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SAFE AND PROBABLY SAFE DRUGS IN ACUTE HEPATIC PORPHYRIA

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Abstract – Acute porphyrias are caused by enzyme defects along the heme synthesis pathway. Patients usually present with abdominal pain, impaired intestinal motility, neurological and psychiatric symptoms, hypertension, tachycardia, hyponatriemia and reddish urine. This article gives an overview over drugs that are recommended in patients with acute hepatic porphyrias and represents a compilation of four so far existing lists.

Key words: Acute Porphyria, medication, treatment of Acute Porphyria, heme, heme arginate

INTRODUCTION

Porphyrias are heterogeneous metabolic disorders that are either hereditary or, in some cases also acquired enzyme defects of the hepatic porphyrin biosynthesis (1,10,12,21). Patients with acute hepatic porphyria (AHP) usually present with abdominal, neuropsychiatric and/or cardiovascular symptoms, whereas chronic hepatic and erythropoietic porphyrias are characterized by dermatological problems due to photodermatosis (5). The symptomatic phase of acute hepatic porphyria is characterized by excessive accumulation and excretion of the porphyrin precursors δ- aminolevulinic acid (ALA), porphobilinogen (PBG) and porphyrins (7,12).

Abbreviations: AHP, acute hepatic porphyria; **ALA**, 5-aminolevulinic acid; **ALAS**, aminolevulinic acid synthase; **CXR**, xenobiotic-sensing nuclear receptor; **PBG**, porphobilinogen; **PBG-D**, porphobilinogen-deaminase; **ALAS 1**, 5- aminolevulinic acid synthase 1

Usually the development of an acute porphyria crisis is closely related to the intake of porphyrinogenic medication, fasting, physical stress, alcohol, cigarette smoking or infections. Porphyrinogenicity of certain drugs was first published by L. Wetterberg and M.O Doss (26,8). The role of individual drugs in triggering acute porphyria has recently been described by Thunell (21,22,23,24).

A few porphyria centers around the world publish recommendations on medications in AHP. Among them, the annually published German Drug Collection (Rote Liste®) (11). contains information on safe drugs based on published information and data collected for 30 years in more than 900 patients with AHP (8). Moreover, European (www.drugs-porphyria.org), South African (www.porphyria.uct.ac.zaown), and American lists of porphyrinogenic drugs have been published or are publicly available (27,28,2). This article compares and comments on these four lists.

RATIONALE FOR SELECTION OF SAFE AND PROBABLY SAFE DRUGS

The South African list classifies drugs into four categories: 1. safe, 2. use but with caution, 3. use only with extreme caution and if no alternative, 4. avoid: high risk. The European list subdivides drugs into five categories: 1. not porphyrinogenic, 2. probably not porphyrinogenic, 3. possibly porphyrinogenic, 4. probably porphyrinogenic, 5. porphyrinogenic. The German list "Rote Liste®" (Rote Liste® Service GmbH) and an American list characterize drugs as "safe" or "not safe" (11,2). Furthermore, in this article we base our recommendations on theoretical knowledge and experimental findings to evaluate the safety of a drug. For example, we decided to eliminate rifampicin as a safe drug in the current version of the German drug list, since rifampicin was identified as ligand for heme synthesis stimulating nuclear receptors (6,11,21,22,3,24, 19,13).

Using the four lists, we recommend that thiopental, erythromycin, chloramphenicol, co-trimoxazole, nitrofurantoin, rifampicin, ketoconazol, indinavir, ritonavir, methyldopa, carbamazepine, phenobarbital, phenytoin, primidone, valproic acid, dihydroergotamine and norethisterone should be avoided in patients with AHP. Drugs like amitryptiline, dextropropoxyphene, lidocaine, spironolactone, cyclizine and azathioprine that are not recommended uniformly in all four lists were excluded and not addressed in our current list.

SAFE AND PROBABLY SAFE DRUGS IN AHP

Safe and probably safe drugs in acute hepatic porphyrias are listed in Table 1.

TABLE 1. Safe and probably safe drugs in AHP *

Anaesthesia	Allergy, Immune System and Respiratory Tract	Cancer
(Atropine)	Acetylcysteine	Anakinra
(Bupivacaine)	(Betamethasone)	Asparaginase
(Glycopyrronium)	Cromoglicic acid	Basiliximab
(Isoflurane)	Epinephrine	Bleomycin
(Neostigmin)	Etanercept	Cisplatin
(Pancuronium)	Immunoglobulins	Daclizumab
(Rocuronium)	Infliximab	Filgrastim
Suxamethonium	(Loratadine)	Lenograstim
	Salbutamol	Pegfilgrastim
	(Triamcinolone)	Trastuzumab

Circulation and Heart	Coagulation	Diuretics
Adenosine	Abciximab	Amiloride
(Acetylsalicylic acid)	Antithrombin III	(Furosemide)
Atenolol	Dalteparin	(Hydrochlorothiazide)
(Atropine)	Dipyridamole	
Candesartan	Enoxaparin	
Digoxin	Heparin	
Dobutamine	Streptokinase	
Dopamine	Urokinase	
Enalapril	(Warfarin)	
Eprosartan		
Glyceryltrinitrate		
Lisinopril		
Magnesium		
Metoprolol		

