

*Physiol. Res. 55 (Suppl. 2): S67-S73, 2006*

## European Porphyria Initiative (EPI): A Platform to Develop a Common Approach to the Management of Porphyrias and to Promote Research in the Field

J.-CH. DEYBACH<sup>1</sup>, M. BADMINTON<sup>2</sup>, H. PUY<sup>1</sup>, S. SANDBERG<sup>3</sup>, J. FRANK<sup>4</sup>,  
P. HARPER<sup>5</sup>, P. MARTASEK<sup>6</sup>, E. MINDER<sup>7</sup>, S. PARKER<sup>8</sup>, S. THUNELL<sup>5</sup>  
G. ELDER<sup>2</sup>

<sup>1</sup>Centre Français des porphyries, Hôpital Louis Mourier, Colombes CEDEX, France, <sup>2</sup>Porphyria Service, Department of Medical Biochemistry and Immunology, University Hospital of Wales, Cardiff, UK, <sup>3</sup>Molekulare Dermatologie, Hautklinik der RWTH, Aachen, <sup>4</sup>Porfyricentrum Sverige, Karolinska Universitetssjukhuset, Huddinge, Stockholm, <sup>5</sup>Laboratory of Porphyria metabolism, 1st Medical Faculty Charles University, Czech Republic, <sup>6</sup>Chefärztin Zentrallabor, Stadtspital Triemli, Zürich, <sup>7</sup>Orphan Europe, La Défense, France, <sup>8</sup>Laboratory of Clinical Biochemistry, Haukeland University Hospital, Bergen, Norway

Received February 4, 2005

Accepted April 25, 2005

---

### Summary

Porphyrias are uncommon inherited diseases of haem biosynthesis for which the diagnosis and treatment varies in individual countries. Despite the existence of guidelines recommended by porphyria experts concerning the diagnosis and management of the acute porphyrias, and of specialist centres in most European countries, many clinicians still do not apply these guidelines. The European Porphyria Initiative (EPI) network was formed in 2001 in order to compare experience among countries to attempt to develop a common approach to the management of the porphyrias, particularly concerning recommendation of safe and unsafe drugs, and to facilitate international collaborative clinical and biological research.

The main achievements of EPI during this period have been:

- Drafting and agreeing to consensus protocols for the diagnosis and management of acute hepatic porphyrias
- Creation of a multilingual website, particularly focusing on guidelines for common prescribing problems in acute porphyria and on providing information for patients that is now available in 10 languages: [www.porphyrria-europe.org](http://www.porphyrria-europe.org).

EPI's current objectives are to develop the EPI platform, expand to new countries, extend to non-acute porphyrias and design European research and clinical trials in porphyria. The project will focus on:

1. Setting up a European laboratory external quality assurance scheme (EQAS) for biochemical and molecular investigations and their interpretation
2. Establishing a consensus drug list in collaboration with the Nordic porphyria network
3. Improving patient counseling
4. Developing large multi-centre, multi-national research projects. Due to the rarity of the porphyrias, it would be very difficult for any one country to provide this data with a sufficient number of patients and within a reasonable timescale.

The progress achieved will facilitate improvements in the treatment and development of new therapeutic strategies. It will set a pattern for establishing, and subsequently harmonising, between countries best clinical practice for a rare but important group of diseases, and will help to develop the optimal therapy and ensure its cost effectiveness.

## Key words

Porphyrias • Haem • European Porphyria Initiative

## Introduction

The porphyrias are uncommon inherited metabolic disorders of haem biosynthesis in which specific patterns of overproduction of haem precursors are associated with characteristic clinical features. Each type of porphyria is the result of a specific decrease in the activity of one of the enzymes of haem biosynthesis.

The porphyrias are inherited by a dominant autosomal mechanism, except in the cases of congenital erythropoietic porphyria and ALA-D deficiency (both extremely rare), which are inherited by a recessive autosomal mechanism. Porphyrias are classified as erythropoietic or hepatic in type, depending on the primary organ in which excess production of porphyrins or their precursors takes place.

Acute attacks occur in 4 of the porphyrias (acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), variegate porphyria (VP) and ALA-D deficiency); their diagnosis and management have been extensively reviewed (Anderson *et al.* Scriver, eighth edition, Deybach 2004).

The attacks consist of acute abdominal pain with vomiting and constipation, sometimes associated with neuro-psychiatric manifestations and may be followed by prolonged disability or end fatally.

