Seizure 2001; **10**: 596–599
doi:10.1053/seiz.2001.0555, available online at http://www.idealibrary.com on IDEAL®

CASE REPORT

Anticonvulsants-induced chorea: a role for pharmacodynamic drug interaction?*

MEGDAD ZAATREH[†], MICHAEL TENNISON[†‡], O'NEILL D'CRUZ[†‡] & ROBERT L. BEACH[§]

Departments of [†]Neurology and [‡]Pediatric Neurology, University of North Carolina, Chapel Hill, North Carolina, USA; [§]Department of Neurology, Upstate Medical Center Syracuse, New York, USA

Correspondence to: Megdad Zaatreh, MD, Yale University, Department of Neurology, P.O. Box 208018, New Haven, CT 06520-8018, USA. *E-mail*: mmzid@med.unc.edu

Chorea is a rare side effect of anticonvulsants. We describe three patients who developed chorea secondary to anticonvulsant combination use. A mechanism to explain this finding is proposed.

After identification of an index case with anticonvulsant-induced chorea, we reviewed the electronic data base records for all patients with seizures followed in the epilepsy clinics at our university-based hospital for cases of dyskinesia associated with anticonvulsants. Two additional patients, one adult and one pediatric patient were identified.

Three patients developed chorea while receiving combination anticonvulsants. Two patients had transient chorea that resolved with withdrawal of one of the drugs. All three patients were using phenytoin and lamotrigine in combination when the chorea started, chorea improved with tapering one of the medications.

Polytherapy with certain anticonvulsants may predispose patients to drug-induced chorea. A particular increased risk was seen with combinations that have phenytoin and lamotrigine. This could be due to an additive or a synergistic effect on central dopaminergic pathways.

Key words: phenytoin; lamotrigine; anticonvulsant; chorea; dyskinesia.

INTRODUCTION

Dyskinesias induced by anticonvulsants are a reported side effect[1]. Most cases have been associated with phenytoin therapy, although carbamazepine[2], gabapentin[3–5], felbamate[6] and valproate[7] have also been implicated. Choreoathetosis, dystonia and orofacial dyskinesias have been described[1].

We report three patients who developed choreoathetoid movements on anticonvulsants. All those patients were using phenytoin and lamotrigine in combination as part of their anticonvulsant regimen when they developed chorea. No patient had these movements while on either phenytoin or lamotrigine monotherapy at normal, or toxic, concentrations.

PATIENTS AND METHOD

After identification of the index case (Patient one), the electronic database of epilepsy patients was queried to identify patients with epilepsy and movement disorders. All patients with the diagnosis of epilepsy or seizures seen in the adult and pediatric clinics between January 1992 and December 1998 were included. Searching included any patient with the diagnosis of epilepsy or seizures and any of the following: movement disorders, chorea, dyskinesia, and ballismus. A review of these patients found one adult and one pediatric patient who experienced choreoathetosis. Information about those patients, including history, physical examination and laboratory investigation were reviewed. These cases are presented and the implications of those findings are discussed.

RESULTS

Case 1

The first patient is a 46-year-old right-handed woman with intractable right temporal lobe complex partial seizures, beginning when she was 17 years old.

*Parts of this paper have been presented in a poster form in the American Neurological Association (ANA) meeting in Seattle, October 1999.

1059–1311/01/080596 + 04 $35.00/0

She had no generalized seizures. She had no other medical problems and her family history was negative for seizures or abnormal movements. She was treated with phenytoin, carbamazepine, primidone and valproic acid in various combinations. She used phenytoin (alone and in various combinations, including concomitant use with carbamazepine) for almost 15 years without any abnormal movements. Phenytoin was discontinued secondary to gingival hypertrophy and lamotrigine was started a few months later and maintained in combination with carbamazepine. At lamotrigine level of 14 μg ml^{-1} she experienced mild dizziness but no abnormal movements. Two years later she was evaluated for epilepsy surgery and she underwent right anterior temporal lobectomy.

