Drug treatment in acute porphyria

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The acute hepatic porphyrias are rare pharmacogenetic diseases inherited as autosomal dominant conditions of low penetrance. The genetic defect is a 50% deficiency of an enzyme of the haem biosynthetic pathway. Patients may develop 'neurovisceral attacks' which include severe abdominal pain, neuropsychiatric manifestations and potentially fatal respiratory paralysis. Attacks occur generally after puberty, are much commoner in females and may be precipitated by endogenous hormonal changes, dieting, alcohol, severe infections, and many drugs. Treatment includes analgesia, early administration of haem, and general supportive measures. Patients are at greater risk of a severe attack on first presentation since an abdominal emergency may be simulated and inappropriate medication, including that for general anaesthesia may exacerbate the crisis. The urine should be tested for raised porphobilinogen, which is pathognomonic of the acute attack, if there is the slightest doubt about diagnosis. The genotype of blood relatives of index cases must be determined so that carriers may avoid drug and other precipitants. Some drugs have been established as safe or unsafe by clinical use, but information about many drugs is not available or is based only on their properties in rodents or in tissue culture systems. The relevance of these to the human condition remains controversial, but drugs shown to be porphyrinogenic in animal systems should be avoided if there is a known safe alternative. Where it is essential to use a drug not known to be safe, close biochemical and clinical observation may warn of an impending attack.

Keywords: acute porphyria, drugs, safe, unsafe, haem, treatment

Introduction

The acute hepatic porphyrias [1, 2] (acute intermittent porphyria [AIP], variegate porphyria [VP] and hereditary coproporphyria [HC]) are inherited autosomal dominant conditions, each associated with a 50% deficiency of one enzyme of the haem biosynthetic pathway (porphobilinogen deaminase [PBG-D], protoporphyrinogen oxidase, or coproporphyrinogen oxidase for AIP, VP and HC respectively). Clinical features include severe abdominal pain, vomiting, tachycardia, hypertension, pain, weakness or paralysis of limbs, mental disturbance, and more rarely convulsions. These 'neurovisceral' attacks, identical in the three acute porphyrias, are due to abnormalities of the autonomic, peripheral, and central nervous system. Deterioration may be rapid with onset of dysarthria or other features of bulbar involvement and potentially fatal respiratory paralysis. Light-dependent skin rashes may additionally occur in VP and HC.

The predominant and most severe acute porphyria in Europe and in the USA is AIP with a gene prevalence of 1 in ~10 000 but a case incidence of 1 in 100 000 or less, reflecting a low penetrance of 10%. Attacks or 'crises' occur after puberty in both sexes but are much commoner in females with the highest incidence in the second and third decades and decrease after the menopause. In South Africa, due to a founder effect,

the commonest acute porphyria is VP which may affect 1 in 1000 of the white Afrikaner population.

Diagnosis of a first attack may be delayed since the clinical features are non-specific and the conditions are rare, but once suspected, confirmation is readily obtained by rapid and simple colorimetric tests with Ehrlich's *p*-dimethylaminobenzaldehyde reagent, demonstrating the pathognomonic increase of porphobilinogen (PBG) [and 5-aminolaevulinic acid (ALA)] in the urine.

During attacks there is increased activity of 5-aminolaevulinate synthetase (ALA-S), the first and normally rate-limiting enzyme of the haem pathway, which is subject to 'negative feedback end-product control' by haem. Excess PBG results since the second enzyme of the pathway, 5-aminolaevulinate dehydratase (ALA-D) is not limiting, but in AIP the 50% deficiency of the third enzyme, PBG-D, acts as a bottleneck and PBG 'overflows' and is excreted in the urine. In VP and HC, there is in addition an excess of porphyrins produced which may cause light-dependent skin rashes. The biochemical changes are believed to be initiated by a reduction in the level of haem in a hepatic 'free haem' regulatory pool.

Attacks can be induced by endogenous sex hormone changes, dietary restriction, alcoholic drinks, severe infections, or 'stress', and may occur without an identifiable reason, but the most frequent cause is administration of drugs. Injudicious drug use before the diagnosis of porphyria is made may increase the severity of an attack and may be

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fatal. The importance of early diagnosis of a first attack cannot therefore be sufficiently stressed.

First degree relatives of patients must be tested for the genetic defect so that carriers may avoid precipitating drugs and other factors. Since PBG and ALA levels in their urine may be normal, diagnosis must be pursued with more specialized procedures which may include fluorescence spectroscopy of plasma (for VP) [3], enzyme assays in erythrocytes [4] or leucocytes [5], faecal, urinary or plasma porphyrin analyses [6], or characterisation of DNA [7].

Treatment of acute attacks

General measures

Treatment of porphyric attacks has been mainly supportive and includes withdrawal of precipitating agents, maintenance of a high calorie and carbohydrate intake with glucose, which represses ALA-S [8] and may therefore have a specific effect, attention to fluid and electrolyte balance, avoiding overhydration and hyponatraemia, which may result in convulsions, appropriate analgesia, control of vomiting, tachycardia and hypertension, and general supportive measures for neuropathy. Even severely paralysed patients requiring artificial ventilation may make a full recovery.

