Review Article

Acute porphyria: The drug demon etiology

Abstract

Drugs are one of the important factors that precipitate acute attacks in patients with porphyria. Various *in vitro* and preclinical animal models exist for determining porphyrogenicity of a drug, but these predictions are not very reliable. Ambiguities still remain with many drugs as to whether they are safe in patients with porphyria. An algorithm for determining the porphyrogenic potential using evidence from anectodotal reports, lipophilicity, affinity of a drug to the Cytochrome enzymes (CYP450), ability to induce or irreversibly inhibit either CYP450 2C9 or CYP450 3A4 and the ability to induce hepatic 5-aminolevulinate synthase has been devised. Management of an acute attack of porphyria involves symptomatic treatment and administration of haem arginate. Several international networks have been initiated that serve as good sources of information for the safe use of drugs to be used in porphyria.

Key words:
Idiosyncratic drug reactions, porphyrogenicity, porphyrogenic drugs

Introduction

Porphyrias are a group of metabolic disorders that result from the accumulation of intermediates of heme biosynthesis.[1] The name "porphyrins" in Greek means "purple".[2] The disease is known to occur with a prevalence ranging between 1 and 10 per 100,000 population worldwide[3] and is considered an orphan disease.[4] Porphyria is inherited either as an autosomal dominant or recessive (the exceptions are porphyria cutanea tarda and X-linked protoporphyria that may occur sporadically) and is due to deficient activity in any of the many heme-synthesizing enzymes.[5-7] The incidence has been reported to be greater in women.[8] Eight types of porphyria[9,10] have been identified as depicted in Figure 1, of which porphyria cutanea tarda is the most common subtype and acute intermittent porphyria (AIP) is the most common acute porphyria. Symptoms reported in patients with attacks of acute porphyria include abdominal pain, followed by constipation, nausea and vomiting, tachycardia, hypertension, urine discoloration, fever, seizures, and respiratory paralysis.[11] Amongs the many mechanisms that have been elucidated for the neuronal damage in porphyria, two of them seem to be the most plausible: Direct neurotoxicity of alpha aminolevulinic acid or porphobilinogen and diminished intraneuronal heme level.[12,13] Elevated plasma and urinary levels of porphyrin are diagnostic for the disease.[11,14] AIP is caused by a deficiency of hydroxymethyl bilane synthase (HMBS) that results from a mutation in the HMBS gene.[15] Various hormones, drugs, fasting, alcohol, infection, and stress have also been implicated to precipitate an acute attack of porphyria.[16] This review is an in-depth analysis of drugs triggering acute symptoms in patients with porphyria.

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Drugs Precipitating Acute Porphyria

Drugs are the most common factors that are associated with acute attacks in patients with porphyria.[1] Drugs as causative agents are primarily based on anecdotal case reports that have accumulated over time.[17] In addition, some of them have been shown to be porphyrogenic in animal studies.[18] Although, there are no strict criteria to evaluate the porphyrogenic potential of a drug, various animal models exist for the evaluation.

In vitro testing

Extensive studies with rodents and chick embryo hepatocytes *in vitro*, *in vivo* have been done to determine

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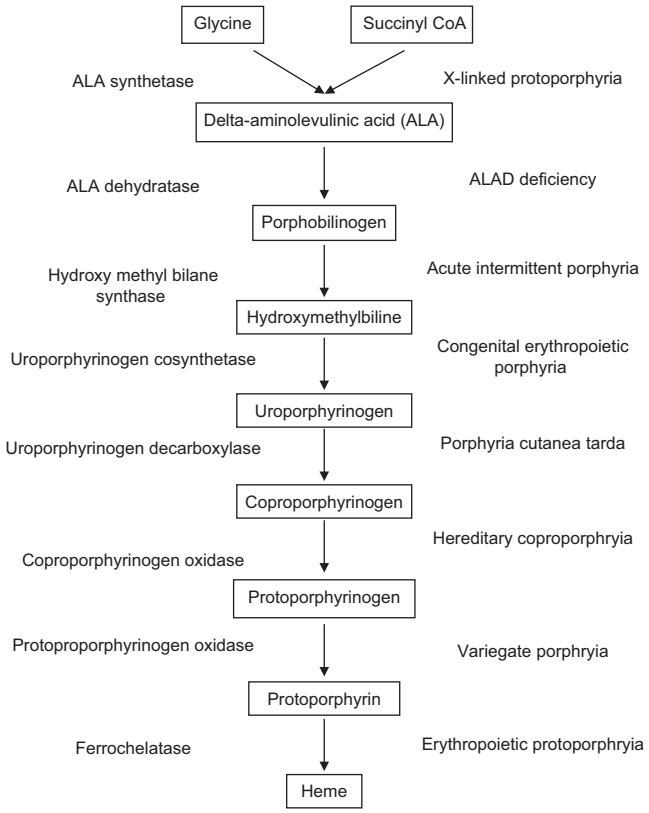

