

Anaesthesia recommendations for patients suffering from **Porphyria**

Disease name: Porphyria

ICD 10: E80.0, E80.1, E80.2

Synonyms: ALA dehydratase deficiency porphyria (ADP), Acute intermittent porphyria (AIP), Congenital erythropoietic porphyria (CEP), Erythropoietic protoporphyria (EPP), Hereditary coproporphyria (HCP) Porphyria cutanea (PCT), Plumboporphyria (PP) Variegated porphyria (VP), X-linked protoporphyria (XLP)

Porphyrias are a group of metabolic disorders, mainly inherited, in which there are defects in the heme biosynthetic pathway that may lead secondarily to overproduction of one or more heme precursors. Heme is essential for transport of oxygen from the lungs to tissues and removal of carbon dioxide from tissues to the lungs for excretion (hemoglobin) and biotransformation (respiratory chain, cytochromes P-450, and other heme-containing enzymes). Eight different enzymes are involved in the biosynthesis of heme; The activity of the entire pathway is chiefly related to end-product repression of activity of the first and normally rate-controlling enzyme of the pathway, namely 5-aminolevulinic acid (ALA) synthase. Partial deficiency of heme leads to up-regulation of ALA synthase by several molecular mechanisms, whereas sufficiency or excess of heme leads to down-regulation of ALA synthase through effects on gene transcription, decreased stability of its mRNA, decreases in its transport into mitochondria, and decreases in half-life of the mature mitochondrial form of the synthase.

Medicine in progress



Perhaps new knowledge

Every patient is unique

Perhaps the diagnostic is wrong



Find more information on the disease, its centres of reference and patient organisations on Orphanet: www.orpha.net

Disease summary

The enzyme deficiency disorders follow either an autosomal dominant, autosomal recessive or x-linked inheritance except the sporadic PCT. There are eight different forms of porphyria, nonacute and acute forms, depending on the chief site of overproduction of heme precursors. Porphyrins are classically divided into hepatic or erythropoietic types. Another useful classification is according to cardinal clinical manifestations: Four of the diseases may give rise to acute attacks with neuro-visceral manifestations [the acute or inducible porphyrias AIP, VP, HCP, PP] and these are an issue concerning anesthesia., Other forms cause cutaneous manifestations. However, for two of the diseases, namely, hereditary coproporphyria and variegate porphyria, patients may have both neuro-visceral and cutaneous manifestations. The non-acute porphyrias do not exhibit the acute symptoms of neurological disorders, abdominal pain and electrolyte abnormalities and in particular they are not triggered by anesthetic agents or any drugs. Therefore they do not present a serious peri-operative risk.

Incidence: Acute porphyric attacks hardly ever occur before puberty. They are mainly disease of women in their child-bearing years [Ages 18-50 years]. In most countries, acute intermittent porphyria is the most common and most severe form of acute porphyria, with symptomatic disease occurring in 1:10 000 to 1:20 000. In patients with psychiatric disorders, the prevalence may be higher, perhaps as high as 1:500. The prevalence of genetic defects in the hydroxymethyl bilane synthase (hmbS) gene [also known as porphobilinogen deaminase] is far higher, about 1/1600 persons in Western Europe, emphasizing the importance of other genetic or acquired factors in pathogenesis. Both, symptomatic and asymptomatic heterozygotes, have 50 percent or greater of porphobilinogen deaminase activity in the majority of patients; a total deficiency is not reconcilable with life. 90 percent of individuals with the deficiency exhibit no clinical signs. Hormonal and nutritional factors, as well as pharmacologic agents (induction of ALA (amino levulinic acid) -synthetase) may exacerbate the disorder. Initiating factors for an overproduction are infections, starvation, alcohol, induction of hepatic CYP 450 by drugs (such as barbiturates) pregnancy, hormones.

Other Symptoms: Acute attacks occur after puberty, commonly in females, cause abdominal pain, obstipation, Nausea, autonomic instability with hypertension, tachycardia, neuropathy, muscle weakness, paresthesia, neuropsychiatric abnormalities, depression, electrolyte abnormalities, hemolytic anemia, hepatic failure, or cirrhosis.