Propranolol		
Sotalol		
Valsartan		

Gastrointestinal Tract	**Hormones**	**Infection (bacterial)**
Cimetidine	Epoietin alfa	Amikacin
Lactulose	Glucagon	Amoxicillin-clavulanate
(Loperamide)	(Goserelin)	(Azithromycin)
(Ondansetron)	Insulin	Benzylpenicillin
Ranitidine	Levothyroxine	(Cefotaxime)
Senna	Liothyronine	(Ceftriaxone
Ursodeoxycholic acid	Oxytocin	(Cefuroxim)
	Tetracosactide	(Ciprofloxacin)
		(Ertapenem)
		Gentamicin
		(Imipenem)
		(Meropenem)
		Methenamine
		(Moxifloxacin)
		Netilmicin
		(Ofloxacin)
		Phenoxymethylpenicillin
		Piperacillin
		Teicoplanin
		Tobramicin
		Vancomycin

Infection (fungal)	**Infection (viral)**	**Metabolism**
(Amphotericine)	(Abacavir)	Alendronic acid
(Caspofungine)	Aciclovir	(Bezafibrate)
	(Didanosine)	Cholestyramine
	(Famciclovir)	Insulin
	(Foscarnet)	Metformin
	Ganciclovir	(Nicotinic acid)
	(Lamivudine)	Risedronic acid
	(Ribavirin)	
	(Tenofovir)	
	Valaciclovir	
	Valganciclovir	

Neurology	**Pain**	**Psychiatry**
(Gabapentin)	Acetylsalicylic acid	Chloralhydrate
Magnesium	Buprenorphine	Chlorpromazine
(Vigabatrin)	(Fentanyl)	Fluoxetine
	Morphine	Fluphenazine
	(Paracetamol)	(Haloperidol)
	Pethidine	Lithium
		(Lorazepam)

* In parentheses: drugs with minor restrictions outlined in the South African and European lists (use but with caution, probably not porphyrinogenic, respectively)

DISCUSSION

In this article we compare four international lists of drugs in AHP and also included our own experiences with more than 900 patients over 30 years (German Competence Center for Porphyria Diagnosis and Consultation, Marburg and Karlsruhe, Porphyria Center Saxony, Chemnitz and Dresden). We selected 125 safe or probably safe drugs for treatment of symptoms and complaints in patients with AHP.

Because AHP is a rare disease, only case reports and carefully observed patients in specialised centres for porphyria provide reliable information on safe drug use. However, case reports lacking biochemical data on urinary ALA, PBG and porphyrin excretion should be interpreted with caution, since misdiagnosis of AHP is common.

Porphyrinogenic drugs induce cytochrome synthesis via the rate-limiting enzyme ALAS 1 in the liver. Synthesis of apo-cytochromes and heme synthesis are closely linked and regulated by nuclear receptors (14,17). The final product heme regulates the production of porphyrin precursors and porphyrins in the liver via repression of the key enzyme ALAS 1 (4).
The nuclear proteins PXR and CAR were identified as receptors for porphyrinogenic substances such as rifampicin and phenobarbital (19,13).

Drugs, which are considered safe, can probably exhibit porphyrinogenic properties when the heme pool is depleted. This, as well as individual differences in cytochrome metabolism of drugs could possibly explain conflicting evaluation in different lists (20).
Age, gender, enzyme or transporter protein polymorphisms, nutritional status, sex hormones, infection or inflammation, alcohol and stress are important modulators of heme cosumption and ALAS 1 induction in response to a given drug (20,25,16,6).

DRUGS WITH UNCERTAIN EFFECT ON AHP

The use of drugs with uncertain or porphyrinogenic effects on AHP is appropriate only in life threatening circumstances, and when the patient is closely monitored and heme arginate therapy is available.

GENERAL TREATMENT OF AHP

The patient should be admitted into an intensive care unit, porphyrinogenic medication should be terminated immediately, and analgesic therapy as well as glucose infusion (“glucose effect”) with electrolyte adjustment should be started. Recently, the regulatory links between hepatic heme biosynthesis and glucose metabolism through PGC-1α-nuclear receptors has been elucidated (9,15,24). This is the explanation for the suppressive effect od glucose on ALAS 1.

Intravenously applied human hemin (heme arginate, Normosang ®, Orphan Europe) at a dose of 3 mg/kg body weight on four consecutive days restores the hepatic free heme pool, improves the function of hepatic heme proteins, effectively represses ALAS 1 and decreases the overproduction and consequently the urinary excretion of ALA and PBG within a few days.

After infusion, preferably into a large vein to reduce local irritation, the vessel should be washed with saline for 15 minutes. We suggest to dilute the hemarginate with 100 ml of human albumin (4-20 % depending on local availability) instead of saline solution to avoid vein damage. Hemin is available in the United States as a lyophilized powder (Panhematin®; Abbott Laboratories), whereas heme arginate (Normosang®) does not have FDA approval.

Ultimately, liver transplantation may be considered in case of severe complicated disease (18). Correction of the hepatic enzyme defect using adenoviral vectors or transplantation of hepatocytes may be options for the future.

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