Treatment with haem

Consistent with haem depletion being a key event in initiating or perpetuating the biochemical abnormalities, infusion of haem, (available in Europe in stable form as haem arginate, [Normosang, Leiras or Orphan Europe]) rapidly reduces plasma and urine levels of ALA and PBG, presumably by replenishing the hepatic 'free haem' pool. Evidence that it also shortens duration of attacks and limits their severity has been more difficult to demonstrate. The only available placebo-controlled trial showed only marginal benefit [9], but the view now generally held is that haem infusion is a major and specific advance in treatment, is more effective than glucose, and should be given early in the attack [10, and references therein]. Once neurological damage, such as axonal degeneration has occurred, functional restoration would be slow, even with remission of the attack. Co-administration of inhibitors of haem-oxygenase such as tin protoporphyrin or tin mesoporphyrin [11] prolong the biochemical remission produced by haem arginate [12], but it is not yet clear whether this is clinically meaningful. There is concern also about photosensitivity and possible toxic effects on the brain due to tin protoporphyrin [12, 13]. Zinc mesoporphyrin may prove more promising [14].

Details of management of patients in attacks have been extensively reviewed [1, 2, 15, 16, 55]. Safe drugs commonly required are shown in Table 1. This review will now be concerned with the general background of drug safety evaluation, dissemination of information, and selected areas of drug use, mainly in patients in remission or with latent porphyria (carriers of an abnormal gene who have had no attacks).

Table 1 Drugs used in acute porphyric attacks.

Drug	Indication
Haem arginate	Induce remission
Glucose	
Aspirin	Pain
Dihydrocodeine	
Paracetamol	
Diamorphine	
Morphine	
Pethidine	Vomiting
Chlorpromazine	
Promazine	Neurosis/psychosis
Chlorpromazine	
Promazine	
Trifluoperazine	
Prochlorperazine	Epilepsy
Diazepam (intravenous)	
Clonazepam	
Magnesium sulphate	
Propranolol	Hypertension/tachycardia
Labetalol	
Atenolol	
Guanethidine	
Bethanidine	
Mecamylamine	
Neostigmine	Constipation
Danthron	
Senna	

Drugs and porphyria

The observation that patients with AIP or VP tended to recover from attacks 'in the wild', but developed more severe and often fatal attacks when treated in hospital, led to the identification of a number of drugs, notably barbiturates and sulphonamides, potentially lethal for these patients, and to the recognition that AIP [17] and VP [18] were 'pharmacogenetic' diseases [19].

Experimental porphyria

Extensive studies with rodents and chick embryo liver *in ovo* or in culture, or rat hepatocytes in culture have been done in attempts to define the basis of drug porphyrinogenicity. Certain drugs, such as phenobarbitone, markedly increase ALA-S [20], cytochromes P450 and porphyrins in chick embryo liver [21] but only modestly in normal rodents. These models could additionally be 'primed' [22, 23] by exposure to organic compounds with specific molecular groups, such as 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC) or allylisopropylacetamide (AIA) or to other agents which cause partial blocks in the haem biosynthesis pathway, to increase their response to test drugs added later, with analogy to latent hepatic porphyria in man [24]. Porphyrinogenicity is demonstrable experimentally by increase in ALA-S activity, or increased porphyrin synthesis, or increased urinary excretion of ALA and PBG in whole rodents. The response is associated with impairment of

haem synthesis, or of its regulation in different ways [21], including increased requirement for haem by induction of (apo)cytochromes P450, 'mechanism' based effects, involving destruction of cytochromes P450, or inactivation and N-alkylation of its haem moiety generating potent inhibitors of ferrochelatase, the last enzyme of the pathway. A variety of compounds act indirectly, through the generation of reactive oxygen species, to inhibit uroporphyrinogen decarboxylase, the fifth enzyme in the biosynthesis of haem, while sulphonamides [25] probably inhibit PBG-D directly. The common consequence of the actions of all these compounds is presumed to be a lowering of 'free haem', leading to derepression of ALA-S. Further diversity arises, however, from mounting evidence that drugs may induce ALA-S by an as yet undefined, but more direct mechanism, independent of haem utilization [26–29]. Experimental porphyria is heterogenous therefore, not only with regard to the drugs which may cause it, but also with their site of action and with the test system used [30]. Porphyrinogenic compounds tend to be lipid-soluble and thus water-solubility, and ease of phase II metabolism (e.g. glucuronidation or acetylation of the first metabolic product) reduce the likelihood of porphyrinogenicity within a particular class of compounds [21], but no predictable structure-porphyrinogenic activity relationship has emerged.

A further difficulty is that none of the animal or tissue models provides information on neuropathy. The recently developed transgenic mouse model of human AIP, in which PBG-D activity has been reduced to ~31%, not only has the biochemical features of the human disease but also a similar neuropathy [31], and is likely to lead to major advances in our understanding of these disorders.

Clinical acute porphyria

Human information is sparser but there is direct evidence from liver biopsies that ALA-S is high during attacks [32–35] and in addition, decreased function of hepatic cytochromes P450-dependent oxidations has been shown [36, 37] which can be corrected by haem infusion [38–40]. This is consistent with a lowered 'free haem' level (by whatever mechanism, including a drug-related increase in cytochrome P450 requirement) leading to induction of ALA-S, and the increased excretion of the porphyrin precursors ALA and PBG described above, in the presence of a partial block in the haem pathway, as in the case of PBG-D deficiency in AIP. It is still not known, however, how these findings relate to the neuropathy of the clinical attack. The notion that infused haem enters nerve tissue, corrects a functional deficiency, as shown in the liver, and leads to a remission of the porphyric attack is plausible but has not been established.