Typical surgery

None

Because patients typically present with severe abdominal pain, there is increased likelihood that patients with acute porphyrias will be subjected to exploratory laparotomies, appendectomies, and/or cholecystectomies. Typically, at surgery there is no evidence of acute appendicitis or cholecystitis, and such surgeries do not prevent recurrence of symptoms.

Type of anaesthesia

General or regional anaesthesia, both are possible under avoidance of initiating factors and unsafe or unclear medication.

Necessary additional diagnostic procedures (preoperative)

- Consultation with an experienced anaesthesiologist in advance to better plan surgery and anaesthesia management
- Consultation with a physician with special expertise in evaluation and management of the porphyrias is desirable
- Consultation with a neurologist if there are neurologic signs
- Urine sampling for preliminary staging of porphyria precursors
- No stress
- No starvation; maintenance of adequate intake of carbohydrates and energy [kCal].

Particular preparation for airway management

None, only in special cases with known or suspected airway abnormalities.

Particular preparation for transfusion or administration of blood products

None.

Particular preparation for anticoagulation

None.

Particular precautions for positioning, transport or mobilisation

- No UV light source
- Soft positioning, gel cushion.

Probable interaction between anaesthetic agents and patient's long term medication

No fasting, no corticosteroids for initial PONV prophylaxis, induction medication: propofol (avoid barbiturates!), pre-operative glucose supplementation.

Anaesthesiologic procedure

- Preoperative preparation together with experienced anaesthesiologist, surgeon or other physician with expertise in porphyria management.
- (Urine sampling and laboratory values for preoperative staging of precursors)
- Maintenance of fluid and carbohydrates (300g/day), no fasting
- Premedication with midazolam if considered necessary,
- PONV prophylaxis: no corticosteroids, use Droperidol
- Preparation in a stressfree setting with soft positioning.
- Induction of anesthesia using Morphine, Propofol and Vecuronium for relaxation, Maintenance using Desflurane
- Reversal of muscle relaxation if necessary with Atropine, Neostigmine
- Postoperative analgesia, Morphine, Ibuprofen or regional anesthesia technique using Bupivacaine

Particular or additional monitoring

- Provide perioperative care, presurgical admission for iv hydration with glucose containing fluids (300 g/day) to down-regulate ALA synthase-1
- Intensify clinical monitoring (temperature, nausea, vomiting, diarrhoea, seizures psychotic signs, peripheral neuropathy)
- Laboratory (serum sodium, colour of urine, 5- amino-levulinic acid, porphobilinogen)
- Provide care on Intermediate care or intensive care unit if necessary.

Possible complications

The disease may be disabling, but in most cases it does not lead to a fatal outcome. Late diagnosis, however, and delayed onset of treatment may result in life-threatening complications like renal insufficiency, liver cirrhosis or in rare cases a lethal course.

A common symptom is abdominal pain. Together with symptoms like ileus, distention, constipation or diarrhoea, nausea, vomiting it may be often misinterpreted as acute abdomen.

Muscle weakness, sensory loss and peripheral neuropathy, due to axonal degeneration of neurons, may be seen. However it is not common in all acute attacks; progression up to respiratory or bulbar paralysis and death may occur if proper diagnosis and treatment are delayed.

Seizures are not uncommon due to hyponatremia, hypomagnesaemia, or neurologic effects and treatment may be challenging because of exacerbation by most commonly used anti-convulsants (barbiturates, hydantoins, lamotrigine, or other potent inducers of cytochromes P-450). It appears that levetiracetam and vigabatrin are safe for use for treatment and prophylaxis of seizures complicating the acute porphyrias.

