Epileptic Disord 2020; 22 (3): 349-52

Eslicarbazepine for focal epilepsy and acute intermittent porphyria*

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Received January 6, 2020; Accepted March 12, 2020

ABSTRACT – Porphyrias are rare genetic disorders which cause a deficiency in the enzymes involved in the biosynthesis of heme. The treatment of epilepsy in patients with acute intermittent porphyria can be difficult since many anticonvulsants can increase heme synthesis and trigger porphyric attacks. We report a patient with focal epilepsy successfully treated with eslicarbazepine without exacerbation of porphyria.

Key words: eslicarbazepine, carbamazepine, hepatic porphyria

Treatment of epilepsy in patients with co-morbid porphyria is often challenging. Several antiepileptic drugs (AEDs), through their hepatic metabolism and consequent induction of heme synthesis, may precipitate acute attacks in patients with clinically latent hepatic porphyria (Solinas and Vajda, 2004; Thunell *et al*., 2007). Phenobarbital, phenytoin, and carbamazepine (CBZ) are generally avoided as they are known hepatic inducers and therefore strongly porphyrogenic. Tiagabine, lamotrigine, and sodium valproate have also been reported as potentially porphyrogenic (Solinas and Vajda, 2004). Although it belongs to the same chemical family as CBZ, eslicarbazepine (ESL) could be an attractive treatment option for these patients because it is a weak enzyme inducer, which in theory should reduce its porphyrogenic propensity (Galiana *et al*., 2017).

Case study

The patient was a 36-year-old woman diagnosed with non-lesional focal epilepsy at the age of 10 years. Seizures were polymorphic and could include visual, epigastric, cephalic or affective (fear) auras followed by impaired awareness and hypersalivation. Progression to head deviation, asymmetric tonic posturing and bilateral tonic-clonic seizures was not uncommon. Seizure frequency varied from a few per year to monthly catamenial seizures, either isolated or in clusters. Standard and continuous

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doi:10.1684/epd.2020.1171

*This work has been presented as a poster presentation at the 2019 Canadian League Against Epilepsy Annual Meeting.

Table 1. Urinary, plasmatic and faecal porphyrins and heme precursors in a patient with epilepsy and co-existing acute intermittent porphyria under treatment with different antiepileptic drugs.

	Normal	At four weeks after the onset of an AIP attack	At five weeks after the onset of an AIP attack and following treatment with haematin and glucose	During the transition from PGB to ESL	At 12 months under ESL
Urinary porphobilinogen (μmol/24h)	0-11	288	-	-	63
Urinary D-aminolevulinic acid (μmol/24h)	11-57	153	-	-	-
Total urinary coproporphyrins (nmol/24h)	0-350	1148	335	256	-
Total urinary uroporphyrins (nmol/24h)	0-65	4283	463	93	-
Plasmatic porphyrins (nmol/L)	0-15	24	-	-	-
Faecal porphyrins (nmol/g)	<75	59	-	-	11

AIP: acute intermittent porphyria; ESL: eslicarbazepine; PGB: pregabalin.

electroencephalographic recordings over the years have revealed abnormalities most consistently found over left mid-temporal leads. The patient was first started on CBZ at age 11 years (partial response); clobazam was later added at age 14 years (partial response); add-on lamotrigine and then topiramate did not help. Eventually, her seizure condition became much better controlled with one to two convulsive seizures per year using a combination of CBZ, clobazam and levetiracetam (age 29 to 32 years). Epilepsy surgery was considered and a pre-surgical work-up was performed. However, she was deemed at the time not a good surgical candidate due to her pleomorphic semiology, the lack of an obvious epileptogenic lesion on brain magnetic resonance imaging or a hypometabolic area on positron emission tomography, and most importantly, her reluctance to undergo an invasive EEG study.

At the age of 32 years, she was admitted due to an episode of psychosis. Although she had presented in the past with transient psychosis in the context of multiple seizures at age 29 years, this second psychotic episode was not preceded by obvious seizures. The hospital stay was complicated by seizures and a pericardial effusion requiring placement of a pericardial drain. Investigations revealed positive serum antinuclear antibodies (ANA), anti-Ro/SSA and anti-histone which prompted consideration for systemic lupus erythematous (SLE). Furthermore, elevated serum, urinary and faecal porphyrins as well as urinary porphobilinogen and D-aminolevulinic acid (*table 1*) suggested a diagnosis of acute intermittent porphyria (AIP), later supported by the identification of a mutation in the hydroxymethylbilane synthase (*HMBS*) gene (p. R167W c.499C→T). Considering the known porphyrogenic propensity of CBZ and the possibility that it could have been responsible for a drug-induced systemic lupus syndrome, CBZ was discontinued (replaced with lacosamide). The patient was also treated with haematin, intravenous glucose, colchicine and corticosteroids. The patient was eventually discharged on a combination of levetiracetam, clobazam, and lacosamide.