Relationship between clinical and experimental porphyria

Do studies with animals or their tissues have clinical relevance? One view is that porphyrinogenicity of a drug in any of these systems is indicative of a likely similar effect in genetic carriers of an acute porphyria and that all such compounds must be avoided. The alternative view is that extrapolation to man is never justified since it is not possible

to establish valid comparisons between human and animal systems, nor allow for equivalent dosage, duration of exposure, or metabolism. What is the evidence?

The soundest evidence of a clinically relevant porphyrinogenic effect is precipitation of attacks in patients, and where this is in line with *in vitro* results, it provides an endorsement of the predictive value of such tests. If safety has been established clinically, the results of experimental tests are not relevant to clinical decision making. It was hoped, however, that animal or *in vitro* studies could provide definitive clinical information particularly about newly introduced agents. Unfortunately the correlation is not absolute; some clinically established safe drugs are porphyrinogenic in test systems [41] and perhaps of greater concern, compounds not porphyrinogenic experimentally have induced attacks (Table 2). Experimental results often differ between test systems [30], but even attempts to grade the porphyrinogenic response by comparing the effect of different doses of the drug with that of a known porphyrinogenic 'standard' drug such as a barbiturate [42] do not remove the uncertainties.

Drug lists and drug safety in porphyria

Value and limitations

Drugs which are thought to be safe and unsafe in acute porphyria are catalogued elsewhere [1, 2, 15, 16, 41, 43, 44] and lists are made available, often with additional general information, to patients and to their physicians by specialist centres in the UK and in a number other countries [45–47]. The British National Formulary [48] provides a list of unsafe drugs. Information is accessible also at a number of Websites, including those of the American Porphyria Foundation, a patients' affinity group, and the South African Medicines Formulary. In France a list is available on Minitel. The lists are hybrids of clinical and experimental results. Unsafe drugs are defined in three broad categories: 1) drugs associated with human attacks, 2) drugs which are porphyrinogenic entirely in animal or *in vitro* tests, and 3) a 'contentious' group in which there is conflicting evidence of porphyrinogenicity within different experimental systems, but no human

Table 2 Drugs with divergent experimental and clinical porphyrinogenicity.

Unsafe drugs experimentally not porphyrinogenic

Chlordiazepoxide
Diclofenac
Frusemide
Imipramine
Metoclopramide
Pentazocine
Piroxicam
Rifampicin
Sulpiride
Theophylline

Safe drugs experimentally porphyrinogenic

Bupivacaine
Fentanyl
Propofol
Quinine

information. The safe drugs are listed using corresponding criteria, but in particular that none has been reported to be associated with human attacks. The information provided ranges therefore from high probability that it is correct for some drugs, to uncertainty for others. Some drugs could appear on both lists. Difficulties arise regarding the status of drugs about which there is either no clinical information, or where the clinical information is based on isolated reports only, whether the drug is reported to be safe or unsafe. These limitations are clearly stated with the lists some of which also carry a legal disclaimer for their author(s).

A selection of safe and unsafe drugs based on clinical information is shown in Table 3. The safe drugs, together with those listed in Table 1 cover a wide but not comprehensive range of therapeutic indications. Well-documented reports of drug usage in porphyria patients, both safe and unsafe, will increase the value of these lists. Attempts to centralise information gathering have been made by the establishment of an international Committee on the Review of Porphyrinogenicity of Drugs (CORP).

Other difficulties cannot be circumvented. The number of subjects available for study at any one time is generally small and their susceptibility to induction of attacks by drugs

or other precipitating factors may be variable and influenced by other disease, endogenous endocrine cycling, concomitant use of other drugs, their age and the state of activity of their porphyria at the time of exposure. This variability applies to subjects in remission regardless of the severity of previous attacks [49, 50]. For these reasons it may not be possible to draw valid conclusions about whether a drug is safe or unsafe from even well studied single cases, although a number of anecdotes with similar findings may increase reliability. Other important factors to consider in assessing drug safety are dose, potency and duration of exposure.

Identified genetic carriers of AIP with no previous attacks (latent porphyrics) have a smaller risk of a crisis following exposure to drugs or other precipitating factors than subjects in remission [50], as would be expected from the low penetrance of the condition. A more permissive approach to patients in the 'quiescent phase' of the disease (which includes subjects in remission, as well as those with no previous attacks) has been advocated with respect to alcohol, the use of female sex hormones and other drugs [50, 56]. It is still not possible, however, to predict individual risk, although subjects with elevated urinary PBG may be more likely to have attacks [50]. Although more than 100 (and increasing) different mutations of the PBG-D gene have been characterised [7, 51–55], the clinical phenotype is essentially uniform, and no relationship has emerged between the type of mutation and penetrance. The prevalent view remains therefore that all carriers of the genetic defect should avoid unsafe drugs and known precipitating factors. Individual circumstances may define the balance between risk and benefit, but many physicians prefer to err on the side of caution. Even when the only evidence that a drug is porphyrinogenic is based on *in vitro* systems there is reluctance to use it if another drug known to be safe is available. In conditions which may lead to serious morbidity or mortality and for which there are no established safe drugs, essential treatment must be given regardless, with the prospect of the need for prompt treatment should a crisis develop. Such situations may include some cardiac arrhythmias, severe infections resistant to known safe antibiotics, tuberculosis, and severe epilepsy.

