Successful Felbamate treatment of epilepsia partialis continua
Traitement efficace de l'épilepsie partielle continue avec le Félbamate

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Abstract

Authors report two patients with epilepsia partialis continua refractory to many pharmacological treatments who responded to Felbamate. The first patient was a 41 year-old male with a large cavernous angioma of the right hemisphere, who developed epilepsia partialis continua (EPC) with interictal Todd's palsy in the absence of new bleeding. High doses of Primidone, Clorazepate, Topiramate, and Diazepam resulted in profound sedation but no effect on EPC. He had previously failed Phenytoin, Phenobarbital, Carbamazepine, Valproate, and Gabapentin. Felbamate was titrated up to 3600 mg/d., and EPC stopped over three days, and he regained full power in his left hand. Felbamate was discontinued after a month, because of its potential chronic toxicity. EPC did not recur. The second patient was a 27 year-old female with EPC of the left arm since age 15. She became seizure-free on Felbamate, but when the drug became unavailable to her a year later, EPC returned, and EEG showed right polyspikes/waves of low amplitude coming from the central and anterior parietal regions, which were synchronous with her arm movements by video and EMG. She declined surgery. These cases suggest that Felbamate might be useful as a drug of last resort for pharmacoresistant EPC.
Key-Words: Epilepsia Partialis Continua- Felbamate- Pharmacoresistance- Todd's palsy

Résumé

Les auteurs rapportent deux patients dont l'épilepsie partielle continue (EPC) était résistante a de nombreux anticonvulsivants, et chez qui une réponse favorable a été notée sous Félbamate. Le premier patient était un home de 41 ans, qui souffrait d'un angiome caverneux occupant un gros volume dans l'hémisphère droit. Son EPC du bras droit, accompagnée d'une paralysie de Todd, ne répondit pas a des doses élevées de Primidone, Clonazepam, Clorazepate et Topiramate, qui causaient une sédation sévère. Le Felbamate fut augmenté jusqu'a 3600 mg/jour, et l'EPC ainsi que la paralysie de Todd ont disparu, Le Félbamate fut arrêté après un mois, sans retour d'EPC. La seconde patiente était une femme de 27 ans qui souffrait d'EPC du bras droit depuis l'âge de 15 ans. L'EPC disparut sous traitement au Félbamate mais a récidivé quand ce traitement fut interrompu un an plus tard. L'EEG a montré des anomalies épileptiques da basse amplitude provenant des régions pariétales antérieurs et centrales droites, qui furent synchrones de ses mouvements du bras grâce aux données vidéo-EEG et EMG. Cette patente a refusé toute chirurgie.
Ces cas suggèrent que le Félbamate, malgré sa toxicité, pourrait être considéré comme une bonne alternative dans les cas d'EPC réfractaire aux médicaments antiépileptiques usuels.
Mots-clés: Epilepsia Partialis Continua- Félbamate- Pharmacorésistance- Paralysie de Todd

Introduction:

In 1895, Kojewnikoff described a very unique type of seizure which he named "Epilepsia Partialis Continua" (EPC) [1]. This phenomenon can be considered the status epilepticus equivalent of simple partial motor seizures. It manifests itself with focal motor clonic seizures, which remain localized to the part of the body in which they originated. Motor activity is often persistent, lasting for weeks or even longer. Consciousness is preserved, but post-ictal weakness is frequently present [2, 3]. Bancaud showed that EPC can be the expression of a stable neurological lesion or that of a progressive disease such as Rasmussen's syndrome [4]. This condition is remarkably pharmacoresistant, and antiepileptic drugs, with a few notable exceptions, do not seem to significantly alter its course [5]. Here we report 2 cases of EPC associated with a stable cavernous angioma of the brain in the first case and without any clear lesion on MRI in the second case, except a mild FLAIR image showed increased signal in the right centrum semi-ovale; both cases responded to felbamate, a medication which has been reported to be extremely effective in experimental models of self-sustaining status epilepticus.

