SAFE USE OF PERAMPANEL IN A CARRIER OF VARIEGATE PORPHYRIA: A CASE REPORT

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Summary

Objectives. Treatment of chronic epilepsy in acute porphyrias may be difficult because many antiepileptic drugs can cause activation of clinically-latent conditions.

Methods. A 44 year-old lady with drug-resistant chronic epilepsy and a previous genetic diagnosis of variegate porphyria was referred to our epilepsy centre. We started her on perampanel, a structurally novel selective non-competitive AMPA receptor antagonist recently approved for the treatment of partial and secondarily generalized seizures in humans. There are no previous reports about the outcome of exposure to perampanel of carriers of acute porphyria.

Results. Perampanel was assessed *in silico* to be probably not porphyrogenic. Administration of the drug up to 4 mg/day did not lead to elevation of urinary porphobilinogen excretion, nor to any symptoms of acute porphyria after more than 23 months of treatment.

Conclusions. Perampanel up to 4 mg/day was tolerated in long-term therapy in this carrier of protoporphyrinogen oxidase deficiency. However, since perampanel is a weak inducer of cytochrome P450 enzymes, vigilance should be maintained for clinical and biochemical signs of activation of acute porphyria when used in a carrier of acute porphyria.

Management of epilepsy associated with porphyrias - what to use and what not to use (http://www.drugs-porphyria.org, accessed 20/10/2015; http://www.wmic.wales.nhs.uk/pdfs/porphyria/2015%20Porphyria%20safe%20list.pdf, accessed 20/10/2015).

Acute symptomatic seizures occur in approximately 10–20% of patients with acute intermittent porphyria in relapse, while there are rarer reports of porphyria in people with chronic epilepsy, mostly drug-resistant. The association between epilepsy and porphyria is unclear. Porphyria might be the cause of chronic symptomatic epilepsy (if so, this would be rare or frequently undiagnosed) or there might be a chance association, given that epilepsy is common. Nevertheless, in drug-resistant epilepsy, metabolic causes such as the porphyrias need to be considered, especially when the seizure frequency increases on higher doses of certain antiepileptic drugs (AEDs). Acute porphyric attacks can be potentially fatal and such attacks are usually precipitated, in susceptible individuals, by exposure to commonly used drugs, including certain AEDs. Correctly determining the safety of use of certain drugs in people with porphyria is therefore important. Once the diagnosis of porphyria-related seizures is confirmed, treatment of the porphyria itself will be needed: management will include appropriate selection of a non-porphyrinogenic AED (as the induction of hepatic haemosynthesis by enzyme-inducing AEDs can exacerbate the symptoms of porphyria, or bring on acute attacks).

Clinical experience, and findings from experimental systems, using whole animal or cell culture models, have been used to determine porphyrogenicity (the potential of a drug to induce an acute porphyric attack) and to classify drugs as safe or unsafe in freely available drug lists (e.g. http://www.drugs-porphyria.org; http://www.wmic.wales.nhs.uk/pdfs/porphyria/2015%20Porphyria%20safe%20list.pdf).

In acute porphyric attacks, seizures can be treated with intravenous diazepam, levetiracetam, or propofol if status epilepticus develops; a single or few seizures may not require AED treatment in the long term, provided the porphyria itself is properly managed.

Antiepileptic drugs that are considered to be SAFE for use in the acute porphyrias (not porphyrinogenic or probably not porphyrinogenic)	**Antiepileptic drugs that should not be used in the acute porphyrias (porphyrinogenic or probably porphyrinogenic)**
Clobazam	Carbamazepine
Clonazepam	Ethosuximide
Gabapentin	Felbamate
Lacosamide	Oxcarbazepine
Lamotrigine	Phenobarbital
Levetiracetam	Phenytoin
Paraldehyde	Primidone
Piracetam	Stiripentol
Pregabalin	Tiagabine
Retigabine	Topiramate
Vigabatrin	Valproic acid
Zonisamide	

Uncertain (possibly porphyrinogenic or not yet classified)

Acetazolamide

Eslicarbazepine

Perampanel

Rufinamide

Background

The porphyrias form a heterogeneous group of inherited metabolic disorders, each of which results from deficiency of a specific enzyme in the multi-step heme biosynthetic pathway. [1]

Variegate porphyria (VP) is an autosomal dominant form of hepatic porphyria associated with disease-predisposing mutations in the gene for protoporphyrinogen oxidase (PPOX). The phenotypic expression of the condition is the result of deficiency of this enzyme, which converts protoporphyrinogen to protoporphyrin in the penultimate step of heme biosynthesis.