Comments on selected topics in management

General anaesthesia and surgery

Experience of general anaesthesia and surgery in patients with acute porphyria (mainly AIP) is extensive [49, 57, 58] and the use and safety evaluation of drugs in anaesthesia have been reviewed [44, 58]. Even major surgery can be safely performed with suitably chosen general anaesthetic procedures (Table 4). Knowledge that the subject has acute porphyria is of paramount importance to a safe outcome, and indeed to the patient's survival. Most fatalities and severe crises have occurred following general anaesthesia induced with thiopentone [57, 58] (often for laparotomy for a presumed abdominal emergency) when the patient was already in an acute but undiagnosed attack. Patients in acute attack, however precipitated, may have enhanced susceptibility to other precipitating factors. Observations that subjects in remission have not relapsed following use of agents

Table 3 Selected safe and unsafe drugs in acute porphyria. All the unsafe drugs listed have precipitated attacks, but none of the safe drugs has been implicated. The information was compiled in part from Medline searches and from refs 2, 16, 47. Additional safe drugs are listed in Tables 1 and 4.

Safe drugs	Unsafe drugs
Acetazolamide	Anticonvulsants
Allopurinol	Barbiturates
Amiloride	Chloramphenicol
Aminoglycosides	Chlordiazepoxide
Atropine	Chlorpropamide
Benzhexol	Diphenhydramine
Bromides	Enalapril
Bumetanide	Ergot compounds
Bupivacaine	Erythromycin
Buprenorphine	Ethanol
Chloral hydrate	Flucloxacillin
Clavulanic acid	Flufenamic acid
Codeine phosphate	Griseofulvin
Digoxin	Hydrochlorothiazide
Famotidine	Imipramine
Fentanyl	Lisinopril
Glyceryl trinitrate	Methyldopa
Guanethidine	Metoclopramide
Heparin	Nifedipine
Insulin	Oral contraceptives
Iron	Orphenadrine
Metformin	Pentazocine
Penicillins (but see exceptions)	Piroxicam
Procaine	Pivampicillin
Propylthiouracil	Progesterone
Quinidine	Pyrazinamide
Quinine	Rifampicin
Salbutamol	Sulphonamides
Temazepam	Terfenadine
Thyroxine	Theophylline
Warfarin	Verapamil

Table 4 Drugs probably safe for general anaesthesia in acute porphyria. Compiled from literature searches of individual drugs, but mainly from ref 57. See also Tables 1 and 3.

<i>Drug</i>	<i>Function</i>
Propofol Midazolam	Intravenous induction
Nitrous oxide Cyclopropane Ether	Inhalation
Suxamethonium Curare	Muscle relaxant
Fentanyl	Analgesia (see also Tables 1 and 3)
Temazepam Chlorpromazine Droperidol	Anxiolytic
Atropine Neostigmine Adrenaline Phentolamine Salbutamol Hydrocortisone Propranolol Procainamide Domperidone	Miscellaneous

recognised as major precipitants, including thiopentone [49], highlight the variability of response in porphyria patients, but cannot be relied on clinically since the response is unpredictable. It is still considered highly dangerous therefore, to administer a recognised precipitant such as a barbiturate to a subject with acute porphyria, whether in attack, in remission or latent. There has been a reduction in mortality and severity of porphyric attacks observed over the last 25 years [43, 50, 59], probably due to restriction in the availability of barbiturates and other sedatives, to greater awareness by physicians of the dangers of many drugs to patients with acute porphyria, to the screening of blood relatives of index cases, and perhaps to the introduction of haem in treatment regimes. There may always be, however, some patients whose porphyric attack will be misdiagnosed as an abdominal emergency because of the absence of historical clues and because the index of suspicion is too low to lead to examination of the urine for PBG. It is notable that almost one third of AIP patients may still present as sporadic cases [60]. One safeguard would be routine pre-operative testing of urine for PBG for all abdominal emergencies, and another, perhaps even less practical, would be to use 'porphyria safe' anaesthetic agents for all such patients.

Sex hormones

It is generally accepted that combined oestrogen and progestogen contraceptive preparations are contra-indicated in porphyria patients because they are likely to induce attacks. There are several reports, however, that they may

reduce or even prevent attacks in some women who have repeated premenstrual crises, presumably modulated by cyclical hormonal changes [50, 61, 62]. This pattern which may continue for years, of frequent porphyric attacks, with pain and even paralysis is a major therapeutic challenge. Another way to attenuate cyclical sex-hormonal changes is by the use of LH-RH analogues such as buserelin and a number of small trials provide evidence of benefit [63, 64]. There is still uncertainty, however, about the long-term use of such preparations, which suppress ovulation, and the best means of administration. One patient was successfully treated with 6-monthly testosterone implants after failing to respond to buserelin [65]. Progestogens may be more hazardous than oestrogens in precipitating attacks of AIP, but oestrogen alone, even administered transcutaneously for postmenopausal symptoms has precipitated attacks [66]. Precipitation of an acute attack which included hypertension and neuropsychiatric symptoms, has been noted after 6 months of apparently safe use of a conventional HRT preparation in a patient who had been in remission for 20 years (personal unpublished observation), but others report usage with no untoward effects [50].