Postoperative care

- Provide sufficient perioperative care in the recovery room for all patients and provide additional care on Intermediate care or intensive care unit in extensive surgery.
- Continue iv. hydration with glucose containing fluids (300 g/day) to suppress synthesis of ALA synthase-1
- Provide heme intravenously (3mg/kg BW per day for three- five days) if needed [Treatment of choice for acute porphyric attacks]
- Intensify monitoring for: hypothermia, psychotic symptoms, nausea, vomiting, diarrhea, seizures)
- Laboratory (control serum sodium, magnesium levels, colour of urine, 5- aminolevulinic acid, porphobilinogen).

Information about emergency-like situations / Differential diagnostics

caused by the illness to give a tool to distinguish between a side effect of the anaesthetic procedure and a manifestation of the disease

In case of symptoms like:

- Unclear Convulsions, seizures: Start Acute crisis treatment with glucose and heme, in the form of heme arginate (Normosang) or hydroxy heme (Panhematin, Recordati)

In cases with symptoms like: (Be alert, these might be first signs of an acute attack. Consider relation to porphyria and start treatment)

- Vertigo
- Acute cephalic pain
- Muscular weakness
- Syncope

- Systemic arterial hypertension, hypertensive crisis
- Acute renal insufficiency
- Hepatic insufficiency
- Acute trouble of the vision
- Acute severe pain
- Acute infection
- Pyrexia
- Acute abdominal pain
- Vomiting; severe constipation [obstipation]

Ambulatory anaesthesia

It is better not to perform ambulatory anaesthesia.

Obstetrical anaesthesia

Consultation with experienced anaesthesiologist early in pregnancy to better plan surgery and procedures, examination, laboratory testing

Determination of anesthesia type.

During delivery: sufficient pain therapy, early insertion of epidural catheter.

Literature and internet links

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Amendment 1 - Prescription of drugs

Prescription of drugs

Several lists of drugs have been developed over the past 40 years or so. All are based chiefly upon expert opinion and upon basic knowledge of the pharmacology of the drugs, such as whether drugs are known to be inducers of cytochromes P-450.

The main drugs lists are those of The Swedish Porphyria Centre, NAPOS, the European Porphyria Initiative, the American Porphyria Foundation, and the South African/University of Capetown. These lists have similar methods of classifying drugs and do not always agree.

For example, The Scandinavian [NAPOS] scheme uses the following categories:

- Not porphyrinogenic (NP)
- Probably not porphyrinogenic (PNP)
- Possibly porphyrinogenic (PSP),
- Probably porphyrinogenic (PRP)
- Porphyrinogenic (P)
- Not yet classified (NC)

Select drugs accordingly: NP, PNP, PSP, PRP, P with first choice classified as NP or PNP.

Before prescribing any drug labeled PSP, PRP or P, it has to be justified:

- is there a real need for the drug?
- is there no safer alternative available?
- is there a benefit from using the drug of choice?
- is there a risk of provoking an acute attack and the consequences?
- Is the risk considered justified by the expected benefit

Amendment 2 – List of drugs

Before prescribing any drug labeled PSP, PRP or P, it has to be justified:

- is there a real need for the drug?
- is there no safer alternative available?
- is there a benefit from using the drug of choice?
- is there a risk of provoking an acute attack and the consequences?
- Is the risk considered justified by the expected benefit

List of drugs

A: “Note” List based on Fleischer IE, Anesthesia and uncommon diseases

Considered as safe:

i.v. anaesthetics: *Midazolam, Lorazepam, Propofol*

Volatile anaesthetics: *Nitrous oxide, Desflurane*

Opiates: *Morphine; meperidine*

Muscle relaxants: *Vecuronium, Succinylcholine*

Local anaesthetics: *Bupivacaine, Procaine*

Maintaining and Termination anaesthesia: *Atropine, Atenolol, Droperidol, Labetalol, Neostigmine*

Considered unsafe:

i.v. anaesthetics: *Barbiturates, Etomidate*

Volatile anaesthetics: *Enflurane*

Opiates: *none*

Muscle relaxants: *none*

Local anaesthetics: *none*

Maintaining and Termination anaesthesia: *Guocorticoids, Hydralazine*

Considered unclear:

i.v. anaesthetics: *Ketamine, Diazepam*

Volatile anaesthetics: *Isoflurane, Halothane*

Opiates: *Alfentanil, Sufentanil*

Muscle relaxants: *Atracurium, Pancuronium*

Local anaesthetics: *Lidocaine*

Maintaining and Termination anaesthesia: *none*

B: Note: Based on list in "Patient's and Doctor's Guide to Medication in Acute Porphyria," Swedish Porphyria Association and Porphyria Centre Sweden. Also see the website Drug Database for Acute Porphyrias (www.drugs-porphyria.com) for a searchable list of safe and unsafe drugs.