The diagnosis of an acute attack of porphyria requires demonstration of increased urinary excretion of the haem precursor, porphobilinogen (PBG). Further investigation is needed to identify the type of porphyria, but this should not be allowed to delay treatment.

Specific treatment using intravenous haem should be started as soon as the diagnosis is established unless the attack is mild and clearly resolving. Any drugs or other potential provoking agents should be withdrawn. Care should be taken to avoid the risk of hyponatraemic seizures from the inappropriate use of intravenous fluids.

Family screening to identify those with the latent disease is essential for management of the autosomal dominant porphyrias. Patients and asymptomatic individuals who have inherited an acute porphyria must receive appropriate counselling, particularly about how to minimise the risk of an acute attack by avoiding drugs and other provoking factors. Despite the existence of a consensus on the diagnosis and management of the acute

porphyrias, these guidelines are not applied, in practice, by all clinicians managing patients and their families; for example:

Diagnosis may be made solely on the basis of a 'positive' screening test for PBG and specific, quantitative measurement of urinary PBG omitted; or only urinary porphyrins may be measured (coproporphyrin excretion is often increased in acutely ill patients).

Treatment is still based on high carbohydrate infusions which are no longer necessary when haem preparations are available.

Experience suggests that haem treatment is safe during pregnancy (Elder *et al.* 2001); but this does not appear to be sufficiently widely known (Engelhardt *et al.* 2004).

Misinterpretation of information on drug lists; when prescribing, the benefit from using the drug of choice should always be assessed against the risk of provoking an acute attack and the likely consequence of not using it. Cases of women with breast cancer who have not been proposed optimum treatment for the cancer in order to avoid the risk of an acute attack have been reported (Deybach - unpublished)

In almost every European country at least one porphyria diagnostic and advisory centre exists; however, these centres often do not collaborate and may even be in competition with each other. This approach goes against the progression of knowledge and the drive within Europe to centralize data on rare diseases.

The EPI project was founded in an attempt to resolve these problems.

## European Porphyria Initiative (EPI)

### Objective

The EPI network was formed in order to compare experience between countries, attempt to develop a common approach to the management of the porphyrias and to facilitate international collaborative clinical and biological research and development.

### Description of projects

EPI set out to provide a forum for European co-operation and exchange of information on the porphyrias

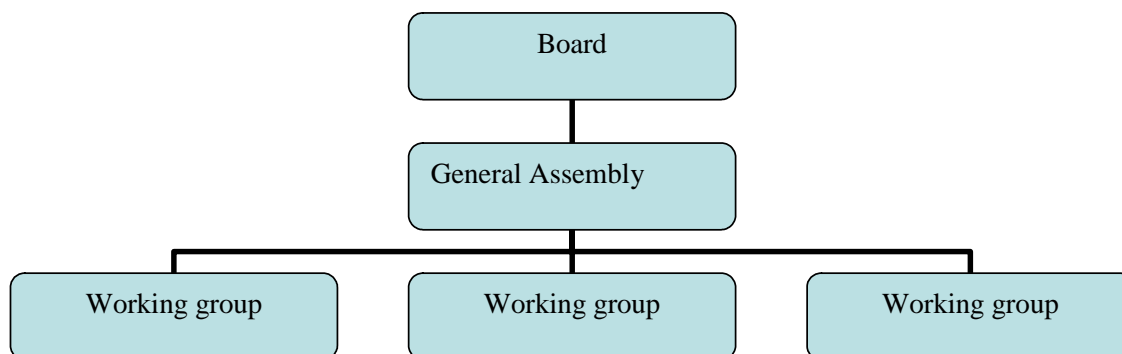


Fig. 1. EPI structure and management in 2005

Table 1. Information for people with acute porphyria

1. WHAT IS ACUTE PORPHYRIA?
2. WHAT IS AN ACUTE ATTACK OF PORPHYRIA?
3. HOW MANY TYPES OF PORPHYRIA ARE THERE?
4. HOW IS ACUTE PORPHYRIA INHERITED?
5. WHAT IS THE RISK OF SYMPTOMS AMONG THOSE WHO HAVE INHERITED AN ACUTE PORPHYRIA GENE?
6. HOW IS AN ATTACK OF ACUTE PORPHYRIA DIAGNOSED?
7. WHEN IS THE BEST TIME TO BE TESTED FOR AN ACUTE PORPHYRIA?
8. HOW ARE RELATIVES SCREENED FOR ACUTE PORPHYRIA?
9. WHAT CAN I DO TO REDUCE THE RISK OF HAVING AN ACUTE ATTACK?
10. SPECIAL PROBLEMS
11. PARTICULAR ISSUES FOR WOMEN
12. TREATMENT OF ACUTE ATTACKS
13. SKIN PROBLEMS IN THE ACUTE PORPHYRIAS
14. CONCLUSION
15. PATIENT SUPPORT GROUPS