Antibiotics

The choice of antibiotics may be difficult when the infection is with agents resistant to the established safe antibiotics: penicillins (except flucloxacillin and pivampicillin), clavulanic acid, and aminoglycosides. Cephalosporins, chloramphenicol, and erythromycin are now found in the unsafe category of most lists, although chloramphenicol surprisingly is listed as 'probably safe' [1] citing early experience [43]. Vancomycin has been used safely in a patient in crisis [67]. Lack of information about drugs not specifically reported to have induced attacks may inhibit their use. Thus metronidazole is listed as safe [2] on this criterion, but with the qualification that experimentally, variable results on its porphyrinogenicity have been obtained; others list it as unsafe [e.g. 47]. In these situations, consideration of the risk to benefit ratio of the indication to treat will be decisive. High risk may have to be accepted, as in treatment for tuberculosis, since there are no validated safe and effective drug combinations for its treatment in patients with acute porphyria even though streptomycin and probably ethambutol are safe.

Anticonvulsants

All first line antiepileptic drugs have induced attacks, leaving only magnesium sulphate and bromides, which are difficult to use and unsatisfactory in the long-term, as wholly safe. The benzodiazepines are considered unsafe [48] and there are reports of acute attacks following the use of diazepam, chlorthalidoxepoxide, oxazepam, flunitrazepam and nitrazepam [68]. Nevertheless diazepam has been used safely to control status epilepticus and clonazepam for seizure prophylaxis [69] despite the anticipated risk [70]. Clinical experience with the new generation of anticonvulsant drugs is limited, but encouraging reports are emerging regarding the safe use of gabapentin [71, 72], which is not significantly metabolized in human liver.

Anxiety, depression, psychosis

Should it be essential to treat anxiety or depression, it becomes apparent from the various lists [2, 43] that most of the drugs available are unsafe, most on the 'hard' evidence that they have precipitated attacks. Thus tricyclics such as imipramine and congeners, and monoamine oxidase inhibitors are contraindicated, and little information is available about the specific serotonin re-uptake inhibitors, although there is a single case report of the safe use of fluoxetine [73]. It is of much interest therefore that the tricyclic lofepramine, hitherto on the unsafe list, caused no clinical or biochemical activation in four patients with AIP [74]. Benzodiazepines are sometimes used as anxiolytics, but the safety of these drugs as a class for porphyria patients is equivocal, although temazepam is perhaps safe [2, 48]. Their use may in any event be inappropriate on general medical grounds. Intermittent use of modest doses of chlorpromazine, which has a long-established record of safety, may be of value in these circumstances, as may a β -adrenoceptor blocker such as propranolol. For psychotic features, whether in the acute attack or within periods of remission, chlorpromazine probably remains the drug of choice, with no reports available that newer psychotropic drugs are superior or safer.

Cardiovascular drugs

Cardiovascular drugs represent an important area of therapeutics for porphyria patients, specifically because raised blood pressure and renal functional impairment are common not only in the porphyric attack but also in long-term survivors. The explosive development of new classes of drugs has not been matched by a corresponding increase in the availability of drugs with proven safety in porphyria. Anti-hypertensive drugs with an established safety record are few and are mainly represented by β -adrenoceptor blockers such as propranolol, and guanethidine or bethanidine, therapeutically obsolete inhibitors of amine release from adrenergic nerve endings. Thiazide diuretics are unsafe, and attacks have been reported with α -methyldopa, the dihydropyridine Ca^{2+} channel blocker nifedipine, with ACE inhibitors, and vasodilators such as hydralazine [2, 48]. No adverse effects have been reported with the specific α -adrenergic receptor blocker doxazosin or with the Ca^{2+} channel blocker amlodipine [75], but experience is very limited and further cautious clinical studies are required. There is no information on angiotensin II receptor antagonists.

In summary, there would seem to be no alternative, when a drug of unknown clinical status is essential, and there are no other choices, to using it in the patient. Close monitoring for increasing levels of PBG and ALA compared with pre-treatment values, optimally in consecutive 24 h urine collections, and clinical observation of symptoms may give early warning of a crisis and lead to early intervention. Results from experimental systems may direct the choice of a particular drug for human evaluation, compared with its congeners [e.g. 74, 75] but no drug can be unequivocally designated safe or unsafe solely on the basis of its porphyrinogenic properties in experimental systems. A

favourable clinical outcome may apply only to the individual studied, and wider experience is required before a drug can be generally accepted as safe. The porphyria drug lists are a valuable source of information but users must understand their limitations and should additionally be able to communicate with a specialist centre.