Documented Porphyrinogenic:

Carbamazepine, Carisoprodol, Chloramphenicol, Clindamycin
Dextropropoxyphene, Dihydralazine, Dihydroergotamine, Drospirenone + estrogen Dydrogesterone
Etonogestrel
Fosphenytoin sodium
Hydralazine, Hydroxyzine,
Indinavir
Ketamine, Ketoconazole
Lidocaine, Lynestrenol, Lynestrenol + estrogen,
Mecillinam, Medroxyprogesterone, Megestrol, Methylergometrine, Methyldopa Mifepristone,
Nicotinic Acid/meclozine/hydroxyzine, Nitrofurantoin, Norethisterone, Norgestimate + estrogen
Orphenadrine,
Phenobarbital, Phenytoin, Pivampicillin, Pivmecillinam, Primidone,
Rifampicin , Ritonavir, Spironolactone, Sulfadiazine +
Trimethoprim , Tamoxifen, Testosterone, injection Thiopental , Trimethoprim ,
Valproic acid , Venlafaxine , Vinblastine, Vincristine , Vindesine , Vinorelbine
Xylometazoline,
Zaleplon, Ziprasidone, Zolmitriptan, Zolpidem, Zuclopenthixol

Probably porphyrinogenic

Altretamine, Aminophylline, Amiodarone, Amitriptyline, Amlodipine, Amprenavir, Aprepitant,
Atorvastatin, Azathioprine
Bosentan, Bromocriptine, Buspirone, Busulfan, Butylscopolamine
Cabergoline, Ceftriaxone +, Cerivastatin, Cetirizine, Cholinetheophyllinate, Clarithromycin, Clemastine,
Clonidine, Cyclizine, Cyproterone
Danazol , Delavirdine, Desogestrel + estrogen, Diazepam, Dienogest + estrogen, Dydrogesterone,
Diclofenac , Diltiazem, Diphenhydramine, Disopyramide, Disulfiram, Drospirenone +,

Estrogen, Ergoloidmesylate, Erythromycin, Estramustine, Ethosuximide, Etoposide, Exemestane

Felbamate, Felodipine, Fluconazole, Flunitrazepam, FLuvastatin

Glibenclamide

Halothane, Hyoscyamine

Ifosfamide, Imipramine, Irinotecan , Isoniazid , Isradipine, Itraconazole

Lamivudine +Zidovudine, Lansoprazole, Lercanidipine, Levonorgestrel, Lidocaine, Lopinavir, Lutropin alfa, Lymecline

Meclozine, Medroxyprogesterone + Estrogen, Metoclopramide, Metronidazole, Metyrapone, Moxonidine

Nandrolone, Nefazodone, Nelfinavir, Nevirapine , Nifedipine, Nimodipine, Nitrazepam, Norethisterone, Nortriptyline

Oxcarbazepine, Oxytetracycline

Paclitaxel, Paroxetine, Phenazone + caffeine, Pioglitazone, Probenecid, Progesterone vaginal Gel

Quinidine

Rabeprazole, Raloxifene, Rifabutin, Riluzole, Risperidone, Rosiglitazone

Saquinavir, Selegiline, Simvastatin, Sulfasalazine

Telithromycin, Terbinafine, Terfenadine, Testosterone Transdermal patch, Tetracycline, Theophylline, Thiamazole, Tibolone, Ticlopidine, Tinidazole, Thiotepa, Topiramate, Topotecan, Toremifene, Tramadol, Trimegestone + Estrogen

