Radiopharmaceuticals in Acute Porphyria

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ABSTRACT

Purpose: The acute porphyrias are a group of rare metabolic disorders of the heme biosynthetic pathway. Carriers of the acute porphyria gene are prone to potentially fatal acute attacks, which can be precipitated by drug exposure. It is therefore important to know whether a drug is safe for carriers of the acute porphyria gene. In this study, radiopharmaceuticals were assessed on their porphyrogenicity (ie, the potential of a drug to induce an attack).

Methods: The assessment was conducted by classifying the drugs according to the Thunell model.

Findings: From 41 radiopharmaceuticals assessed, I-131 norcholesterol, Tc-99m mebrofenin, Tc-99m phytate, Tc-99m sestamibi, and Tl-201 chloride were classified as possibly porphyrogenic.

Implications: I-131 norcholesterol, Tc-99m mebrofenin, Tc-99m phytate, Tc-99m sestamibi, and Tl-201 chloride should not be prescribed for patients experiencing acute porphyria unless an urgent indication is present and no safer alternative is available. In such cases, potential users should seek advice from a porphyria expert. Preventive measures may also be required. (*Clin Ther*. 2016;38:2239–2247)

Key words: acute porphyria, drug safety, porphyrogenicity, radiopharmaceuticals.

INTRODUCTION

The porphyrias are a group of metabolic disorders caused by abnormal function of the heme biosynthesis pathway that results in the specific accumulation of heme precursors.[1] Along this pathway, 8 enzymes (cytosolic and mitochondrial) are responsible for the construction of heme (Figure 1). There are 7 types of porphyria resulting from partial enzyme deficiency; an additional porphyria is characterized by a gain-of-function mechanism.

The types of porphyria can be classified into 2 groups on the basis of the illness they cause. The acute porphyria group includes acute intermittent porphyria, hereditary coproporphyria, variegate porphyria, and a rare 5-aminolevulinic acid (ALA)-dehydratase deficiency porphyria. Patients experiencing 1 of these types experience sudden neurologic symptoms. Variegate porphyria and hereditary coproporphyria can cause either neurologic or cutaneous symptoms, or a combination of both. Acute intermittent porphyria is the most common type, with an estimated gene prevalence in Europe of 1 per 75,000.[2] The other 4 types of porphyria (labeled cutaneous porphyria) include erythropoietic porphyria, porphyria cutanea tarda, erythropoietic protoporphyria, and X-linked dominant erythropoietic protoporphyria. They are characterized by photosensitivity and mainly affect the skin. Because cutaneous porphyria is not associated with acute neurologic symptoms, the current report discusses only the acute porphyrias.

The acute porphyrias cause acute attacks accompanied by typical symptoms such as severe abdominal pain, constipation, nausea, confusion, and seizures. These attacks can be life-threatening.[1] An acute attack can last from several days to 2 weeks. Most patients experience 1 or 2 acute attacks during their lifetime. A minority will experience repeated attacks, sometimes over numerous years.

There are several risk factors for an acute attack, of which high drug exposure is the most important. Other major risk factors include alcohol use, caloric

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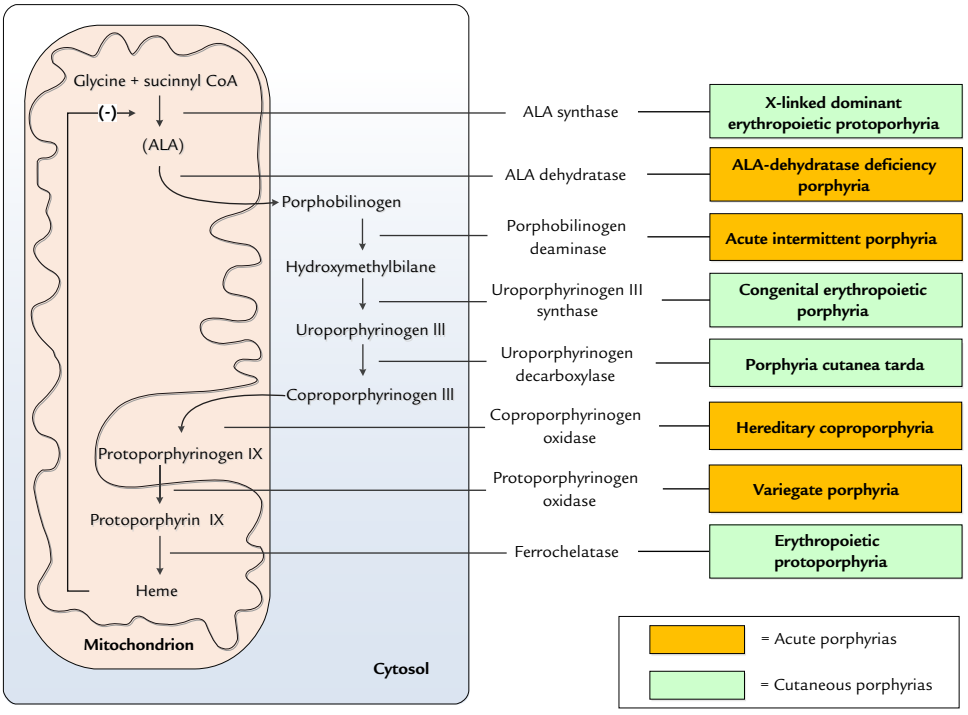

Figure 1. A schematic representation of the heme biosynthetic pathway with the mitochondrial and cytosolic enzymes, which are responsible for the transformation of the intermediates. The types of porphyria and related enzyme deficiencies are presented. ALA = 5-aminolevulinic acid; CoA = coenzyme A. Adapted from Puy et al.[1]

deprivation, infection, stress, and hormonal changes.[2] The latter phenomenon explains why women are 3 times more likely to experience an acute attack than men.

Drug exposure is a significant factor in inducing attacks in patients carrying the acute porphyria gene. In the current hypothesis for the pathophysiology of acute porphyria, an inducible enzyme called ALA synthase (ALAS1) has a critical role. In carriers of acute porphyria, the induction of ALAS1 may overload the next catalytic step, controlled by porphobilinogen deaminase.[3] As a result, porphobilinogen and ALA may accumulate, of which ALA is believed to be the neurotoxic intermediate causing the neurologic symptoms.[1] The mechanism by which the transcription of ALAS1 is induced is mediated by nuclear receptors. These nuclear receptors are DNA-binding proteins and are activated by xenobiotics. Two nuclear receptors, the pregnane xenobiotic receptor (PXR) and the constitutive active receptor (CAR), are responsible for most of the drug-induced transcriptions.[2,4] Each one of these transcription factors can activate, in parallel, the 2 genes needed for cytochrome formation (ie, their apoCYP and ALAS1 target gene) for the biosynthesis of the heme component of the holoenzyme to be formed. The ability of a drug to activate PXR and/or CAR makes the drug a possible porphyrogenic trigger.[3] The activation of PXR and/or CAR may also be induced by drugs binding to cytochrome P450 (CYP) enzymes and thereby inactivating CYP. This action will result in a compensatory heme biosynthesis.[2] The xenobiotic receptors PXR and/or CAR can also be activated by pharmacodynamic actions, physiologic actions, or side effects. The response or action is largely influenced by the sympatico-adrenal system, hypothalamic-pituitary-adrenal axis, and disturbance of the energy homeostasis.[3] Another possible mechanism of induction of ALAS1 is reduction of the heme pool by induction of heme oxygenase.[2]