References

- 1 Kappas A, Sassa S, Galbraith RA, Nordmann Y. The porphyrias. In *The metabolic and molecular bases of inherited disease*, Seventh Edition, eds Scriver CR, Beaudet AL, Sly WS, Valle D, New York: McGraw-Hill, 1995: 2103–2159.
- 2 McColl KEL, Dover S, Fitzsimmons E, Moore MR. Porphyrin metabolism and the porphyrias. In *Oxford Textbook of Medicine*, Third Edition, eds Weatherall DJ, Ledingham JGG, Warrell DA, Oxford: Oxford University Press, 1996: 1388–1399.
- 3 Long C, Smyth SJ, Woolf J, *et al.* Detection of latent variegate porphyria by fluorescence emission spectroscopy of plasma. *Br J Dermatol* 1993; **129**: 9–13.
- 4 Strand LJ, Meyer UA, Felsher BF, Redeker AG, Marver HS. Decreased red cell uroporphyrinogen I synthase activity in intermittent acute porphyria. *J Clin Invest* 1972; **51**: 2530–2536.
- 5 Guo R, Lim CK, Peters TJ. High performance liquid chromatographic assays for protoporphyrin oxidase and ferrochelatase in human leucocytes. *J Chromatogr* 1991; **566**: 383–396.
- 6 Rossi E, Curnow DH. Porphyrins. In *Hplc of small molecules a practical approach*, ed Lim CK, Oxford: IRL Press 1986: 261–303.
- 7 Deybach JC, Puy H. Porphobilinogen deaminase gene structure and molecular defects. *J Bioenerg Biomembr* 1995; **27**: 197–205.
- 8 Tschudy DP. The influence of hormonal and nutritional factors on the regulation of liver heme biosynthesis. In *Handbook of Experimental Pharmacology, Heme and hemoproteins*, eds de Matteis F, Aldridge WN, Berlin: Springer Verlag, 1978: 255–271.
- 9 Herrick AL, McColl KEL, Moore MR, Cook A, Goldberg A. Controlled trial of haem arginate in acute hepatic porphyria. *Lancet* 1989; **1**: 1295–1297.
- 10 Mustajoki P, Nordmann Y. Early administration of heme arginate for acute porphyric attacks. *Arch Intern Med* 1993; **153**: 2004–2008.
- 11 Galbraith RA, Kappas A. Pharmacokinetics of tin-mesoporphyrin in man and the effects of tin-chelated porphyrins on hyperexcretion of heme pathway precursors in patients with acute inducible porphyria. *Hepatology* 1989; **9**: 882–888.
- 12 Dover SB, Moore MR, Fitzsimmons EJ, Graham A, McColl KEL. Tin protoporphyrin prolongs the biochemical remission produced by haem arginate in acute hepatic porphyria. *Gastroenterology* 1993; **105**: 500–506.
- 13 Mark JA, Maines MD. Tin-protoporphyrin-mediated disruption *in vivo* of heme oxygenase-2 protein integrity and activity in rat brain. *Pediatr Res* 1992; **32**: 324–329.
- 14 Cable EE, Pepe JA, Karamitsios NC, Lambrecht R, Bonkowsky HL. Differential effects of metalloporphyrins on messenger RNA levels of δ -aminolevulinic synthase and heme oxygenase. Studies in cultured chick embryo liver cells. *J Clin Invest* 1994; **94**: 649–654.
- 15 Yeung Laiwah AC, McColl KEL. Management of attacks of acute porphyria. *Drugs* 1987; **34**: 604–616.

