Seizure 2003; **12:** 319–322
doi:10.1016/S1059–1311(02)00293-5

CASE REPORT

Nonconvulsive status epilepticus due to a *de novo* contralateral focus during tiagabine adjunctive therapy

DANIELE IMPERIALE[†,¶], PIERO PIGNATTA[‡], PAOLO CERRATO[§], ELISA MONTALENTI[§], CARLO RAVETTI[¶] & PAOLO BENNA[§]

[†]*Neurologic Unit—Maria Vittoria Hospital;* [‡]*Neurologic Unit—Gradenigo Hospital;* [§]*Department of Neuroscience—Molinette Hospital;* [¶]*Neurologic Unit—San Giovanni Bosco Hospital, Torino, Italy*

Correspondence to: Daniele Imperiale, M.D., Neurologic Unit—Maria Vittoria Hospital Via Cibrario 72, 10144 Torino, Italy. *E-mail*: imperid@inwind.it

We describe a 30-year-old woman with an infantile-onset epilepsy due to a left temporal gliotic area who developed a nonconvulsive status epilepticus (NCSE) during tiagabine (TGB) adjunctive therapy. The ictal EEG recording showed a *de novo* right temporal focus not previously evident. After the i.v. administration of 4 mg lorazepam, the NCSE episode rapidly resolved and her usual left temporal EEG abnormalities reappeared. To our knowledge this is the first case of paradoxical seizure exacerbation associated with TGB therapy in which the clinical and EEG features are congruous with a new contralateral focus.

Key words: tiagabine; epilepsy; nonconvulsive status epilepticus; paradoxical effect.

INTRODUCTION

Paradoxical seizure exacerbation including status epilepticus (SE) has been reported for several antiepileptic drugs (AEDs)[1]. Tiagabine (TGB) is a γ-aminobutyric acid (GABA) reuptake inhibitor recently approved as adjunctive therapy for partial seizures with or without secondary generalisation. Nonconvulsive status epilepticus (NCSE) has been reported in patients taking TGB[2–11], but a recent review of safety data opined that TGB adjunctive therapy does not increase the risk of SE and NCSE[12]. We report a case of NCSE in a TGB-treated patient with an intractable epilepsy due to a perinatal gliotic area at the left temporo-parietal level. Notably, the clinical and EEG findings were indicative of a new focus in the contralateral homotopic region.

CASE REPORT

A 30-year-old mildly retarded woman with a right hemiparesis due to a perinatal left temporo-parietal gliotic area was referred to our Epilepsy Service in December 2000 because of a drug-resistant partial epilepsy. The patient suffered from frequent complex partial seizures (CPS) with rare secondary generalisation since late infancy. Many AEDs—carbamazepine, phenytoin, phenobarbital, sodium valproate, benzodiazepines, vigabatrin, lamotrigine, topiramate—had been employed with no satisfactory effect. Her CPS started with a stereotyped change of facial expression followed by staring and unresponsiveness. Thereafter, a tonic deviation of gaze and headturning toward the right occurred. Seizures lasted about 3 minutes with a subsequent confusional state of 10–20 minutes. No SE and NCSE episodes had ever been reported. Interictal EEGs were congruous with a left temporal focus (Fig. 1).

On presentation to our centre, the patient—weighing about 50 kg—was on topiramate 400 mg day^{-1}, carbamazepine 1200 mg day^{-1} and phenobarbital 100 mg day^{-1} but reported almost daily clusters of CPS with rare generalisations. TGB was gradually introduced with weekly increments of 5 mg day^{-1}. One week after TGB reached 45 mg day^{-1}, the patient appeared intermittently confused and was referred to our emergency department. On examination she