In the following two years, the patient's epilepsy deteriorated with focal unaware seizures occurring every two to three months and eight episodes of convulsive status epilepticus despite optimizing dosages and replacing lacosamide with pregabalin. Hematin therapy was eventually discontinued as the patient was convinced it worsened her epilepsy. A decision was made to attempt treatment with ESL, despite the chemical resemblance to CBZ. Indeed, positive ANA and anti-Ro/SSA (7.3; N<0.9), still observed three years after the withdrawal of CBZ, suggested that idiopathic SLE was a more likely diagnosis than CBZ-induced lupus. The substitution of pregabalin with ESL was performed with great caution under video-EEG monitoring in our epilepsy monitoring unit. ESL was initiated with a starting dose of 200 mg daily and slowly titrated to 1,000 mg daily over one week. Baseline levels of urinary uroporphyrins and coproporphyrins were moderately elevated at the time of transition from pregabalin to ESL (*table 1*). The patient had experienced only two focal unaware seizures associated with late or missed

doses and no acute attacks of porphyria after one year of follow-up. Biochemical investigations revealed that stool porphyrins had normalized, while, unsurprisingly, urinary porphobilinogen levels, although lower than those observed during the AIP attack, were still above reference range (*table 1*).

Discussion

The porphyrias are a group of inherited disorders causing a deficiency in the heme synthesis pathway and consequently an accumulation of heme precursors (Solinas and Vajda, 2004; Kauppinen, 2005). The overall prevalence of porphyria is estimated to vary between 0.5 and 10 per 100,000 people, depending on the population and type of porphyria (Kauppinen, 2005). Acute porphyrias are characterized by attacks of neurovisceral manifestations such as seizures, neuropathy, and psychosis (Solinas and Vajda, 2004; Kauppinen, 2005). In our case, a psychotic episode complicated by acute seizures led to the diagnosis of AIP. In larger series, seizures have been reported in 10-20% of patients with AIP (Tran *et al*., 2013) and in 10-20% of patients with SLE (González-Duarte *et al*., 2008). Epilepsy, AIP, and SLE can also coexist independently, which was most likely the case with our patient who had a long-standing history of focal epilepsy.

Whether treating acute seizures in the context of a porphyric attack or spontaneous seizures related to a co-existing epileptic condition, the choice of anticonvulsants must take into account the fact that some can increase heme synthesis and trigger porphyric attacks (notably phenobarbital, phenytoin, carbamazepine, tiagabine, lamotrigine, and sodium valproate). In our particular case, our patient failed to be controlled with anticonvulsants which have been reported to be safe in AIP; levetiracetam, pregabalin, benzodiazepines. Given that our patient had a good response to CBZ for many years, substitution with other dibenzazepine carboxamides with lower hepatic metabolism, such as oxcarbazepine and ESL, was considered. Oxcarbazepine appeared to be safe when used in a patient with focal seizures and hepatic porphyria, however, that patient had porphyria cutanea tarda which is not one of the inducible porphyrias and is not drug sensitive (Elder, 1998; Gaida-Hommernick *et al*., 2001; Pierach, 2002). In our case, ESL was chosen over oxcarbazepine given that it has fewer interactions with the CYP450s system (Peltola *et al*., 2015), thus less likely of being porphyrogenic (Thunell *et al*., 2007). This is somewhat supported by the favourable evolution of our patient's epileptic condition under ESL without exacerbation of the hepatic porphyria.

Marsden and Rees (2014) have reported that urinary porphobilinogen levels may remain elevated for years (or decades) in patients recovering from an AIP attack, as was the case for our patient. Although still above normal range, the reduction in urinary porphobilinogen excretion observed in our patient three years after the AIP attack appears encouraging. Perhaps a better indicator of the management of porphyria is the absence of the recurrence of a porphyric attack despite suboptimal treatment with haematin and the introduction of ESL.

Although ESL significantly improved the control of our patient's epileptic condition without aggravating her porphyria, it is not possible to conclude that ESL cannot cause porphyric attacks based on a single case study. Obviously additional data is required to assess the drug's safety for this condition. Hence, ESL should not be intended as a first-line therapy in patients with AIP but could potentially be considered for those who have failed treatment with safer AEDs. □

Supplementary data.
Summary didactic slides are available on the www.epilepticdisorders.com website.

Disclosures.
None of the authors have any conflict of interest to declare.

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TEST YOURSELF

(1) What AEDs are considered to be relatively safe in patients with acute intermittent porphyria?

(2) Why might eslicarbazepine be safer than carbamazepine for patients with co-morbid hepatic porphyria?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com*, under the section "The EpiCentre".*