Verapamil, Voriconazole

Zidovudine/azt

Possibly Porphyrinogenic

Aceclofenac, Acitretin, Acrivastine, Alfuzosin, Anastrozole, Auranofin, Azelastine

Benzotropine, Benzydamine, Betaxolol, Bicalutamide, Biperiden, Bupropion,

Carvedilol, Chlorambucil, Chlorcyclizine + Guaifenesin, Chloroquine, Chlorprothixene, Chlorzoxazone, Chorionic Gonadotrophin, Ciclosporin, Cisapride, Citalopram, Clomethiazole, Clomiphene, Clomipramine, Clopidogrel, Clotrimazole, Cortisone, Cyclandelate, Cyclophosphamide, Cyproheptadine,

Dacarbazine, Daunorubicin, Desogestrel, Dichlorobenzyl Alcohol, Dithranol, Docetaxel, Donepezil, Doxycycline,

Ebastine, Econazole, Efavirenz, Escitalopram, Esomeprazole, Estradiol/tablets, Estriol/tablets, Estrio/vainal crème, tablet, Estrogen Conjugate,

Fentanyl, Finasteride, Flecainide, Flucloxacillin, Fluoxetine, Flupentixol, Flutamide, Fluvoxamine, Follitropin alfa

Beta Galantamine, Glimepiride, Glipizide, Gonadorelin, Gramicidin, Guaifenesin, Hydrocortisone,

Hydroxycarbamide, Hydroxychloroquine,

Ibutilide, Imatinib, Indomethacin,

Ketobemidone + Ddba, Ketoconazole, Ketorolac,

Lamotrigine, Letrozole, Levodopa + Benserazide, Levonorgestrel Intrauterine, Levosimendan, Lidocaine, Linezolid, Lofepamine, Lomustine,

Malathion, Maprotiline, Mebendazole, Mefloquine, Melperone, Melphalan, Mepenzolate, Mepivacaine, Mercaptopurine, Methadone, Methylprednisolone, Methixene, Metolazone, Metronidazole, Mexiletine, Mianserin, Midazolam, Minoxidil, Mirtazapine, Mitomycin, Mitoxantrone, Moclobemide, Montelukast, Morphine + Scopolamine, Multivitamins, Mupirocin,

Nabumetone, Nafarelin, Naltrexone Nateglinide, Nilutamide, Noscapine,

Omeprazole, Oxybutynin, Oxycodone,

Pantoprazole, Papaverine, Parecoxib, Pentifylline, Pentoxyverine, Phenylpropanolamine + Cinnarizine, Pizotifen, Polidocanol, Polyestradiol, Phosphate, Potassium canrenoate, Pravastatin, Prednisolone, Prilocaine, Proguanil, Propafenone, Pseudoephedrine + Dexbrompheniramine,

Quillaia extract, Quinagolide, Quinine, Quinupristin + Dalfopristin

Reboxetine, Repaglinide, Rizatriptan, Rofecoxib, Ropinirole, Ropivacaine, Roxithromycin,

Sertraline, Sevoflurane, Sibutramine, Sildenafil, Sirolimus, Sodium Aurothiomalate, Sodium oleate + Chlorocymol, Stavudine, Sulindac, Sumatriptan,

Tacrolimus, Tadalafil, Tegafur + uracil, Telmisartan, Thioridazine, Tioguanine, Tolfenamic acid, Tolterodine, Torsemide, Triamcinolone, Trihexyphenidyl, Trimipramine,

Valerian, Venlafaxine, Vinblastine, Vincristine, Vindesine, Vinorelbine,

Xylometazoline,

Zaleplon, Ziprasidone, Zolmitriptan, Zolpidem, Zuclopenthixol

C: „Note“ Drugs accordingly the „Merkblatt Referenzlabor Stadtspital Triemli“ Zürich

Medication in acute porphyrias considered as safe

Indication: medication (trade name)

Allergic Reaction:

- Cetirizin (Zyrtec), Cromoglicin acid (Lomudal), Dexchlorpheniramin (Polaramin). Adrenalin, Corticosteroide.