Preoperatively she received her daily lamotrigine and carbamazepine doses. Postoperatively she was nauseated and lethargic and unable to take oral medications. Phenytoin was given intravenously as a loading dose of 1000 mg then as maintenance of 100 mg every 8 hours. On day 2 she continued to be lethargic, but her neurological examination was nonfocal. Computerized topography (CT) of the head showed expected postoperative changes. Her phenytoin level was 23 μg ml^{-1} with a free level of 1.9 μg ml^{-1}. On postoperative day three, she showed improvement and was able to take oral medications. Carbamazepine and lamotrigine were restarted at her preoperative doses. During postoperative day 4, phenytoin was discontinued, and she developed severe bilateral upper extremity choreoathetosis without facial dyskinesias. The total phenytoin level was 16 μg ml^{-1}, the lamotrigine level was 13 μg ml^{-1} and the carbamazepine level was 7.9 μg ml^{-1}. MRI of the brain showed expected postoperative changes, EEG showed no seizure activity. The next day she continued to experience moderately severe chorea in her hands and arms, which resolved 1 day later. She was discharged home on her regular doses of lamotrigine and carbamazepine with no further seizures or abnormal movements.

Case 2

The second patient is a 47-year-old right-handed woman with intractable right temporal lobe complex partial seizures that started at age 36. Past medical history included hypertension and a remote history of alcoholism. There was no history of seizures or abnormal movements in her immediate family including her four healthy children.

She was initially treated with phenytoin without adequate control. She had never experienced abnormal movements despite multiple documented phenytoin levels above the therapeutic range (maximum 27 μg ml^{-1}). Valproic acid was tried with partial improvement. Phenobarbital provided no benefit and she was unable to tolerate carbamazepine or felbamate. She was evaluated for possible epilepsy surgery but declined. Her lamotrigine was then added to her phenytoin. Two weeks later she complained of intermittent uncontrollable abnormal movements involving her hands both at rest and with activity. Her examination at that time showed normal coordination and no abnormal movements. Her phenytoin level was 21 μg ml^{-1} with a free level of 1.6 μg ml^{-1}. Lamotrigine level was 5.3 μg ml^{-1}. At her next visit, the patient and her husband again complained of abnormal movements involving her hands and arms. She noted difficulties with combing her hair, holding glasses and cups in her hands. Her examination was remarkable for frequent choreoathetoid movements of her arms, which were worse on her right side. The movements occurred at rest and with activity, she had no facial dyskinesia or tremors. Apart from her chorea her coordination and gait were normal.

Complete blood count, chemistry panel including liver functions, antistreptolysin O titer and antinuclear antibody testing were negative. EEG showed no seizure activity with the abnormal movements. The patient was slowly tapered off phenytoin and 1 week later she reported marked improvement in her movements and the disappearance of her functional limitations, which was confirmed by physical examination. She had no more chorea on lamotrigine monotherapy and in a combination of lamotrigine and topiramate for more than 2 years.

Case 3

A 3-year-old boy with Lennox–Gastaut syndrome was admitted to our hospital for treatment of recurrent minor motor seizures complicating a recent otitis media. He had an uncomplicated pregnancy, with normal development until the age of 10 months when he developed frequent tonic posturing of the neck during sleep. His symptoms rapidly evolved into a mixture of daily generalized tonic–clonic, atypical absence, tonic and atonic seizures and he experienced developmental and motor regression. There was no family history of seizures or abnormal movements. Therapy with phenytoin did not help, and no abnormal movements occurred. Phenobarbital and clonazepine were tried, without improvement. Lamotrigine replaced phenobarbital when he was 12 months old and his seizure control improved. Later, a ketogenic diet, vigabatrin, topiramate and felbamate were tried in various combinations with some improvement.

At this admission he was still having seizures on a combination of lamotrigine, clonazepam, felbamate

Table 1: Anticonvulsants used by the three patients with and without chorea.

Patient	Anticonvulsants (monotherapy or combinations) used without chorea	Anticonvulsant combination when chorea developed	Anticonvulsant removed after which chorea improved
One	PHT monotherapy PHT with CBZ PHT with VPA LTG with CBZ	PHT, CBZ and LTG	PHT
Two	PHT monotherapy PHT with PB PHT with VPA LTG monotherapy LTG and TPM	PHT with LTG	PHT
Three	PHT monotherapy PB monotherapy LTG monotherapy LTG with VGT LTG with FBM LTG, FBM, TPM	PHT, LTG, FBM and TPM	PHT

CBZ: carbamazepine; LTG: lamotrigine; VPA: valproic acid; PHT: phenytoin; TPM: topiramate; PB: phenobarbital; VGT: vigabatrin.

and a ketogenic diet. He was started on phenytoin, and discharged. Within a few weeks he developed generalized choreoathetoid movements, which increased with activity, and disappeared during sleep. Movements were prominent in his limbs, without orofacial involvement. MRI of the brain, muscle biopsy, amino and organic acid analyses were normal. EEG showed generalized slow spike and waves. Phenytoin level was 11 μg ml^{-1}, lamotrigine level was not obtained. On discontinuation of phenytoin there was significant improvement in his chorea.