based on consensus by the participating members. This includes advice for clinicians, for example, on recommendations for common prescribing problems and on management, diagnosis and treatment of patients with porphyria and their families; EPI also provides information for patients. This platform will also facilitate international collaborative clinical and biological research. thus conforming to the requirements needed before applying to the various European and national research funding opportunities, for example the INSERM/AFM research network.

#### Structure and management

The EPI board was formed in 2001 and participants include 7 reference centres from France, Germany, Norway, Sweden, Switzerland and the UK; in order to facilitate EPI management, a new structure shall be put in place in 2005:

- **EPI Board:** shall be comprised of a chairman, vice

chairman, secretary, treasurer, working group managers and co-opted members. It shall be responsible for the general management of EPI and shall be the ultimate decision making body.

- **General Assembly:** members shall be comprised of representatives from European porphyria diagnostic and advisory centres (specialist laboratories).

- **Working Groups:** Working groups shall be appointed to address specific matters such as the classification of drugs and European laboratory quality assurance scheme.

#### Results

Since 2001 the EPI board held quarterly board meetings to discuss and agree consensus on the diagnosis, management and preventive treatment of the acute porphyrias. The resulting work has been published on the EPI website [www.porphyrria-europe.org](http://www.porphyrria-europe.org). The website is divided into 4 main sections: information for people with

acute porphyria, information for health care specialists, drugs and porphyria, European diagnostic and advisory centres.

#### *Information for people with acute porphyria*

This section has been translated into 10 languages: English, Dutch, French, German, Hebrew, Italian, Polish, Portuguese, Spanish and Turkish. The contents are listed in Table 1.

#### *Information for health care specialists*

This section provides information for health care specialists on the porphyrias, diagnosis, investigating the

family, treatment and management of pain. Free access (no password) is provided in this section, thus allowing rapid access for individuals requiring an emergency consultation; nevertheless, the section carries a warning sign that the information is primarily written for healthcare specialists.

#### *Information on drugs*

Besides general principles on prescribing and a search engine for the safety of drugs, the originality of this section lies in the recommendations on common prescribing problems; 3 of these recommendations will now be described:

**Table 2.** Recommendations for the use of hormonal contraception in the acute hepatic porphyrias

<p>All lists of drugs that should be avoided in the acute porphyrias (AIP, VP, HCP) include the contraceptive pill. It is there because it is known to provoke attacks of acute porphyria either alone or by interacting with other factors. This presents a problem for many women who have had an attack of porphyria or are related to someone who has. Not surprisingly, questions about the risk of using the contraceptive pill or other hormonal methods of contraception are some of the most common faced by doctors who look after patients with porphyria and their families.</p> <p>Though there is no doubt that the contraceptive pill, and particularly its progestogen component, can provoke acute attacks, it is also well established that many women known to have inherited one of the acute porphyrias take the pill without any adverse effects. Unfortunately, there is no sure way of predicting how a woman with porphyria - whether or not she has previously had symptoms - will react.</p> <p>The only safe policy, therefore, is to use barrier methods of contraception and avoid the pill and other hormonal methods. However, this advice is not always acceptable particularly to women who have never had symptoms, some of whom may already be taking the pill when they are found to have porphyria. So here are some guidelines:</p> <p>Injectable (eg. <i>Depo-Provera</i>) and implanted hormone preparations are particularly dangerous – because they cannot be removed if an attack starts – and should never be used.</p> <p>Women who have had an attack of acute porphyria, even those who have been on the pill well before the attack started, should avoid all hormonal methods of contraception. If, after consultation with their doctor, they decide that they cannot do this, they must appreciate that they are running a real risk of becoming ill again. The same advice applies to women with variegate porphyria or hereditary coproporphyrinemia who have only the skin disease caused by these conditions without the abdominal pain and other symptoms of acute porphyria.</p> <p>Women who have never had symptoms but come from a family with one of the acute porphyrias should be tested to see whether they are affected. If they are, they should follow the advice given above. This is particularly important for those in their teens and early twenties, the age group in which attacks often start. The risk of provoking an acute attack may be highest for women with acute intermittent porphyria, high urinary porphobilinogen (PBG) levels, or both of these together. If, after receiving full information about acute porphyria and discussion of the likely consequences with their doctor, they do decide to start on the contraceptive pill, they should have a urine test for PBG. If the level is high, the decision to go ahead with the pill should be reconsidered. Any woman in this group who starts on the pill should have her urine tested for PBG at regular intervals for several months. If PBG levels increase progressively, the pill should be stopped. She should also report immediately to her doctor if abdominal pain or any other potential indicator of acute porphyria develops.</p> <p>Women who have never had symptoms and have already been taking the pill for some time before they are found to be affected often wish to continue. However even in this group there is a risk that the pill may facilitate the provocation of an acute attack by another drug, alcohol, infection, stress or some other factor. Their urine should be tested for PBG and any decision to continue taken only after discussion with their doctor.</p> <p>The above advice applies only to the combined oral contraceptive pill that contains an oestrogen and a progestogen and to oral and depot progestogen-only preparations. Some intra-uterine devices (eg. <i>Mirena</i>) contain a progestogen that has mainly a local action within the uterus and only enters the bloodstream in very small amounts. Experience to date suggests that this sort of device carries only a very low, if any, risk of provoking an acute attack. Oral emergency contraception preparations contain a high dose of progestogen and are dangerous in porphyria; insertion of an intra-uterine device is therefore the safe alternative.</p> <p>All these remarks apply only to the acute porphyrias. The oestrogen component of the contraceptive pill may precipitate the skin disease, porphyria cutanea tarda, but acute attacks of porphyria do not occur in this condition. In addition, treatment is effective without withdrawing the pill, if this is impracticable.</p>
---