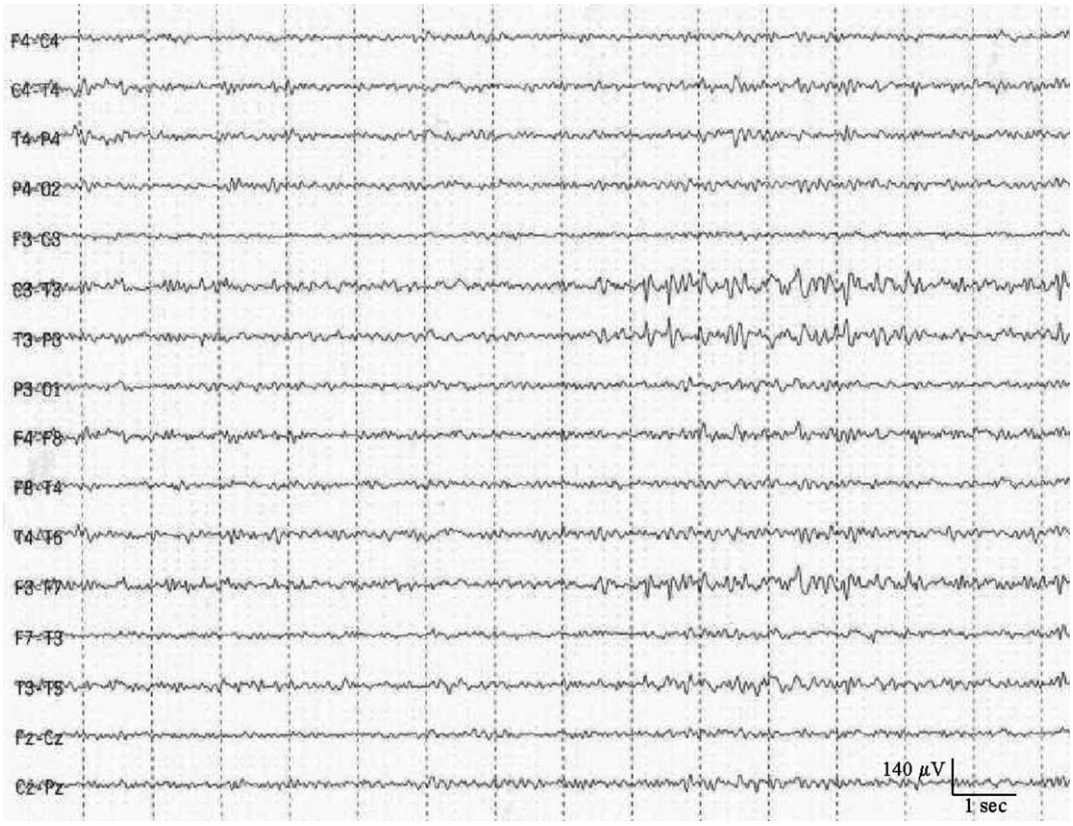

Fig. 1: EEG prior TGB therapy: short bursts of irregular spike-wave discharges at left temporal level.

Fig. 2: EEG during TGB-associated NCSE episode: diffuse slowing of background rhythm and frequent spike-wave discharges on right temporal derivations spreading to contralateral regions.

Fig. 3: EEG after 4 mg lorazepam i.v.: clear improvement of background activity with appearance of left temporal spike-wave discharges associated to rare contralateral sharp waves.

stared, reacted slowly and answered simple questions in a delayed fashion. Moreover, a *de novo* negative myoclonus involving the left arm was evident. Ictal EEG showed a diffuse slowing of background rhythm with frequent spike-wave discharges over right temporal derivations spreading to the contralateral regions (Fig. 2). After the i.v. administration of 4 mg lorazepam, the patient's mental status rapidly returned to normal and the left arm negative myoclonus ceased. EEG background improved and her usual left temporal focus reappeared in association with rare contralateral sharp waves (Fig. 3). A diagnosis of complex partial NCSE was made and TGB was stopped. No other seizures occurred during her stay on our ward and 1 week later the patient was discharged. The family refused any other change of therapy.

At the last follow-up visit in December 2001, her seizure frequency was unchanged but no new NCSE episode was reported.

DISCUSSION

Seizure exacerbation and induction of SE and NCSE have been reported for several AEDs[1]. TGB is a GABA reuptake inhibitor recently approved for the add-on therapy of intractable partial epilepsies. Common side effects (headache, somnolence, dizziness, generalised asthenia) are mild and usually related to rapid dose titration. Prolonged states of impaired consciousness have been described during TGB adjunctive therapy[2–11], but a recent review of safety data opined that TGB does not increase the risk of SE and NCSE[12].

We report a patient with a long-standing epilepsy who developed an NCSE after TGB introduction. Different from other reported cases[2,3,5,8,9,11], the diagnosis of NCSE in our patient was suggested not only by the ictal clinical and EEG findings but also by the prompt response to lorazepam. A link between TGB and NCSE in our patient can be assumed. Indeed, no new event, other than TGB introduction, was reported in the 3 months before that episode. SE and NCSE never occurred in her previous history. The progressive alteration in mental status appeared soon after the TGB dose reached 45 mg day^{-1} (about 0.9 mg kg^{-1} day^{-1}), similar to other patients receiving TGB with enzyme-inducing AEDs[2–6,8,10]. Finally, no other NCSE episode was reported after TGB was stopped and the previous therapy was reintroduced.

The paradoxical exacerbation of seizure activity including NCSE by TGB has been related to its unselective action on GABA-A and GABA-B receptors. GABA-B-specific agonists may determine a primary generalised NCSE in animals and humans[13], but the role of GABA-B receptors in the pathogenesis of complex partial NCSE (as in our patient) remains unclear.