In PPOX-deficiency, the gene carrier state is generally clinically quiescent, but symptoms of variegate porphyria can be triggered by exposure to a variety of precipitating factors, including a wide range of commonly-prescribed medications. Attacks in acute porphyria mainly feature gastrointestinal and neuropsychiatric symptoms. Accumulation of phototoxic porphyrins in the skin may give rise to solar hypersensitivity and bullous dermal lesions. The treatment of epilepsy in acute porphyrias represents a challenge, because many commonly-used antiepileptic drugs strongly induce heme-dependent cytochromes P450 in the liver. In the course of holoenzyme assembly, the demands for heme are met by the liver through acceleration of *de novo* heme biosynthesis. In PPOX-deficiency, on porphyrogenic challenge the pathway may become overloaded, with resulting accumulation of phototoxic porphyrins, as well as presumably neurotoxic pre-porphyrin intermediates.

Perampanel is a structurally novel, selective non-competitive AMPA receptor antagonist recently approved for the treatment of partial and secondarily generalized seizures in humans. We describe a case of epilepsy in a carrier of variegate porphyria, in which perampanel was tried after safety assessment.

Case presentation

This 44 year-old lady was the product of a normal pregnancy and delivery. Her motor and cognitive development were normal. Onset of seizures was at nine years of age, with a tonic-clonic seizure. She has tried many antiepileptic drugs in the past without

full seizure control. At age 29, variegate porphyria was diagnosed following development of a right hemiparesis with ataxic features and dysphasia. DNA analysis showed a deletion [IVS5-(24-16) del CTTAGTCCT] in intron 5 of the *PPOX* gene, likely to be the cause of her variegate porphyria. She was also diagnosed with primary hypothyroidism. At 31, a vagal nerve stimulator was implanted, without benefit. She was also treated with GnRH analogues and low doses of oestrogens, given some correlation between her menstrual cycle and seizure frequency.

She was referred to our centre aged 42. At that time, her antiepileptic medication was gabapentin, levetiracetam, pregabalin and clobazam, all previously assessed not to be porphyrogenic. She was experiencing multiple seizures daily, of a variety of types. There was no report of her previous or current antiepileptic medication precipitating any porphyric crisis. Prolonged EEG-videotelemetry showed interictal abnormalities in the left fronto-temporal region, although some right-sided epileptiform changes were present. Multiple seizures were captured and electroclinical evidence suggested left fronto-temporal origin. Her ECG was normal. Neuropsychometry showed widespread cerebral dysfunction, with verbal and visuo-spatial skills falling below the average range and verbal memory, naming and fluency all falling within the borderline-to-impaired range.

We introduced lacosamide, considered safe in porphyria. Unfortunately she developed a skin rash, without associated symptoms of a porphyric crisis. We could not exclude an allergy to lacosamide and it was therefore discontinued.

Perampanel is amongst the newest antiepileptic drugs. To our knowledge, there is no previous report of its use in acute porphyrias and no patient exposure data were available in the National Acute Porphyria Service (http://www.cardiffandvaleuhb.wales.nhs.uk/national-acute-porphyria-service-naps, accessed 15/03/2013).

Further enquires were made at the Porphyria Centre in Sweden, where perampanel was categorized as “probably not porphyrogenic”, considered to be the lowest risk category after “safe”. The classification was reached by way of *in silico* analysis.[4], where pharmacokinetic data are used for assessment of drug cytochrome (CYP)-

inductive power. In addition, pharmacodynamic mechanisms, physiological actions and side effects of the drug were evaluated for potential capacity for activation or co-activation of nuclear receptors responsible for CYP-induction. The only finding of possible relevance was evidence of weak capacity for CYP3A4 induction, but it was not expected to be of a strength to be significant in the present context. There have been no reports of clinical observations against *in silico* safety assessment results.