**Table 3.** Recommendations for the use of local anaesthesia in the acute hepatic porphyrias

The safety of local anaesthetic agents remains a controversial issue due to experimental evidence that some of the local anaesthetic agents are porphyrogenic in either animal models (e.g. lidocaine) or cell culture (e.g. lidocaine, mepivacaine, prilocaine, bupivacaine). However, despite this laboratory evidence, clinical experience has shown that most of these agents have been used in patients with acute porphyria without any notable adverse effect (HIFT 2000, MCNEILL 1990, BROWN 2002)

*General Points:*  
 These drugs are used in small doses, are metabolised slowly and there is no first pass effect.  
 To date there are no case reports in the literature ascribing an acute attack to the use of local anaesthesia

*Dental Anaesthesia*  
 By far the most common requirement for local anaesthesia occurs when patients require dental treatment. In the majority of cases these procedures can be carried out under local anaesthetic.  
 Suggestions: Bupivacaine (0.25-0.5 %) with adrenaline (1:200,000)  
 Prilocaine (4 %)

*Regional Anaesthesia; Nerve blocks, epidural anaesthesia, spinal anaesthesia*  
 Several reports have documented the safe use of bupivacaine and procaine for epidural anaesthesia during labour. This has involved both extradural (bupivacaine, procaine) and spinal (bupivacaine) anaesthesia.

*Topical anaesthesia;*  
 There is little to suggest that local anaesthetic agents formulated for surface anaesthesia are associated with any significant risk. Examples of formulations and their uses include;  
 Lidocaine; Gel (2 %) for use prior to venepuncture, minor skin procedures or urethral catheterisation;  
 Spray (4-10 %) for use in procedures on the respiratory tract (intubation, bronchoscopy, ENT procedures)  
 Amethocaine; Gel (4 %) for anaesthesia prior to venepuncture or minor skin procedures.  
 Eye drops (0.5-1 %)  
 Oxybuprocaine; Eye drops (0.4 %)

*Drugs which have been used safely as Local Anaesthetic Agents*  
 Amethocaine, Oxybuprocaine, Bupivacaine, Prilocaine, Lidocaine, Procaine, Mepivacaine, Tetracaine

#### European diagnostic and advisory centres (porphyria specialist laboratories)

As part of the EPI project, it was decided to set up a network of specialist European porphyria laboratories in which there will be collaboration and a quality assurance scheme (see Figure 2). As from 2005 all laboratories are required to demonstrate that their services fulfil the following criteria:

- Able to distinguish, using biochemical testing, between all types of porphyria
- Able to offer specialist detailed interpretation of results with clinical advice on management
- Participation in EPI-organised quality assurance schemes. Quality assurance schemes will be organized in 2005 and more information will be available early in 2005
- An application form for specialist laboratories can be downloaded from the EPI website

#### Future perspectives

The core functions of EPI consist of updating and reviewing the website, developing a consensus list

of safe and unsafe drugs and setting up an external quality assurance scheme.

