of the heme biosynthesis pathway. Affecting approximately 1 in 25,000 individuals in the United States [4]. The AHPs include acute intermittent porphyria, hereditary coproporphyria, and variegate porphyria, which are all autosomal dominant diseases, and severe deficiency of ALA dehydratase, which is a very rare autosomal recessive disorder. AHPs often present with abdominal pain, which could be confused with the abdominal and pelvic pain associated with endometriosis. Some women with AHPs experience acute attacks during the luteal phase of their menstrual cycles, and GnRH antagonists, such as leuprolide and histrelin, have shown benefits in reducing these symptoms [5]. Due to similar mechanisms of action as the other GnRH antagonists, elagolix has been used in hopes of AHP relief, but unfortunately, a few of our female patients reported increased frequency of acute porphryic attacks after starting elagolix. These reports led us to test elagolix for porphyrogenicity via a recently described fluorescence-based screening assay in Leghorn Male Hepatoma (LMH) cells [6].

2. Methods

The fluorescence-based screening assay and the cytotoxicity assay were adapted from Ma et al., 2022 [6]. The LMH cells, which are hepatocellular carcinoma cells from male Leghorn chickens treated with diethylnitrosamine [7], were purchased from ATCC (Manassas, VA, USA) and kept in Waymouth medium (Thermo Fisher Scientific, Waltham, MA, USA) supplemented with fetal bovine serum and penicillin-streptomycin. 1 × 10^4 LMH cells were seeded in each well of a black, clear bottom 96-well plate coated with 0.1% gelatin (Thermo Fisher Scientific, Waltham, MA, USA) and incubated overnight at 37 °C. Elagolix and selected other compounds were added in half-log increments from 0 mM to 1 mM in the presence and absence of 250 μM deferoxamine (DFO), an iron chelator that prevents the conversion of the fluorescent intermediate protoporphyrin to heme, increasing the amount of fluorescent protoporphyrin, mimicking the effects of the porphyrias, and improving the sensitivity of the assay. Each trial had three replicates of the positive control, 0.314 mM allyl isopropyl acetamide (AIA), which is a known porphyrogenic chemical that causes biochemical acute porphyria, and three replicates of the negative
control, 0.314 mM acetaminophen. After an 18–24 h incubation period, plates were read at an excitation and an emission wavelength of 410 nm and 625 nm, respectively (Fig. 1a). Concurrently, LMH cells were seeded in a white, solid-bottom 96-well plate under the same conditions to assess cytotoxicity via the ATPLite cytotoxicity assay (Fig. 1b). Background signals were deducted in all fluorescence measurements by the fluorescence emitted from DMSO in the absence of DFO. Data and statistical analyses were performed with the software, GraphPad Prism 8, and the fluorescence ratios were calculated based on the concentrations that yielded the highest fluorescence signals.

3. Results

In the presence of deferoxamine (DFO), an iron chelator that prevents the conversion of the fluorescent intermediate protoporphyrin to heme, the positive control produced fluorescence readings 1.6–1.9 times greater in comparison to the readings produced by the negative control in all experimental groups (Fig. 1a). The readings produced by 1 mM 5-aminolevulinic acid (ALA), the intermediate after the rate-determining enzyme of the heme biosynthesis pathway, was 5.01 times greater than the readings produced by the negative control, indicating porphyrogenicity. The purpose of including ALA in this experiment is to support the validity of the assay. Since this intermediate bypasses the rate-determining enzyme, we expect to have a much higher fluorescence reading, which was seen here. The highest fluorescence reading produced by elagolix was 1.73 times greater than the negative control, which is similar to the fold-change produced by AIA. Fluorescence readings at higher concentrations for the selected drugs may be lower due to cytotoxic effects (Fig. 1b).

4. Discussion

The fluorescence readings produced by the positive and negative controls were as expected. AIA produced the highest fluorescence readings at 0.314 mM, indicating that any drug concentrations that produced readings greater or less than the reading produced by this concentration would correlate to porphyrogenicity or non-porphyrogenicity, respectively. Acetaminophen has been used safely in patients with AHPs for decades so any readings below the highest fluorescence reading produced by acetaminophen (0.314 mM) was considered to be non-porphyrogenic. Since the fold-changes for AIA and elagolix in comparison to acetaminophen were 1.6 and 1.73, respectively, and not statistically different, this indicates that elagolix is porphyrogenic.