Case reports:

Case 1: A 41 year-old male presented to UCLA on 11/16/98 with clonic left forearm movements for a week. Seizures started at the age of 2 years, and were treated with Phenytoin and Phenobarbital. From age 2½ -15 he was seizure-free, and therapy was stopped at age 7. At 15, left hand focal seizures, complex partial and generalized seizures recurred, and at age 24 he accidentally amputated his right thumb and index finger during a complex partial seizure. He went through a series of neurologists

and anticonvulsants (Phenytoin, Phenobarbital, Carbamazepine, Valproate, Primidone, Clorazepate, Felbamate, Gabapentin, Topiramate), eventually reaching good control on Primidone, Clorazepate and Topiramate. MRIs and angiogram disclosed a large cavernous angioma in the right hemisphere. On 11/16/98 patient was admitted to UCLA hospital with epilepsia partialis continua with semi-periodic, 0.5-2 Hz twitching of his left hand, occasionally spreading to forearm and biceps, with postictal paralysis. Physical examination showed right thumb and index amputation, dystonic posturing of his left hand with rythmic 0.1 Hz wrist flexions, mild forearm weakness, severe weakness of all hand muscles, and 3+ biceps, triceps and brachioradialis reflexes on the left. There had been no loss of consciousness, no generalization, no tongue biting, and no urinary or fecal incontinence. The patient threatened suicide because he felt that his left hand weakness and partial right hand amputation made him totally dependent on his mother. MRI showed no bleeding and no change in his cavernous angioma. EEG showed diffuse slowing, predominant on the right. The patient's medications were titrated up (highest daily intake: Primidone 2 gm, Clorazepate 75 mg, Topiramate 1500 mg, IM diazepam 10 mg), however the patient became extremely dysarthric and lethargic, and seizures continued. Felbamate 1200 mg/d. was started on 11/23, and increased to 2400, then to 3600 mg/d. on 11/25. Within 24 hours, movements became limited to 0.3-1Hz flexion of his left index finger. After 48 hours, they occurred only a few times a day for a period of minutes, and the other antiepileptic drugs were reduced. Lethargy and dysarthria improved, and after discharge on 11/25 he was seizure-free and regained full power in his left hand. Felbamate was well tolerated but was tapered over 4 weeks because of concern about hematologic toxicity, and the patient maintained good control and minimal toxicity on primidone 750 mg, topiramate 1200mg and clorazepate 15 mg/day.

Case 2: this 27 year-old Bolivian female with EPC since the age of 15 was seen at NIH in March 2000. Previous treatment with Valproate, Carbamazepine and Clonazepam caused drowsiness but did not modify the EPC. However, in 1993 she was admitted to NIH, started on felbamate and was seizure-free until felbamate became unavailable to her in 1994. She had taken no medications since. Neurological examination revealed only 3+ biceps and brachioradialis reflexes and an equivocal plantar response on the left. MRI was read as normal, but a later FLAIR image showed increased signal in the right centrum semi-ovale, a non-specific finding. EEG/video monitoring showed right polyspikes/waves of low amplitude coming from the central and anterior parietal regions, which were synchronous with her arm movements by video and EMG. Since EPC interfered only minimally with her life, the patient and her physicians decided to postpone treatment.

Comments:

Is Felbamate effective in EPC? This is the second report of successful Felbamate treatment of EPC, which is notoriously unresponsive to AEDs [5]. Echenne reported a case of Felbamate success in a patient with hemimegalencephaly with multiple types of seizures and poor response to AEDs [6]. Other agents have had little success. Thomas et al carefully studied EPC in 32 patients [7]. Seventeen of 25 patients had a poor or no response to anticonvulsants, and 6 of the 7 responders suffered from acute brain lesions, so that the therapeutic success could have been coincidental. Phenytoin, Nimodipine or Phenobarbital may be marginally more effective than Carbamazepine or Valproate [8, 9]. Oral corticosteroid therapy and immunosuppression may be of some benefit in rare cases [10]. In Rasmussen's encephalitis, plasma exchange, gamma globulins [11, 12], gancyclovir [13], intraventricular interferon-alpha have been used, but to date few lasting benefits have been seen. Neurosurgical approaches, such as multiple subpial transsections and hemispherectomy may be used as a last resort [14]. Further studies will tell whether the success of Felbamate in our patients was coincidental.