After discussion with the patient, we started perampanel, with monitoring of urinary porphobilinogen. Her urinary porphobilinogen level pre-treatment and at one and two weeks on treatment were normal. The National Acute Porphyria Service did not recommend further routine urinary monitoring. The dose of perampanel was initially 2 mg *nocte* and was gradually titrated in increments of 2 mg up to 4 mg daily.

She had an initial improvement in seizure frequency with up to fifteen days without any seizures, compared to daily seizures before perampanel. After about three months, she developed unsteadiness and had difficulty transferring from her wheelchair. This adverse effect required admission to hospital and physiotherapy. The dose of perampanel was subsequently reduced to 2 mg daily. She did not develop any symptoms of acute porphyria while on perampanel during 23 months of treatment.

Discussion

While acute symptomatic generalised seizures are recognized features of acute attacks of porphyria the association between porphyria and drug-resistant epilepsy is less clear, with few reported cases.[2]

In the treatment of epilepsy in acute porphyrias, the choice of drugs should be from amongst the non-CYP-inducing antiepileptic drugs [see Box above] so that porphyrogenic acceleration of hepatic heme biosynthesis is avoided. Treatment with the strong CYP-inducers carbamazepine, phenobarbitone, phenytoin, primidone, topiramate, and sodium valproateshould be avoided as far as possible. Tiagabine shows evidence of porphyrinogenicity in *in vitro* studies using cultured liver cells and may be hazardous.

The use of perampanel in the present case of variegate porphyria and drug-resistant epilepsy was not followed by any clinical or biochemical signs of activation of the

disorder. A single observation of tolerance to a drug in a carrier of acute porphyria, however, cannot be taken as proof of non-porphyrogenicity, because of the great variability between carriers, as well as in one carrier over time, in susceptibility to the action of porphyria precipitating agents. Women are more prone than men to attacks of acute porphyria, and in the present case the carrier exposed to perampanel is a female with a history of clinically manifest acute porphyria, indicating that she does not belong to the group of individuals seemingly constitutionally resistant to the phenotypic manifestations of acute porphyria. The circumstance that our patient is potentially vulnerable to porphyrogenic challenge serves to enhance the significance of the observation of her tolerance to perampanel, and helps to validate the *in silico* assessment of probable non-porphyrogenicity of the drug.

Recently, two cases with drug-resistant epilepsy in non-carriers of acute porphyria have been described in the literature. Both presented in convulsive *status epilepticus* and were on treatment with perampanel. Both patients were found to have significantly decreased blood levels of concurrent antiepileptic medication (phenytoin, phenobarbital, rufinamide) in comparison with levels prior to perampanel introduction. In one of the cases, further increasing the perampanel dose resulted in a further drop of the phenytoin level. As demonstrated in cultured human hepatocytes and through drug interaction studies, perampanel is weak inducer of CYP2B6 and CYP3A4/5, as well as of uridine 5'-diphospho-glucuronosyltransferase, while drug transporters are not affected. It is therefore conceivable that the increased rate of elimination of the CYP-metabolized co-administered drugs in the reported cases is an effect of the weak CYP-inductive capacity of perampanel. Until more experience is acquired, initial monitoring of urinary porphobilinogen excretion and subsequent clinical vigilance should be routine in the use of perampanel in acute porphyrias, especially with higher dosage regimes. Monitoring of concomitant antiepileptic drug levels is also indicated. The common side effects, nausea and disturbed appetite, would motivate some attention to nutrition of the patient, to reduce risk for potentially porphyrogenic decrease of caloric intake.

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Disclaimer

In the report, the classifications given for drugs in terms of porphyrogenicity/non-porphyrogenicity are from the literature and generally based on clinical observations, and experimental or *in vitro* findings. In some cases, they are results of pharmacological considerations applied to a genometabolic model of acute porphyria. There are, however, potential souces of error in all presently available techniques for drug porphyrogenicity assessment. Even with care taken to eliminate them errors *lege artis*, it is not possible to take legal responsibility for the drug classifications provided and the data should not be taken as advice .

Competing Interests

None

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