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Drugs in porphyria: From observation to a modern algorithm-based system for the prediction of porphyrogenicity

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ABSTRACT

The acute porphyrias are a group of disorders which result from inherited defects in the enzymes of the heme biosynthetic pathway. Affected patients are prone to potentially fatal acute attacks. These attacks are frequently precipitated by exposure to commonly used drugs. Correctly identifying the safety or otherwise of drugs in porphyria is therefore important. In this review we describe how clinical experience and the findings of experimental systems using whole animal or cell culture models have been interpreted to determine porphyrogenicity, that is the potential of a drug to induce an acute attack in a patient carrying a gene for acute porphyria.

It is now well established that induction of delta-aminolevulinic acid synthase, the rate controlling enzyme of the heme biosynthetic pathway, is fundamental to porphyrogenicity, and that drug-induced hepatic heme depletion via induction or suicidal inactivation of cytochrome P450 is central to this process. The process is now sufficiently well understood that prediction of porphyrogenicity from structural and functional information alone would appear to be justified.

Contents

1. Introduction

The porphyrias are a group of pharmacogenetic disorders (Moore & Hift, 1997; Hift et al., 2003). Patients with certain forms of porphyria may react to many drugs with a serious and potentially fatal complication, known as the acute attack. There is a need for those drugs which are potentially dangerous in porphyria to be identified, so that patients may avoid their use. Consequently many drug safety lists, categorising drugs as safe or unsafe in porphyria, have been published.

Abbreviations: AIA, allyisopropylacetamide; AIP, acute intermittent porphyria; ALA, delta-aminolevulinate (synonym, delta-aminolevulinic acid); ALAS, delta-aminolevulinate synthase (EC 2.3.1.37); CEP, congenital erythropoietic porphyria; CYP, cytochrome P450; DDC, 3,5 diethoxycarbonyl-1,4 dihydro-2,4,6 trimethylpyridine; FECH, ferrochelatase (EC 4.99.1.1); HCB, hexachlorobenzene; HMBS, hydroxymethylbilane synthase (EC 4.3.1.8) (synonym, porphobilinogen deaminase); PBG, porphobilinogen; PCT, porphyria cutanea tarda; PPOX, protoporphyrinogen oxidase (EC 1.3.3.4); UROD, uroporphyrinogen decarboxylase (EC 4.1.1.37); VP, variegate porphyria.

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In this article we review the methods which have been employed to predict a drug's porphyrogenicity, a term we use to describe the propensity of that drug to induce the acute attack in patients carrying a gene for an acute porphyria. We evaluate the utilisation of clinical data, and animal and cell-culture-based experimental systems for the determination of porphyrogenicity, and discuss our experience with the mechanism-based analysis proposed by Thunell et al. (2007) for reliable prediction of porphyrogenicity.

2. Heme biosynthesis

The porphyrias arise from metabolic defects on the heme biosynthetic pathway (Desnick et al., 2004) (Fig. 1). In this pathway the simple substrates succinyl-coA and glycine are combined under the enzymatic control of delta-aminolevulinic acid synthase (ALAS, EC 2.3.1.37) to form delta-aminolevulinate (ALA). Two molecules of ALA then condense to form the monopyrrole porphobilinogen (PBG). Collectively ALA and PBG are known as the porphyrin precursors. Four PBG molecules combine to form the linear tetrapyrrole hydroxymethylbilane, which is in turn converted to the tetrapyrrolic macrocycle uroporphyrinogen-III. This undergoes a subsequent series of decarboxylation and oxidation reactions, followed by the incorporation of elemental iron, to result in heme. Eight enzymes catalyse these reactions. The first and the last three enzymes are mitochondrial, whereas the intermediate enzymes are cytosolic (Desnick et al., 2004).

80 to 90% of the total heme in mammals is synthesised in the erythron, and is eventually incorporated into haemoglobin. The remaining heme is synthesised in all nucleated cells, predominantly in the liver, where it is incorporated into a number of hemoproteins and in particular cytochrome P450 (CYP) (Podvinec et al., 2004). The key synthetic enzymes on the two pathways are shared with the exception of the initial enzyme, ALAS. The non-erythroid and erythroid forms of ALAS are known as the housekeeping (ALAS1) and the erythroid (ALAS2) enzymes respectively, are transcribed from genes which share 73% homogeneity (Elder, 1993) and are located on chromosomes 3 and the X chromosome respectively (Bishop et al., 1990; Woodard & Dailey, 2000; Shoolingin-Jordan et al., 2003; Dailey et al., 2005). ALAS is rate-limiting and effectively controls the rate of heme synthesis. Hepatic ALAS1 is a highly regulated enzyme, fine tuned to maintain appropriate levels of intracellular heme (May et al., 1995), since heme deficiency is deleterious and excess is toxic.