Is the mechanism that maintains EPC similar to that of other types of status epilepticus? Since surround inhibition may limit seizure spread more effectively in motor neocortex than in any other area, because of the tight afferent-efferent relationships which support the activation of long-loop reflexes, EPC may be a unique expression of cortical organization [15, 16], but the mechanism that maintains it may be similar to that seen in other forms of status. Experimental models of refractory SE often respond to NMDA antagonists [17], Felbamate is (among several mechanisms) an NMDA antagonist which is specific for NR2B subunit-containing receptors [18-21] and is neuroprotective in experimental models [22]. Like other NMDA blockers, felbamate is very effective in stopping experimental self-sustaining status epilepticus refractory to benzodiazepines [17]. The effectiveness of Felbamate in our patients raises the speculation that EPC, like limbic status epilepticus, might in part be an NMDA-dependent state [23], in which seizure-induced receptor trafficking increases the number of synaptic NMDA receptors and decreases the number of synaptic GABAA receptors, favoring the development of self-sustaining seizure activity [24]. In our first case, which is clearly a Bancaud type 1, seizures did not recur when Felbamate was stopped, consistent with that interpretation. Case # 2 did not show progression over many years, strongly arguing against the diagnosis of Rasmussen's encephalopathy, but Felbamate only transiently suppressed the seizures. However, when receptor internalization is maintained too long, receptors are transported to lysosomes and destroyed, instead of being recycled [25]. Since this patient was only treated after seizures had continued for several years, the significance of the recurrence of EPC when the drug was stopped is uncertain.

Pathophysiological implications: In experimental animals, self-sustaining status epilepticus (SSSE) is initiated by seizure-induced internalization of GABAA receptors [26], resulting in failure of GABAergic

inhibition. However, SSSE is maintained by a movement of NMDA receptors to the synapse, causing widespread potentiation of excitatory (especially NMDA) synapses, so that established SSSE becomes resistant to many agents with the partial exception of NMDA antagonists [17]. We speculate that a similar mechanism occurs in EPC, in which the focus would be characterized by long-term potentiation of glutamate receptors and desensitization of GABAA receptors, while GABAergic inhibition would be preserved in the surround. Blocking the excess number of NMDA receptors with felbamate or other NMDA antagonists might suppress seizures and restore physiological levels of receptor trafficking, allowing recovery when the damage is still reversible [27, 28].

References:

1-Kojewnikoff AY. Eine besondere Form von corticaler Epilepsie. Neurologie Zentralblatt. 1895; 14: 47-8.

2-Bancaud J, Bonis A, Talairach J, Bordas-ferrer M, Buser P. Syndrome de Kojewnikow et ecces somato-moteur (etude clinique EEG, EMG, et SEEG). Encephale. 1970; 59: 391-430.

3-Gastaut H. Les myoclonies. Rev Neurol. 1968; 119: 1-30.

4-Bancaud J, Bonis A, Trottier S, Talairach J, Dulac O. Epilepsie partielle continue: syndrome et maladie. Rev Neurol. 1982; 138: 802-14.

5-Shomer DL. Focal status epilepticus and epilepsia partialis continua in adults and children. Epilepsia. 1993; 34 Suppl 1: S29-36.

6-Echenne B, Rivier F, Roubertie A, Touzery A, Humbertclaude V. Successful Felbamate treatment of epilepsia partialis continua in a case of hemimegalencephaly. Epilepsia. 1997; 38 Suppl 3: 36.

7-Thomas JE, Reagan TJ, Klass DW. Epilepsia partialis continua. A review of 32 cases. Arch Neurol. 1977; 34 (5): 266-75.

8-Biraben A, Chauvel P, Epilepsia partialis continua. In: Engel J, Pedley TA, editors. Epilepsy: a comprehensive textbook. Lippincott-Raven Publishers; 1998. p. 2447-53.

9-Brandt L, Saveland H, Ljunggren B, Andersson KE. Control of epilepsy partialis continuans with intravenous nimodipine. Report of two cases. J Neurosurg. 1988; 69 (6): 949-50.

10-Walker M, Shorvon S. Treatment of status epilepticus and serial seizures. In: Shorvon S, et al. The treatment of epilepsia. Backwell Science Ltd; 1996. p. 280-2.