DISCUSSION

Anticonvulsant-induced choreoathetosis was first reported in 1962 with phenytoin[8]. A literature search reveals about 80 cases. Reported patients are frequently young and have organic brain abnormalities including mental retardation[1,13]. More than one half of the cases have occurred in association with toxic drug levels[1,9,10]. The use of phenytoin with other medications was reported to an increase the risk of developing abnormal movements[1]. Pharmacokinetic interaction leading to increased free phenytoin level was suggested as a plausible explanation[1]. Both generalized and focal movements have been described[1,11]. Duration of dyskinesia has been variable, but has often responded to discontinuation of the anticonvulsants[1,12]. Dyskinesias have most commonly involved the limbs, but orofacial involvement has been noted in some cases[1,11]. Chorea as a result of lamotrigine therapy was noted as a rare side effect in trials (Lamotrigine package insert). Published reports are limited to an abstract describing new onset choreoathetosis in two young patients treated with lamotrigine[14]. Recently Tourette's syndrome was reported in three patients taking lamotrigine[15].

We describe three patients with new onset choreoathetosis that developed while receiving lamotrigine and phenytoin in combination therapy. The first patient developed transient chorea when her usual lamotrigine and carbamazepine, were supplemented with phenytoin, which was loaded intravenously shortly prior to chorea development. At the time chorea developed, her phenytoin levels were in the normal range (16 μg ml^{-1}). Chorea related to the phenytoin itself is unlikely, as she used it for 15 years before without evidence of abnormal movements despite higher levels. The combination of phenytoin and carbamazepine was also used prior to the surgery without any chorea (Table 1). Although intravenous loading of phenytoin may cause transient chorea[1], this is unlikely in this patient as with the initial load and at a higher phenytoin level (23 μg ml^{-1}) she did not have any chorea. On the combination of lamotrigine and carbamazepine pre- and postoperatively she had no abnormal movements. Prior to her surgery she never used lamotrigine and phenytoin in combination. Her chorea occurred with therapeutic drug levels of these three anticonvulsants, levels which were similar to or lower than previous levels which previously produced no chorea.

The second patient used phenytoin for several years, reaching supratherapeutic levels (up to 27 μg ml^{-1}) intermittently without developing abnormal movements. When lamotrigine was added, she quickly developed choreic hand and arm movements, which resolved with phenytoin withdrawal. Subsequent follow up for this patient showed no chorea on lamotrigine alone, or with a combination of lamotrigine and topiramate (Table 1). In this patient it is also reason-

able to conclude that neither lamotrigine nor phenytoin alone produced chorea, but the combination did.

The third patient experienced the onset of choreoathetosis on a combination of anticonvulsants which included phenytoin and lamotrigine, in addition to felbamate and topiramate. The abnormal movements started shortly after adding phenytoin and significantly improved when phenytoin was discontinued since this patient used phenytoin in monotherapy prior to this without any abnormal movements (Table 1). Chorea is most likely due to the combination therapy. This patient has similar risk factors to other children described with drug-induced chorea[4, 13, 14].

The mechanism by which these patients developed chorea is unknown. Pharmacokinetic interaction between anticonvulsants causing elevated high phenytoin levels is unlikely in our patients as lamotrigine is known not to elevate phenytoin levels[20]. In addition phenytoin levels were not elevated (Table 2).

Table 2: Phenytoin and lamotrigine blood levels (in μg ml^{-1}) when patients had chorea.

Patient	Phenytoin level	Lamotrigine level
One	16	13
Two	21 (free level 1.6)	5.3
Three	11	NA

The pathophysiology of anticonvulsant-induced dyskinesias in general is uncertain, although it has been postulated that phenytoin may cause chorea through enhancement of central dopaminergic pathways in the basal ganglia[1, 9]. Lamotrigine is known to inhibit glutamate release in the central nervous system[16, 17]. In a mouse model of Parkinson's disease, lamotrigine was found to increase basal ganglia dopamine activity leading to increased motor activity[19]. This finding was explained by postulating potentiation of the dopaminergic basal ganglia connections through inhibition of glutamatergic corticostriatal pathways. This mechanism could also explain the worsening of dyskinesia in two of 12 patients with idiopathic Parkinson's disease treated with lamotrigine[18]. Combined lamotrigine and phenytoin effects on central dopaminergic pathways might explain why our patients developed chorea when both anticonvulsants were present in combination. Neither direct enhancement of dopaminergic activity induced by phenytoin, or indirect enhancement by lamotrigine alone was sufficient to provoke abnormal movements. In combination, the effects of lamotrigine and phenytoin appear to be additive or synergistic, resulting in sufficient enhancement of dopaminergic activity to provoke clinically apparent choreoathetosis, this is rather a pharmacodynamic interaction between both anticonvulsants. Removal of one of the medications was sufficient to ameliorate or eliminate the clinical symptoms. These reported cases suggest that patients treated with a combination of lamotrigine and phenytoin may have an increased risk of developing dyskinetic movement disorders.