Figure 1: Types of porphyria

the porphyrogenic potential of various drugs.[19-21] These models were found to be unreliable and associated with low sensitivity as they do not resemble the pathway occurring in human beings. Additionally, a poor specificity was also noted especially with the avian cell culture model.[22] *In vitro* tests can also screen a compound for CYP450 enzyme induction capacity that conveys porphyrogenic potential of the drug.[23]

Preclinical *in vivo* testing

Intraperitoneal injections of hexachlorobenzene (HCB) and iron in mice lead to an increase in the liver porphyrin levels that can be measured by liver homogenate analysis 6–8 weeks after administration.[24] The HCB releases oxygen free radicals and damages the cell membrane of hepatocytes. Similarly, co-administration of HCB with tetrahydrochloroquine precipitates porphyria more intensely than HCB alone in quails.[25] Considering its carcinogenic properties, it is less commonly used currently. Iron chelating agents such as desferrioxamine and 1,2-diethyl-3-hydroxypridin-4-one have been found to inhibit ferrochelatase in mice resulting in porphyrin accumulation 7 days after administration.[26] Endpoints include microscopic analysis of total porphyrin content in liver, activity of 5-aminolevulinate synthase (ALAS) and urinary aminolevulinic acid or porphobilinogen following the drug administration.[27] Porphyria can be induced in dogs by administration of 2-allyl-2-isopropylacetamide.[28] Recently, beagle dogs are also used for the evaluation of porphyrogenicity of a drug.[29] Following 13 weeks after administration in dogs, the animals passed dark red/brown feces, and macroscopic examination revealed mottled dark brown liver with pale foci. Microscopic examination of the hepatocytes revealed "Maltese cross" like structures in polarized light and "Sunburst" pattern in electron microscopy.[29] Both *in vitro* and preclinical *in vivo* testing have been found to overestimate the porphyrogenicity of a drug.[30]

Evidence from humans

Reports from human beings with regard to the porphyrogenic potential of a drug mainly are case reports/series.[17] The diagnosis of acute porphyria is attained both with the clinical symptoms and signs, and laboratory findings such as classic burgundy red discoloration of long stored urine or Watson-Schwartz test using Ehrlich's aldehyde reagent.[31] Furthermore, quantitative estimation of porphobilinogen and aminolevulinic acid in urine can be performed. Plasma levels of porphyrins and erythrocyte hydroxymethylbilane synthase enzyme test will also be useful in establishing the diagnosis of acute porphyric attacks. Stool porphyrin levels are usually within normal range or mildly elevated. All the samples have to be transported to the laboratory in a light protected container. Other nonspecific signs in an attack of AIP include hyponatremia, syndrome of inappropriate secretion of antidiuretic hormone, and mild leukocytosis. Many drugs have been implicated in causing an acute attack in porphyric individuals.[30-34] As discussed at the end of this review, many porphyria networks list each of the drugs as either safe or unsafe to be administered in these individuals. Drugs, when applied topically to the intact skin or mucosa, are usually not porphyrogenic.[1] Many potential pathways have been put forth by which a drug can act as a porphyrogen.[35] Plausible mechanisms include induction of hepatic ALAS, the rate-limiting enzyme in heme synthesis and drug-induced depletion of heme-containing enzymes either by induction or irreversible inhibition of cytochrome P450 (CYP450) group of enzymes.[35] Drugs can also cause inhibition of hepatic porphobilinogen deaminase and depletion of heme pool independent of cytochrome enzymes that leads to induction of ALAS. Alcohol disturbs the decarboxylation of uro- and heptacarboxyporphyrinogen in chronic hepatic porphyrias leading to decreased the elimination of the same by the liver.[36] Antiepileptic drugs have been found to produce N-alkylprotoporphyrin adduct formation that alkylates the prosthetic heme component of CYP450 enzymes.[37] There are instances where a drug has been found to have the potential to precipitate acute attacks in animal studies, but safe in humans as well as drugs that were found to be safe in animals, but porphyrogenic in humans.[38] Further, even the well-known precipitants such as barbiturates consistently do not lead to acute attacks.[39] Hence, to develop an index for assessing the safety of a drug in patients with porphyria becomes important although in

the past an attempt to classify the drugs as safe or dangerous depending on the number of reports of acute porphyria attacks in humans in association with a particular drug and the presence of evidence from various *in vitro* and animal studies was made and but in vain because the metabolism differs between species.[40]