Seizures:

- Gabapentin (Neurontin), Clonazepam (Rivotril), Vigabatrin (Sabril), levetiracetam
- Coping seizure:: 1 x 10 mg Diazepam (Valium) i.v. (only one simple dose)

Nausea, Vomiting:

- Scopolamin, Cyclizine (Marzine), Domperidon (Motilium), Droperidol (Dehydrobenzperidol), Chlorpromazine (Largactil)

Hypertension und Tachycardia:

- ACE-inhibitors: Lisinopril (Corpril, Lisitril, Lisopril, Prinil, Tobicor, Zestril), Enalapril (Acepriil, Elpradil, Enalapril, Enatec, Epril, Reniten, Vascor), [Calcium-channel-blocker: contraindication]
- Beta-blockers u.a.: Atenolol (Tenormin), Propranolol (Inderal, Betaprol) [Acute Attack - Combination Beta-Blocker und Chlorpromazine advantageous. Beware of Orthostatic hypotension or excessive beta-blockade], Labetalol (Trandate).

Diuretics:

- Bumetamid (Burinex), Amilorid (Midamor), Hydrochlorothiazid (Esidrex), Furosemid (Lasix)
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Infection:

- Penicillines: Amoxicillin, Ampicillin, Benzathinpenicillin, Cloxacillin, Phenoxymethylpenicillin.
- Aminoglycosides: Amikacin, Gentamycin, Kanamycin, Netilmycin, Streptomycin, Tobramycin.
- Cephalosporines: Cefoxitin, Cefuroxim, Cefotaxim).
- Others: Vancomycin, Augmentin.

Heart Disease:

- Atropine (Atropine Dispersa, Skiatropin)
- Digitalisglycosides (Digoxin), Procaine (Pronestyl),
- Glyceryltrinitrate (Nitroglycerin), Isosorbid Dinitrate (Isoket), Isosorbid Monohydrate (Corangin).
- Dopamine, Dobutamin, Adrenalin.

Diarrhea, Obstipation, Ileus:

- Loperamide (Immodium), Neostigmin (Prostigmin)

Psychosis, State of Fear- and Arousal:

- Levomepromazine (Nozinan), Haloperidol (Haldol), Fluphenazine (Dapotum), Perphenazine (Trilafon), Chlorpromazine (Largactil), Triazolam (Halcion), Temazepam (Normison).

Pain:

- Acetylsalicylic acid (Aspirin, Aspegic), Paracetamol (z.B. Dafalgan), Ibuprofen (z.B. Brufen), Naproxen (Apranax, Naprosyn, Proxen), Flurbiprofen (Froben, Ocuflur), Indomethacin (z.B. Bonidon, Confortid, Indocid), Buprenorphine (Temgesic), Codeine (Paracodin, Codein Knoll, Tricodein Solco), Pethidine (Centralgin, Pethidin Amino, Pethidin Streuli), Morphin

Sleeplessness:

- Oxazepam (Seresta), Lorazepam (Temesta)

Local Anesthetics:

- Procaine (Syntocain), Bupivacaine (Carbostesin, Carbostesin-Adrenalin): maximum 10 ml of 5 mg/ml solution], Levobupivacaine (Chirocain): maximum 10 ml of 5 mg/ml solution.

Vaccination:

- Influenza-vaccination recommended, all vaccinations are acceptable.

Antidepressants:

- Lithium salts, Fluoxetine (Fluctine).

Coughing / Cold:

- Acetylcysteine (Fluimucil), Codeine (Codein, Makatussin), Dextromethorphan (Bexin), Pseudoephedrine (Otrinol).

Miscellaneous

- Anticoagulants (Marcoumar, Heparin, fraktioniated Heparin), Vitamins, Corticosteroids ex.. Triamzinolon (Kenacort), Dexamethasone (Milicorten), Synacthen, Insulin, Metformin (z.B. Glucophage).