REFERENCES

1. Harrison, M. B., Lyons, G. R. and Landow, E. R. Phenytoin and dyskinesia: a report of two cases and review of the literature. *Movement Disorder* 1993; **8**: 19–27.
2. Schwartzman, M. J. and Leppik, I. E. Carbamazepine-induced dyskinesia and ophthalmoplegia. *Cleveland Clinic Journal of Medicine* 1990; **57**: 367–372.
3. Reeves, A. L., So, E. L., Sharbrough, F. W. and Krahan, L. E. Movement disorders associated with the use of gabapentin. *Epilepsia* 1996; **37**: 988–990.
4. Chudnow, R. S., Dewey, R. B. Jr and Lawson, C. R. Choreoathetosis as a side effect of gabapentin therapy in severely neurologically impaired patients. *Archives of Neurology* 1997; **54**: 910–912.
5. Buetefish, C. M., Gutierrez, A. and Gutmann, L. Choreoathetotic movements: a possible side effect of gabapentin. *Neurology* 1996; **64**: 851–852.
6. Keerick, J. M., Kelley, B. J, Maister, B. H., Graves, N. M. and Leppik, I. E. Involuntary movement disorders associated with felbamate. *Neurology* 1995; **45**: 185–187.
7. Lancman, M. E., Asconape, J. J. and Penry, J. K. Choreiform movements associated with the use of valproate. *Archives of Neurology* 1994; **51**: 702–704.
8. Peters, H. A. Anticonvulsant drug intolerance. *Neurology* 1962; **12**: 299.
9. Luhdorf, K. and Lund, M. Phenytoin-induced hyperkinesia. *Epilepsia* 1977; **18**: 409–415.
10. Chalhub, E. G. and De Vivo, D. C. Phenytoin-induced choreoathetosis. *Journal of Pediatrics* 1976; **89**: 153–165.
11. Shulman, L. M., Singer, C. and Weiner, W. J. Phenytoin-induced focal chorea. *Movement Disorder* 1976; **11**: 111–113.
12. Filloux, F. and Thompson, J. A. Transient chorea induced by Phenytoin. *Journal of Pediatrics* 1987; **110**: 639–641.
13. Koukkari, M. W., Vanefsky, M. A., Steinberg, G. K. and Hahn, J. S. Phenytoin-related chorea in children with deep hemispheric vascular malformations. *Journal of Child Neurology* 1996; **11**: 490–491.
14. Frost, M. D., Ritter, F. J., Hoskin, C., Mims, J. and Espo-Lillo, J. Movement disorder associated with lamotrigine treatment in children and adolescents (abstract). *Epilepsia* 1996; **37**: 112.
15. Lombroso, C. T. Lamotrigine-induced tourettism. *Neurology* 1999; **52**: 1191–1194.
16. Leach, M. J., Marden, C. M. and Miller, A. A. Pharmacological studies on lamotrigine, a novel potential antiepileptic drug: II. Neurochemical studies on the mechanism of action. *Epilepsia* 1986; **27**: 490–497.
17. Meldrum, B. S. Excitatory amino acid transmitters in epilepsy. *Epilepsia* 1991; **32**: S1–S3.
18. Shinotoh, H., Vingerhoets, F. J. G., Lee, C. S. *et al.* Lamotrigine trail in idiopathic Parkinsonism: a double-blind, placebo-controlled, crossover study. *Neurology* 1997; **48**: 1282–1285.
19. Starr, M. S., Starr, B. S. and Kaur, S. Stimulation of basal and L-DOPA-induced motor activity by glutamate antagonists in animal models of Parkinson's disease. *Neuroscience and Biobehavioural Review* 1997; **21**: 437–446.
20. Bottiger, Y., Svensson, J. O. and Stahle, L. Lamotrigine drug interactions in a TDM material. *Therapeutic Drug Monitoring* 1999; **21**: 171–174.