Evaluation of Porphyrogenicity of a Drug

In humans, the most abundant heme-containing proteins are hemoglobin, synthesized in bone marrow and the CYP450 group of metabolizing enzymes in the liver.[41] Drugs increase the demand for heme synthesis either by inducing or irreversibly inhibiting these enzymes. A liphophilic drug will have more affinity to bind to the CYP450 group of enzymes.[42] Among the various CYP450 enzymes, CYP2C9 and CYP3A4 constitute the majority (almost 30–40% of the total liver enzymes) and almost 50% of the drugs are metabolized by them.[43] Hence, it has been proposed that lipophilic drugs with a profound induction or inhibition of either CYP2C9 or 3A4 are likely to be porphyrogenic.[44] Another possible way is through induction of ALAS through an increase in their transcription by binding to nuclear receptors[45,46] such as constitutively active receptor and pregnane xenobiotic receptor. Hence, if a drug acts as a ligand for these receptors, there is more chance for it to precipitate acute attacks. Apart from these, hepatic uptake of the majority of the drugs is also determined by the extent of plasma protein binding. A drug with a low plasma protein binding may have more hepatic exposure and correspondingly, an increased porphyrogenic risk. Based on these considerations, an algorithm has been proposed by Thunell *et al*.[47] to determine the porphyrogenicity of a drug as shown in Figure 2.

Treatment

Treatment of an attack of an acute drug-induced porphyria is mainly supportive and includes withdrawal of any offending agent and administration of haem arginate at 3–4 mg/kg/day for 4 days is the treatment of choice.[31] It acts by repressing ALAS and as the drug is an orphan, it's expensive and procuring it is very challenging, especially for a developing nation.[48] Intravenous dextrose at high doses (300–500 g/day) that suppresses ALAS can be used in situations when haem arginate is unavailable.[49] If the patient has progressive ascending neurological paralysis or bulbar muscle weakness, ventilator support with appropriate antiepileptics, sedatives have to be administered. Opioid analgesics may be administered in the case of abdominal pain and among the anti-epileptic drugs; phenytoin, barbiturates, carbamazepine, and sodium valproate are better avoided. Gabapentin, a newer anti-epileptic with no effect on hepatic enzymes, appears to be a safe and effective alternative with a promising future.[50,51] Liver transplantation may be an option for patients with repeated life-threatening acute attacks resulting in poor quality of life, requirement of ventilatory support, and progressive loss of venous access due to haem infusion.[52]

Porphyria Networks

Considering the rarity of porphyria and paucity of information available regarding the drugs that precipitate acute attacks, several porphyria groups/consortium have been developed worldwide that provide specialist testing and clinical advice regarding porphyria. Being an orphan disease, the limited knowledge available in this disease is shared and resources are used to the fullest possible. Some of the notable ones are European Porphyria Network,[19] Porphyria Consortium,[53] Norwegian Porphyria Centre,[54] Alberta Porphyria Society,[55] American Porphyria Foundation,[56] British and Irish Porphyria Network[57] and Australia Porphyria Centre.[58] Each of these groups enlists drugs and their potential to induce porphyric attacks depending on the strength of evidence available from various animal studies and clinical reports. They serve as a good source of information for both the patients and treating physicians to take decisions on appropriate drugs that can be prescribed to patients of porphyria despite some information conflicting. In addition, porphyria registry has been created by the European Porphryia Network in 2012 that serves as a multi-center, international, observational prospective cohort study to include all patients who have been diagnosed of having porphyria. This registry aims primarily to conduct an investigation of the natural history, efficacy of treatment regimens and actual clinical practice for people with porphyria across Europe.[59]

Conclusion

To conclude, drugs are the most common factors precipitating acute porphyric attacks. Various *in vitro* and animal models exist for determining porphyrogenicity of a drug exist but the prediction is not reliable. Although several international networks have been initiated serving as a good source of information to both the patients and physicians, many drugs are unclassifiable clearly. Algorithm for determining the porphyrogenic potential using anecdotal reports, lipophilicity and affinity of a drug to cytochrome enzymes (CYP450), ability to induce or irreversibly inhibit either CYP450 2C9 or CYP450 3A4 and ability to induce ALAS has been developed. Main-stay of treatment of an acute attack of porphyria involves general measures and administration of haem arginate.