Interestingly, our patient developed an NCSE episode due to a contralateral focus not previously evident. She complained of frequent stereotyped CPS and rare generalisations since late infancy. No previous ictal EEG was available but all her interictal recordings were indicative of a left temporal focus (Fig. 1), congruous with the perinatal temporo-parietal gliotic area. The NCSE episode during TGB treatment was completely different from her usual seizures and the ictal EEG showed a new contralateral focus (Fig. 2). AED induction of seizures related to a new contralateral focus has been reported in a CBZ-treated infant with tonic–clonic seizures and left interictal EEG abnormalities but never in adult cases[14]. The right-sided focus in our patient could already exist in the context of a multifocal epilepsy with extremely rare or absent clinical manifestations. The increase of GABA synaptic levels related to TGB therapy may have triggered that focus into an NCSE episode. A fascinating interpretation is that TGB adjunctive therapy may have unmasked a hypothetical 'mirror focus' related to the long-standing left-sided focus. The 'mirror focus' concept derives from the observation that an independent epileptic focus can develop in the contralateral homotopic area to which the primary focus sends direct synaptic projections and its formation is related directly to the duration of illness and inversely to the age of seizure onset[15].

The features of the NCSE and the BDZ effect in our patient suggest a proconvulsant action for TGB-mediated transmission through GABA-B sites. To our knowledge this is the first report of a TGB-associated NCSE whose ictal clinical and EEG findings are congruous with a *de novo* contralateral epileptic focus.

REFERENCES

1. Perucca, E., Gram, L., Avanzini, G. and Dulac, O. Antiepileptic drugs as a cause of worsening seizures. *Epilepsia* 1998; **39**: 5–17.
2. Schapel, G. and Chadwick, D. Tiagabine and non-convulsive status epilepticus. *Seizure* 1996; **5**: 153–156.
3. Eckardt, K. M. and Steinhoff, B. J. Nonconvulsive status epilepticus in two patients receiving tiagabine treatment. *Epilepsia* 1998; **39**: 671–674.
4. Trinka, E., Moroder, T., Nagler, M., Staffen, W., Loscher, W. and Ladurner, G. Clinical and EEG findings in complex partial status epilepticus with tiagabine. *Seizure* 1999; **8**: 41–44, doi 10.1053/seiz.1998.0223.
5. Ettinger, A. B., Bernal, O. G., Andriola, M. R. *et al.* Two cases of non-convulsive status epilepticus in association with tiagabine therapy. *Epilepsia* 1999; **40**: 1159–1162.
6. Holtkamp, M., Pfeiffer, M., Buchheim, K. and Meierkord, H. Tiagabine and non-convulsive status epilepticus. *Nervenarzt* 1999; **70**: 1104–1106.
7. Knake, S., Hamer, H. M., Schomburg, U. and Oertel, W. H. Tiagabine-induced absence status in idiopathic generalized epilepsy. *Seizure* 1999; **8**: 314–317, doi 10.1053/seiz.1999.0303.
8. Balslev, T., Uldall, P. and Buchholt, J. Provocation of non-convulsive status epilepticus by tiagabine in three adolescent patients. *European Journal of Paediatric Neurology* 2000; **4**: 169–170, doi 10.1053/ejpn.2000.0293.
9. Piccinelli, P., Borgatti, R., Perucca, E., Tofani, A., Donati, G. and Balottin, U. Frontal nonconvulsive status epilepticus associated with high-dose tiagabine therapy in a child with familial bilateral perisylvian polymicrogyria. *Epilepsia* 2000; **41**: 1485–1488.
10. Skodda, S., Kramer, I., Spittler, J. F. and Gehlen, W. Non-convulsive status epilepticus in two patients receiving tiagabine add-on treatment. *Journal of Neurology* 2001; **248**: 109–112.
11. Fitzek, S., Hegemann, S., Sauner, D., Bonsch, D. and Fitzek, C. Drug-induced nonconvulsive status epilepticus with low dose of tiagabine. *Epileptic Disorders* 2001; **3**: 147–150.
12. Shinnar, S., Berg, A. T., Treiman, D. M. *et al.* Status epilepticus and tiagabine therapy: review of safety data and epidemiologic comparisons. *Epilepsia* 2001; **42**: 372–379.
13. Solomon, G. E. and Labar, D. Hypothesis that tiagabine-induced NCSE is associated with GABAergic hyperfunction, with GABA(B) receptors playing a critical role, is supported by a case of generalized NCSE induced by baclofen. *Epilepsia* 1998; **39**: 1383.
14. Dhuna, A., Pascual-Leone, A. and Talwar, D. Exacerbation of partial seizures and onset of nonepileptic myoclonus with carbamazepine. *Epilepsia* 1991; **32**: 275–278.
15. Morrell, F. and deToledo-Morrell, L. From mirror focus to secondary epileptogenesis in man: an historical review. *Advances in Neurology* 1999; **81**: 11–23.