- 16 Moore MR, McColl KEL. Therapy of the acute porphyrias. *Clin Biochem* 1989; **22**: 181–188.
- 17 Waldenstrom J. Studien uber Porphyrie. *Acta Med Scand* 1937; Suppl 82: 1–254.
- 18 Dean G. The prevalence of the porphyrias. *SA J Lab Clin Med* 1963; **9**: 145–151.
- 19 Maxwell JD, Meyer UA. Pharmacogenetics in the field of drug metabolism: drug sensitivity in hereditary hepatic porphyria. In *Heme and hemoproteins*, eds de Matteis F, Aldridge WN, Berlin: Springer Verlag, 1978: 239–254.
- 20 Granick S. The induction *in vitro* of the synthesis of δ -aminolevulinic acid synthetase in chemical porphyria: a response to certain drugs, sex hormones, and foreign chemicals. *J Biol Chem* 1966; **241**: 1359–75.
- 21 Marks GS, McCluskey SA, Mackie JE, Riddick DS, James CA. Interaction of chemicals with cytochrome P-450: implications for the porphyrinogenicity of drugs. *Clin Biochem* 1989; **22**: 169–175.
- 22 De Matteis F. Drug interactions in experimental hepatic porphyria. A model for the exacerbation by drugs of human variegate porphyria. *Enzyme* 1973; **16**: 266–275.
- 23 Anderson KE. Effects of antihypertensive drugs on hepatic heme biosynthesis, and evaluation of ferrochelatase inhibitors to simplify testing of drugs for heme pathway induction. *Biochim Biophys Acta* 1978; **543**: 313–327.
- 24 De Matteis F. Hepatic porphyrias. In *Handbook of Experimental Pharmacology, Heme and hemoproteins*, eds de Matteis F, Aldridge WN, Berlin: Springer Verlag, 1978: 129–155.
- 25 Peters PG, Sharma ML, Hardwicke DM, Piper WN. Sulphonamide inhibition of rat hepatic uroporphyrinogen 1 synthetase activity and the biosynthesis of heme. *Arch Biochem Biophys* 1980; **201**: 88–94.
- 26 Sinclair PR, Healey JF, Sinclair JF, Bonkowsky HL. Induction of 5-aminolevulinate synthase in chick embryo liver by propylisopropylacetamide does not involve destruction of cytochrome P450. *Biochem J* 1981; **200**: 709–710.
- 27 Hamilton JW, Bement WJ, Sinclair PR, Sinclair JF, Wetterhan KE. Expression of 5-aminolaevulinate synthase and cytochrome P450 mRNAs in chicken embryo hepatocytes *in vivo* and in culture. Effect of porphyrinogenic drugs and haem. [erratum *Biochem J* 1989; **257**: following 934] *Biochem J* 1988; **255**: 267–275.
- 28 Dogra SC, Hahn CN, May BK Superinduction by cycloheximide of cytochrome P450H1 and 5-aminolevulinate synthase gene transcription in chick embryo liver. *Arch Biochem Biophys* 1993; **300**: 531–534.
- 29 Jover R, Hoffmann K, Meyer UA. Induction of 5-aminolevulinate synthase by drugs is independent of increased apocytochrome P450 synthesis. *Biochem Biophys Res Commun* 1996; **226**: 152–157.
- 30 Marks GS. The effect of chemicals on hepatic heme biosynthesis. In *Handbook of Experimental Pharmacology, Heme and hemoproteins*, eds de Matteis F, Aldridge WN, Berlin: Springer Verlag, 1978: 201–237.
- 31 Lindberg RL, Porcher C, Grandchamp B, *et al.* Porphobilinogen deaminase deficiency in mice causes a neuropathy resembling that of human hepatic porphyria. *Nat Genet* 1996; **12**: 195–199.
- 32 Tschudy DP, Perloth MG, Marver HS, Collins A, Hunter G Jr, Rechcigl M Jr. Acute intermittent porphyria: the first 'overproduction disease' localized to a specific enzyme. *Proc Natl Acad Sci USA* 1965; **53**: 841–847.
- 33 Nakao K, Wada O, Kitamura T, Uono K, Urata G. Activity of aminolevulinic acid synthetase in normal and porphyric livers. *Nature* 1966; **210**: 838–839.
- 34 Strand LJ, Felsher BF, Redeker AG, Marver HS. Heme biosynthesis in intermittent acute porphyria: decreased hepatic conversion of porphobilinogen to porphyrins and increased delta aminolevulinic acid synthetase activity. *Proc Natl Acad Sci USA* 1970; **67**: 1315–1320.
- 35 Sweeney VP, Pathak MA, Asbury AK. Acute intermittent porphyria. Increased ALA synthetase activity during an acute attack. *Brain* 1970; **93**: 369–380.
- 36 Anderson KE, Alvares AP, Sassa S, Kappas A. Studies in Porphyria V. Drug oxidation rates in hereditary hepatic porphyria. *Clin Pharmacol Ther* 1976; **19**: 47–54.
- 37 Ostrowski J, Kostrzewska E, Michalak T, Zawirska B, Medrzejewski W, Gregor A. Abnormalities in liver function and morphology and impaired aminopyrine metabolism in hereditary hepatic porphyrias. *Gastroenterology* 1983; **85**: 1131–1137.
- 38 Herrick A, McColl KL, McLellan A, Moore MR, Brodie MJ, Goldberg A. Effect of haem arginate therapy on porphyrin metabolism and mixed function oxygenase activity in acute hepatic porphyria. *Lancet* 1987; **ii**: 1178–1179.
- 39 Bonkovsky HL, Healey JF, Lourie AN, Gerron GG. Intravenous heme-albumin in acute intermittent porphyria: evidence for repletion of hepatic hemoproteins and regulatory heme pools. *Am J Gastroenterol* 1991; **86**: 1050–1056.
- 40 Mustajoki P, Himberg JJ, Tokola O, Tenhunen R. Rapid normalization of antipyrine oxidation by heme in variegate porphyria. *Clin Pharmacol Ther* 1992; **51**: 320–324.
- 41 Disler PB, Blekkenhorst GH, Eales L, Moore MR, Straughan J. Guidelines for drug prescription in patients with the acute porphyrias. *SA Med J* 1982; **61**: 656–660.
- 42 Zimmer S, Taub H, Marks GS. A comparison of the porphyrin-inducing activity of barbiturates and benzodiazepines in chick embryo liver cells. *Can J Physiol Pharmacol* 1980; **58**: 991–995.
- 43 Eales L. Porphyria and the dangerous life-threatening drugs. *SA Med J* 1979; **56**: 914–917.
- 44 Blanloeil Y, Deybach JC, Portier D Joyau M, Nordmann Y. Anaesthesia for hepatic porphyrias. *Ann Fr Anesth Reanim* 1989; **8**: 109–125.
- 45 Moore MR, McColl KEL. *Porphyria drug lists*. Glasgow: Hunter Press, 1990.
- 46 Hift RJ, Meissner PN, Meissner DM. *Porphyria. A guide for people with porphyria and their doctors*. Cape Town: Medical Research Council and University of Cape Town Liver Research Centre, 1989.
- 47 Wilson JHP, de Rooij FWM. *Gastro-intestinal neurologic and psychiatric manifestations of acute porphyria*. Rotterdam: Porphyria Research Centre, 1994.
- 48 Anonymous. Acute porphyrias. In *British National Formulary*, Number 33, ed Mehta DK, London: British Medical Association, 1997: 409–410.
- 49 Mustajoki P, Heinonen J. General anesthesia in 'inducible' porphyrias. *Anesthesiology* 1980; **53**: 15–20.
- 50 Kauppinen R, Mustajoki P. Prognosis of acute porphyria: Occurrence of acute attacks, precipitating factors, and associated diseases. *Medicine* 1992; **71**: 1–13.
- 51 Nordmann Y, de Verneuil H, Deybach J-C, Delfau M-H, Grandchamp B. Molecular genetics of porphyrias. *Ann Med* 1990; **22**: 387–391.
- 52 Grandchamp B, Picat C, Mignotte V, *et al.* Tissue-specific splicing mutation in acute intermittent porphyria. *Proc Natl Acad Sci USA* 1989; **86**: 661–664.
- 53 Gu XF, de Rooij F, Voortman G, *et al.* Detection of eleven mutations causing acute intermittent porphyria using denaturing gradient gel electrophoresis. *Hum Genet* 1994; **93**: 47–52.
- 54 Kauppinen R, Mustajoki S, Pihlaja H, Peltonen L, Mustajoki