Elagolix is a weak-to-moderate inducer of cytochrome P450 3A, which is an enzyme that can increase the demand for heme synthesis. Inducers of CYP 3A are known to be porphyrogenic and risky for use in AHP as they can exacerbate the symptoms of AHPs [8]. This, along with reports of elagolix worsening porphyrinic symptoms in patients with AHPs where they experienced acute abdominal pain and neuropathic symptoms (Bonkovsky, unpublished observations), supports our conclusion that elagolix is porphyrogenic. According to a 2020 pharmacokinetic study completed in humans, the therapeutic dose of elagolix, which is 200 mg, led to a maximal plasma concentration of 774 ng/mL, or approximately 1 µM [8]. Although this concentration is lower than the concentration found in our in vitro fluorescence screening assay that led to porphyrogenicity, the concentrations of the drug reached in hepatocytes, especially with chronic use, may be higher. This fluorescence-based screening assay is also completed in Leghorn chicken hepatic cells without defects in the heme synthetic pathway, not in human hepatic cells from patients with the AHPs. Furthermore, the duration of exposure of the LMH cells was only 16–24 h. In conclusion, elagolix is porphyrogenic and should be avoided in patients with known AHPs with biochemical or clinical activity. If used, these patients should be monitored closely as it may induce or exacerbate acute porphyrinic attacks. Women without known AHPs who describe increased, rather than decreased, abdominal pain or other symptoms following initiation of elagolix should be tested for the AHPs [9].

Author contributions

H.L.B. and C.D.M. conceptualized and designed the study. C.D.M. performed, analyzed and contributed to all the experiments. C.D.M. and H.L.B. wrote the manuscript.

Declaration of Competing Interest

The authors report no conflict of interest. This project was supported by the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, USA (U54 DK 083909) and by unrestricted grant funding from the American Porphyria Foundation.

Data availability

Data will be made available on request.

References

[1] P. Parasur, P. Ozcan, K.L. Terry, Endometriosis: epidemiology, diagnosis and clinical management, Curr. Obstet. Gynecol. Rep. 6 (1) (2017) 34–41.
[2] V.N. Lamb, Elagolix: first global approval, Drugs. 78 (14) (2018) 1501–1508.
[3] H.S. Taylor, L.C. Giudice, B.A. Lessey, et al., Treatment of endometriosis-associated pain with elagolix, an oral GnRH antagonist, N. Engl. J. Med. 377 (1) (2017) 28–40.
[4] V.M.S. Ramamujam, K.E. Anderson, Porphyria diagnostics part 1: a brief overview of the porphyrins, Curr. Protoc. Hum. Genet. 86 (2015), 17.20.11–17.20.26.
[5] L. Zhao, X. Wang, X. Zhang, et al., Therapeutic strategies for acute intermittent porphyria, Intract. Rare Dis. Res. 9 (4) (2020) 205–216.
[6] C.D. Ma, C.G. Van Horn, M. Wan, C. Bishop, H.L. Bonkovsky, Assessment of porphyrogenicity of drugs and chemicals in selected hepatic cell culture models through a fluorescence-based screening assay, Pharmacol. Res. Perspect. 10 (3) (2022) e00951.
[7] T. Kawaguchi, K. Nomura, Y. Hiraizumi, T. Kitagawa, Establishment and characterization of a chicken hepatocellular carcinoma cell line, LMH1, Cancer Res. 47 (16) (1987) 4460–4464.
[8] M. Sheelby, A.R. Polepally, A. Nader, et al., Clinical pharmacology of elagolix: an oral gonadotropin-releasing hormone receptor antagonist for endometriosis, Clin. Pharmacokinet. 59 (3) (2020) 297–309.
[9] M. Balwani, B. Wang, K.E. Anderson, et al., Acute hepatic porphyria: recommendations for evaluation and long-term management, Hepatology. 66 (4) (2017) 1314–1322.