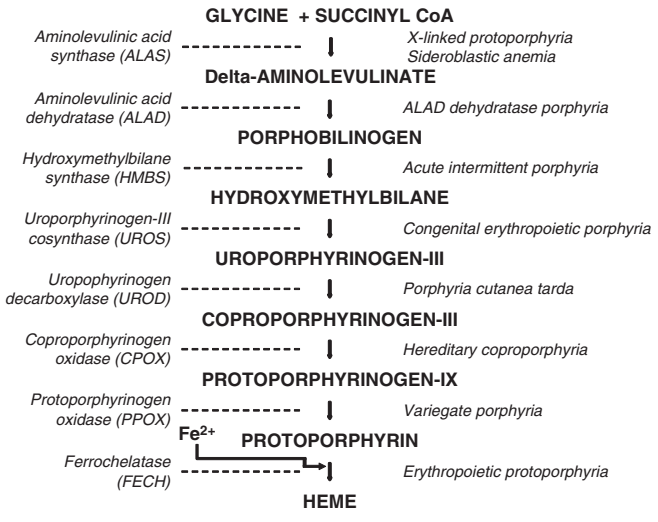

Fig. 1. The heme biosynthetic pathway. Successive steps are catalysed by the enzyme listed on the left of the diagram.

3. The acute porphyrias

Reduced activity of any of these enzymes may lead to an accumulation of the porphyrins and porphyrin precursors prior to that metabolic step. This is reflected in an altered pattern of accumulation or excretion of porphyrins and their precursors in blood, tissues, urine or stool. Each pattern is specific to the defective enzyme and therefore to a specific form of porphyria (Fig. 1). Most of the porphyrias represent inborn errors of metabolism, resulting from germline mutations in the DNA coding for that enzyme (Desnick et al., 2004).

Four of the porphyrias, classed as the acute porphyrias, may present with a potentially fatal complication known as the acute attack (Elder et al., 1997). These are acute intermittent porphyria (AIP), variegate porphyria (VP), hereditary coproporphyria and ALA dehydratase porphyria. AIP has an estimated gene prevalence in Europe of 1 per 75000: VP is approximately half as prevalent (Puy et al., 2010). In two regions, porphyrias are locally common as a result of geographical founder effects: AIP in the northern regions of Sweden, where the gene prevalence is 1 per 1000 (Floderus et al., 2002), and South Africa, where the gene prevalence of VP amongst the population of European descent is estimated at 1.2 per 1000 (Koegelenberg, 2003).

The acute attack is characterised by autonomic dysfunction, presenting as acute abdominal pain, tachycardia, hypertension, intestinal dysmotility and neuropsychiatric disturbance. Severely affected patients develop a motor neuropathy which may result in profound quadriparesis, respiratory failure and death in the absence of mechanical ventilation (Hift & Meissner, 2005; Thunell, 2010). A number of factors may induce the acute attack: most notably drug exposure (Kauppinen & Mustajoki, 1992; Elder et al., 1997; Hift & Meissner, 2005). Additional precipitants are caloric deprivation (Handschin et al., 2005; Delaby et al., 2009), the menstrual cycle (Innala et al., 2010), infection and stress (Eales, 1979; Bylesjö et al., 2009).

Three forms of porphyria: porphyria cutanea tarda (PCT), congenital erythropoietic porphyria (CEP) and erythropoietic protoporphyria, are characterised by photosensitivity but not associated with acute attacks. All drugs may be used freely in these patients (with the exception of iron and oestrogens in PCT, which are associated etiologically with this disorder).

4. Drugs, porphyria and clinical practise

The first case of a drug-induced porphyria was reported in 1889. Following administration of the newly introduced hypnotic sulphonal, a woman developed a fatal illness associated with the passage of high concentrations of porphyrins in the urine (Stokvis, 1889). This association was later recognised in a number of other cases, who were labelled as having “acute toxic hematoporphyria” (Gunther, 1922). Though exposure to sulphonal might indeed have precipitated an acute attack of porphyria in patients with pre-existing latent porphyria, With subsequently commented on the unexpectedly high incidence of porphyria in patients treated with sulphonal, and therefore suggested that the drug may in fact have precipitated a porphyria-like syndrome in otherwise normal individuals (With, 1971).

A porphyric attack following administration of barbiturates was first reported in 1906 (Dobchansky, 1906). Their potency in inducing the acute attack was subsequently established by Waldenstrom (1937) in Sweden, and Dean (1956) and Eales (1979) in South Africa. From an early stage it was clear that not all drugs shared the potential to induce porphyria equally, those which showed this property being termed “porphyrogenic” whereas those that did not were labelled “non-porphyrogenic”, and were considered unsafe and safe for use in porphyria respectively. Regulating the drug exposure of patients carrying a gene for porphyria was recognised as an essential part of the management of such patients.