**Fig. 2.** EPI website list of partners in December 2004

**Table 4.** Recommendations in the management of convulsions and epilepsy in patients with acute porphyria

<p>Seizures may occur (a) as a manifestation of acute porphyria, where they may be secondary to the hyponatraemia that develops in up to 35 % of acute attacks or (b) due to a cause unrelated to porphyria. Treatment firstly involves terminating the seizure and then assessing the likely cause and planning the most appropriate therapy. In the case of hyponatraemia this involves slow correction of the electrolyte imbalance by fluid restriction and isotonic or hypertonic saline where necessary.</p> <p>A major problem in the management of seizures is that many of the commonly used anticonvulsants can precipitate or worsen acute attacks. Therefore where a primary seizure disorder is suspected this should be fully investigated by an epilepsy expert to ensure that treatment is absolutely necessary.</p> <p><i>I. Acute seizure or status epilepticus during an acute attack</i></p> <p>Termination of an acute convulsion should be with an intravenous benzodiazepine such as lorazepam, diazepam or clonazepam. The choice of diazepam may be controversial but it is almost certainly safe as a single intravenous dose. Under no circumstances should phenytoin or phenobarbitone be used.</p> <p>Where benzodiazepine treatment fails, paraldehyde or magnesium sulphate should be considered.</p> <p>Where general anaesthesia is required propofol is the drug of choice.</p> <p><i>II. Epilepsy</i></p> <p>a) New diagnosis of epilepsy in patient known to have an acute porphyria</p> <p>Wherever possible an anticonvulsant should be chosen from the list of safe alternatives below. When control of epilepsy is particularly difficult or no safe alternative is effective, discussion with a recognised porphyria expert may help in the selection of an appropriate drug regime that minimises risk to the patient. Close biochemical monitoring by regular measurement of urine porphobilinogen is advisable under these circumstances.</p> <p>b) New diagnosis of acute porphyria in an epilepsy patient on anticonvulsants</p> <p>Where the patient is on an anticonvulsant that carries a particularly high risk (e.g. carbamazepine, phenytoin, phenobarbitone, primidone, ethosuximide) changing to a safer alternative is advisable. However, change of therapy may occasionally provoke either acute porphyria or epilepsy and the patient should always be informed of the risk and carefully monitored.</p> <p>In some cases the risk of changing anticonvulsant therapy, e.g. in a patient whose seizures are difficult to control, may outweigh that of inducing an acute attack. In these circumstances, the patient should be informed of the risk and advised to seek medical help should symptoms of acute porphyria develop.</p> <p><b>ANTI-EPILEPTIC DRUGS AVAILABLE</b></p> <p>(P; denotes porphyrogenic in cell culture/animal model, C; denotes drug known to cause acute attacks in patients)</p> <p><u>Use:</u> Clobazam, Clonazepam<sup>7</sup> Lorazepam<sup>8</sup> Gabapentin<sup>1,2</sup> Acetazolamide (Vigabatrin<sup>1</sup>) #Paraldehyde</p> <p><u>Use with Caution:</u> Valproate<sup>4,6</sup> Diazepam<sup>8</sup></p> <p><u>Avoid (Evidence):</u> Carbamazepine<sup>5,6</sup> (P,C) Phenytoin<sup>7</sup> (P,C) Phenobarbitone (P,C) Primidone (P,C) Ethosuximide (P,C) Tigabine<sup>1,3</sup> (P) Lamotrigine<sup>1</sup> (P) (Felbamate<sup>1^</sup>)(P) Topiramate<sup>1,2</sup> (P) Oxcarbazine (P)</p> <p><u>No data:</u> Levetiracetam*</p> <p># Vigabatrin is associated with the development of irreversible visual field defects and is very rarely prescribed in adults. Use should be supervised by a neurologist experienced in epilepsy management.</p> <p>^ Felbamate is associated with bone marrow suppression and would only be used with great caution.</p> <p>* Levetiracetam is not dependant on hepatic cytochrome P450 system elimination and does not induce hepatic enzymes. The main route of excretion of parent drug and metabolites is renal.</p> <p>In view of this it would be expected to be safe (HAHN 97, ZADRA 98, KRIJT 2001, MCGUIRE 1988, REYNOLDS 1981, LARSON 1978, LAMBRECHT 1999)</p>
---

International collaboration to collect all available information on the porphyrogenicity of drugs is necessary; The Nordic porphyria centres have set up a rigorous, comprehensive, high-tech database classifying drugs into 5 risk categories (not porphyrinogenic, probably not porphyrinogenic, possibly porphyrinogenic, probably porphyrinogenic, documented porphyrinogenic). The manager of the Nordic group is also manager of the EPI drug working group whose objective is to draft and agree to/on a consensus drug list.