11-Rogers SW, Andrews PI, Gahring LC, Whisenand T, Cauley K, Crain B, Hughes TE, Heinemann SF, McNamara JO. Autoantibodies to glutamate receptor GluR3 in Rasmussen's encephalitis. Science. 1994; 265 (5172): 648-51.

12-Barontini F, Maurri S, Amantini A. "Epilepsia partialis continua" due to multifocal encephalitis: favourable outcome after immunoglobulin treatment. Ital J Neurol Sci. 1994; 15 (3): 157-61.

13-McLachlan RS, Levin S, Blume WT. Treatment of Rasmussen's syndrome with ganciclovir. Neurology. 1996; 47 (4): 925-8.

14-Molyneux PD, Barker RA, Thom M, van Paesschen W, Harkness WF, Duncan JS. Successful treatment of intractable epilepsia partialis continua with multiple subpial transections [letter]. J Neurol Neurosurg Psychiatry. 1998; 65 (1): 137-8.

15-Lamarche M, Chauvel P. Movement epilepsy in the monkey with an experimental motor focus. Electroencephalogr Clin Neurophysiol Suppl. 1978; (34): 323-8.

16-Chauvel P, Trottier S, Vignal JP, Bancaud J. Somatomotor seizures of frontal lobe origin. Adv Neurol. 1992; 185-232.

17-Mazarati AM, Wasterlain, CG N-methyl-D-asparate receptor antagonists abolish the maintenance phase of self-sustaining status epilepticus in rat. Neurosci Lett. 1999; 265: 187-90.

18-McCabe RT, Wasterlain CG, Kucharczyk N, Sofia RD, Vogel JR. Evidence for anticonvulsant and neuroprotectant action of felbamate mediated by strychnine-insensitive glycine receptors. J Pharmacol Exp Ther. 1993; 264: 1248-52.

19-Bettini, et al. Identification and characterization of novel NMDA receptor antagonists selective for NR2A- over NR2B-containing receptors. J Pharmacol Exp Ther. 2010; 335: 636-44.

20-Bialer M, Johannessen SI, Levy RH, Perucca E, Tomson T, White HS. Progress report on new antiepileptic drugs: a summary of the Tenth Eilat Conference (EILAT X). Epilepsy Res. 2010 Dec; 92 (2-3): 89-124.

21-Shin A, Kim H, Thayer S. Subtype selective NMDA receptor antagonists induce recovery of synapses lost following exposure to HIV-1 Tat. Br J Pharmacol. 2012 Jun; 166 (3):1002-17.

22-Wasterlain CG, Adams LM, Hattori H, Schwartz PH. Felbamate reduces hypoxic-ischemic brain damage in vivo. Eur J Pharmacol. 1992; 212: 275-8.

23- Wasterlain CG, Liu H, Mazarati AM, Baldwin RA, Shirasaka Y, Katsumori H, Thompson KW, Sankar R, Pereira de Vasconselos A, Nehlig A. Self-sustaining status epilepticus: a condition maintained by potentiation of glutamate receptors and by plastic changes in substance P and other peptide neuromodulators. Epilepsia. 2000; 41 Suppl 6: S134-43.

24-Chen JW, Wasterlain CG, Status Epilepticus: pathophysiology and management in adults. Lancet Neurol. 2006; 5: 246-56.

25-Arancibia-Cárcamo IL, Yuen EY, Muir J, Lumb MJ, Michels G, Saliba RS, Smart TG, Yan Z, Kittler JT, Moss SJ. Ubiquitin-dependent lysosomal targeting of GABA(A) receptors regulates neuronal inhibition. Proc Natl Acad Sci U S A. 2009 Oct 13; 106 (41): 17552-7.

26-Naylor DE, Liu H, Wasterlain C. Trafficking of GABA(A) receptors, loss of inhibition, and a mechanism for pharmacoresistance in status epilepticus, J Neurosci. 2005; 25: 7724-33.

27-Hughes JR, Fuller T. The use of felbamate in patients with periodic lateralized epileptiform discharges (PLEDs). Clin Electroencephalogr. 1995 Jul; 26 (3): 180-3.

28-Mazarati AM, Baldwin RA, Sofia RD, Wasterain C.G. Felbamate in experimental model of status epilepticus. Epilepsia; 2000, 41: 123-127.