- P. Acute intermittent porphyria in Finland: 19 mutations in the porphobilinogen deaminase gene. *Hum Mol Genet* 1995; **4**: 215–222.
- 55 Llewellyn DH, Scobie GA, Urquhart AJ, *et al.* Acute intermittent porphyria caused by defective splicing of porphobilinogen deaminase RNA: a synonymous codon mutation at –22 bp from the 5' splice site causes skipping of exon 3. *J Med Genet* 1996; **33**: 437–438.
 - 56 Kauppinen R, Timonen K, Mustajoki P. Treatment of the porphyrias. *Ann Med* 1994; **26**: 31–38.
 - 57 Dover SB, Plenderleith L, Moore MR, McColl KEL. Safety of general anaesthesia and surgery in acute hepatic porphyria. *Gut* 1994; **35**: 1112–1115.
 - 58 Harrison GG, Meissner PN, Hift RJ. Anaesthesia for the porphyric patient. *Anaesthesia* 1993; **48**: 417–421.
 - 59 Jeans JB, Savik K, Gross CR, *et al.* Mortality in patients with acute intermittent porphyria requiring hospitalization: A United States case series. *Am J Med Genet* 1996; **65**: 269–273.
 - 60 Whatley SD, Roberts AG, Elder GH. De-novo mutation and sporadic presentation of acute intermittent porphyria. *Lancet* 1995; **346**: 1007–1008.
 - 61 Perlroth MGH, Marver HS, Tschudy DP. Oral contraceptive agents and the management of acute intermittent porphyria. *JAMA* 1965; **194**: 1037–1042.
 - 62 Gross U, Honcamp M, Daume E, Frank M, Dusterberg B, Doss MO. Hormonal oral contraceptives, urinary porphyrin excretion and porphyrias. *Horm Metab Res* 1995; **27**: 379–383.
 - 63 Anderson KE. LHRH analogues for hormonal manipulation in acute intermittent porphyria. *Semin Hematol* 1989; **26**: 10–15.
 - 64 Herrick AL, McColl KE, Wallace AM, Moore MR, Goldberg A. LHRH analogue treatment for the prevention of premenstrual attacks of acute porphyria. *Q J Med* 1990; **75**: 355–363.
 - 65 Savage MW, Reed P, Orrman-Rossiter SL, Weincove C, Anderson DC. Acute intermittent porphyria treated by testosterone implant. *Postgrad Med J* 1992; **68**: 479–481.
 - 66 Wetterberg L, Olsson MB, Alm-Ågvald I. Estrogen treatment caused acute attacks of porphyria. *Lakartidningen* 1995; **92**: 2197–2201.
 - 67 Hift R, Sohnies U, Meissner PN. Safety of vancomycin in acute porphyria. *Br J Clin Pharmacol* 1990; **29**: 273–275.
 - 68 Moore MR, Disler PB. Drug-induction of the acute porphyrias. *Adv Drug React Ac Pois Rev* 1983; **2**: 149–189.
 - 69 Suzuki A, Aso K, Ariyoshi C, Ishimaru M. Acute intermittent porphyria and epilepsy: safety of clonazepam. *Epilepsia* 1992; **33**: 108–111.
 - 70 Bonkowsky HL, Sinclair PR, Emery S, Sinclair JF. Seizure management in acute hepatic porphyria: risks of valproate and clonazepam. *Neurology* 1980; **30**: 588–593.
 - 71 Tatum IV WO, Zachariah SB. Gabapentin treatment of seizures in acute intermittent porphyria. *Neurology* 1995; **45**: 1216–1217.
 - 72 Yandel MI, Watters MR. Treatment of complex partial status epilepticus unmasking acute intermittent porphyria in a patient with resected anaplastic glioma. *Clin Neurol Neurosurg* 1995; **97**: 261–263.
 - 73 Vas FJ, Salcedo MS. Fluoxetine treatment of depressive symptoms in acute intermittent porphyria. *J Clin Psychiatr* 1991; **52**: 138.
 - 74 Dover SB, Graham A, Moore MR, McColl KEL. Lofepamine—a safe anti-depressant in acute hepatic porphyria? *J Psychopharmacol* 1994; **8**: 104–108.
 - 75 Gorchein A. Drug treatment of hypertension in acute intermittent porphyria: doxazosin and amlodipine. *Br J Clin Pharmacol* 1997; **43**: 339–340.

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