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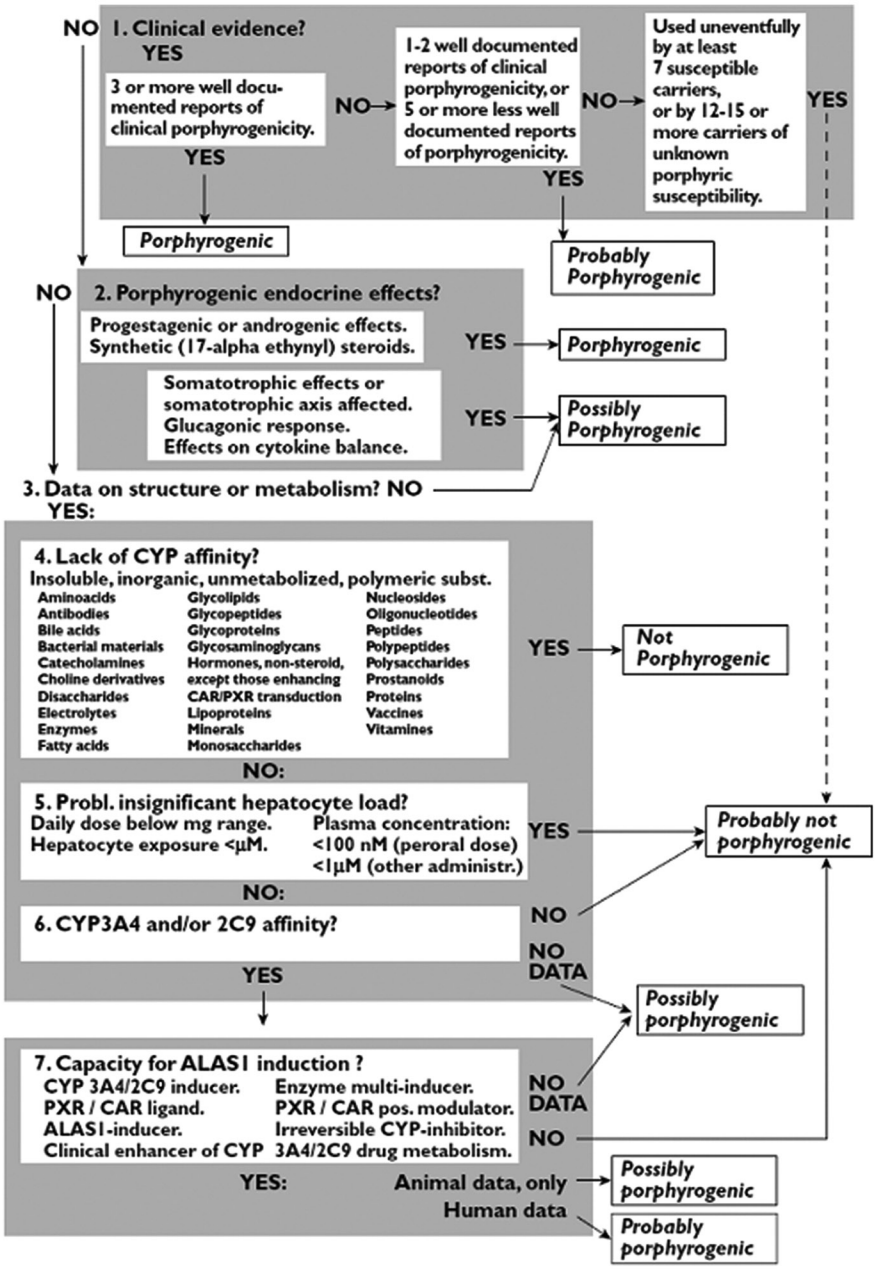

Figure 2: Steps in evaluating the porphyrogenicity of a drug (adapted with permission from Thunell *et al.*)

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