The EPI platform will also focus on large multi-

centre, multi-national research projects looking at the association of porphyria and other chronic manifestations and identification of unusual variant forms of porphyria. This type of research is only possible with the large pool of patients available in the European population.

### Acknowledgements

EPI was supported by a grant from the INSERM U-656 GIS-MALADIES RARES 2001/2003 research network on rare disorders.

## References

- ANDERSON KE, SASSA S, BISHOP DF, DESNICK RJ: Disorders of heme biosynthesis; X-linked sideroblastic anemia and the porphyrias. The metabolic & molecular bases of inherited disease; eighth edition, Vol II, chapter 124, 2991.
- DEYBACH JC, PUY H: The Porphyrias. Conn's Current Therapy, 56th ed., section 6, chapter 122, RAKEL RE, BOPE ET (eds), WB Saunders Company Elsevier USA, 2004, pp 494-500.
- ENGELHARDT K, TRINKA E, FRANZ G, UNTERBERGER I, SPIEGEL M, BEER R, PFAUSLER B, KAMPFL A, SCHMUTZHARD E: Refractory status epilepticus due to acute hepatic porphyria in a pregnant woman: induced abortion as the sole therapeutic option? *Eur J Neurol* **11**: 693-697, 2004.
- ELDER G, HIFT R: Treatment of acute porphyria. Hospital Medicine, July 2001, Vol 62, No 7.
- JAMES, MFM, HIFT RJ: Porphyrias. *Br J Anaesth* **85**: 143-153, 2000.
- MCNEILL, MJ, BENNET A: Use of regional anaesthesia in a patient with acute porphyria. *Br J Anaesth* **64**: 371-373, 1990.
- BROWN, WELBURY: The management of porphyria in dental practice. *Br Dent J* **193**: 145-146, 2002.
- HAHN M, GILDEMEISTER OS, KRAUSS GL, PEPE JA, LAMBRECHT RW, DONOHUE S, BONKOVSKY HL: Effects of new anticonvulsant medications on porphyrin synthesis in cultured liver cells: potential implications for patients with acute porphyria. *Neurology* **49**: 97-106, 1997.
- ZADRA M, GRANDI R, ERLI LC, MIRABILE D, BRAMBILLA A: Treatment of seizures in acute intermittent porphyria: safety and efficacy of gabapentin. *Seizure* **7**: 415-416, 1998.
- KRIJT J, KRIJTOVA H, SANITRAK J: Effect of tiagabine and topiramate on porphyrin metabolism in an in vivo model of porphyria. *Pharmacol Toxicol* **89**: 15-22, 2001.
- MCGUIRE GM, MACPHEE GJ, THOMPSON GG, MOORE MR, BRODIE MJ: Effects of sodium valproate on haem biosynthesis in man: implications for seizure management in the porphyric patient. *Eur J Clin Invest* **18**: 29-32, 1988.
- MCGUIRE GM, MACPHEE GJ, THOMPSON GG, PARK BK, MOORE MR, BRODIE MJ: The effects of chronic carbamazepine treatment of haem biosynthesis in man and rat. *Eur J Clin Pharmacol* **35**: 241-247, 1988.
- REYNOLDS NC Jr, MISKA RM. Safety of anticonvulsants in hepatic porphyrias. *Neurology* **31**: 480-484, 1981.
- LARSON AW, WASSERSTROM WR, FELSHER BF, CHIH JC: Posttraumatic epilepsy and acute intermittent porphyria: effects of phenytoin, carbamazepine, and clonazepam. *Neurology* **28**: 824-828, 1978.
- LAMBRECHT RW, GILDEMEISTER OS, PEPE JA, TORTORELLI KD, WILLIAMS A, BONKOVSKY HL: Effects of antidepressants and benzodiazepine-type anxiolytic agents on hepatic porphyrin accumulation in primary cultures of chick embryo liver cells. *J Pharmacol Exp Ther* **291**: 1150-1155, 1999.

---

## Reprint requests

J-Ch. Deybach, Centre Français des Porphyries, Hôpital Louis Mourier, Colombes CEDEX, France. E-mail: Jc.deybach@wanadoo.fr