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Clinical study

Tiagabine-induced generalised non convulsive status epilepticus in patients with lesional focal epilepsy

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Summary *Purpose.* To report 3 cases with focal lesional epilepsy that had non-convulsive status epilepticus (NCSE) induced by treatment with tiagabine (TGB) and review the previously published cases. Drugs that enhance GABAnergic transmission are recognised to promote absence seizures in patients with generalised epilepsy syndromes and may on occasions even induce NCSE. However, that TGB can also induce NCSE in focal lesional epilepsy is not widely recognised in clinical practice. *Method.* The clinical history, EEG and MRI findings were reviewed in 3 patients with lesional focal epilepsy who presented to our epilepsy programs over a 12 month period with TGB-induced NCSE. All previously reported cases in the English medical literature were reviewed. *Results.* The three patients had longstanding complex partial and secondarily generalised seizures refractory to multiple different anti-epileptic drugs. In two cases, MRI demonstrated a focal malformation of cortical development in the left parieto-occipital region and in the third left mesial temporal sclerosis. Following commencement of TGB in one patient and dose escalation in two, prolonged episodes of confusion and poor responsiveness were noted. Prolonged EEG monitoring demonstrated continuous high amplitude, generalised, 2–4 Hz delta activity with intermingled spikes during the episodes of unresponsiveness, consistent with NCSE. The clinical and EEG activity normalised following the administration of IV clonazepam followed by dose reduction or withdrawal of the TGB. Eleven previously reported cases of patients with partial epilepsy and a focal underlying lesion on MRI were identified, all of whom had similar features to that seen in our cases. *Conclusions.* These cases illustrate that TGB may induce generalised NCSE in patients with focal lesional epilepsy, in addition to those with generalised syndromes. We hypothesise that patients may have developed an acquired alteration in the sensitivity of their thalamocortical circuitry that renders them more sensitive to the effects of drugs that enhance GABAnergic activity.

Keywords: non-convulsive status epilepticus, tiagabine, focal lesional epilepsy, seizure aggravation

INTRODUCTION

Drug-induced exacerbation of epileptic seizures is well described and has been reported to occur with most anti-epileptic drugs (AEDs).[1] The mechanisms underlying seizure aggravation by AEDs are poorly understood and the problem is often under recognised by clinicians, resulting in delay in removing the causative drug.[1,2] Seizure aggravation can occur either as a manifestation of drug toxicity, or as a specific drug effect at what is usually therapeutic drug doses and blood levels. Certain drugs have a particular propensity to exacerbate specific epilepsy syndromes. A well-documented example of this specific drug effect is with AEDs that increase gamma amino butyric acid (GABA) activity within the brain. This may result in aggravation of absence type seizures, including the induction of non convulsive status epilepticus (NCSE), in patients with other generalised epilepsy syndromes.[1]

Tiagabine acts via inhibition of neuronal and glial reuptake of GABA, thereby increasing brain GABA levels and overall neuronal inhibition. Tiagabine has been documented to induce NCSE in patients with generalised epilepsy syndromes, presumed due to an excess of GABA mediated hyperpolarisation of thalamic relay neurones resulting in enhancement of oscillatory thalamocortical activity.[3–5] It is not recommended for the treatment of generalised epilepsies, but is considered an effective and safe treatment for patients with focal epilepsy.[6] Here, we report a series of three patients encountered in our Epilepsy Programs over a 12 month period with well defined focal lesional epilepsy, who presented with NCSE secondary to tiagabine therapy. In addition, we have reviewed all previous cases reported in the English medical literature of documented tiagabine-induced NCSE occurring in patients with lesional focal epilepsy.

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METHODS

Identification of cases

Three patients with partial epilepsy with a focal underlying lesion on MRI were admitted over a 12-month period for inpatient video-EEG monitoring for investigation of confusion. All three were found to have NCSE related to the recent increase in dose of tiagabine, which resolved with the cessation or reduction in dose of tiagabine.

Literature review

An extensive search of the medical literature was performed using Medline from 1966 to 2003. The key words used for the search were tiagabine, NCSE and seizure aggravation. Six articles were identified reporting 11 patients with partial epilepsy, with a focal lesion on neuroimaging, who had induction of NCSE following the introduction or increase in dose of tiagabine.[5,7–11]

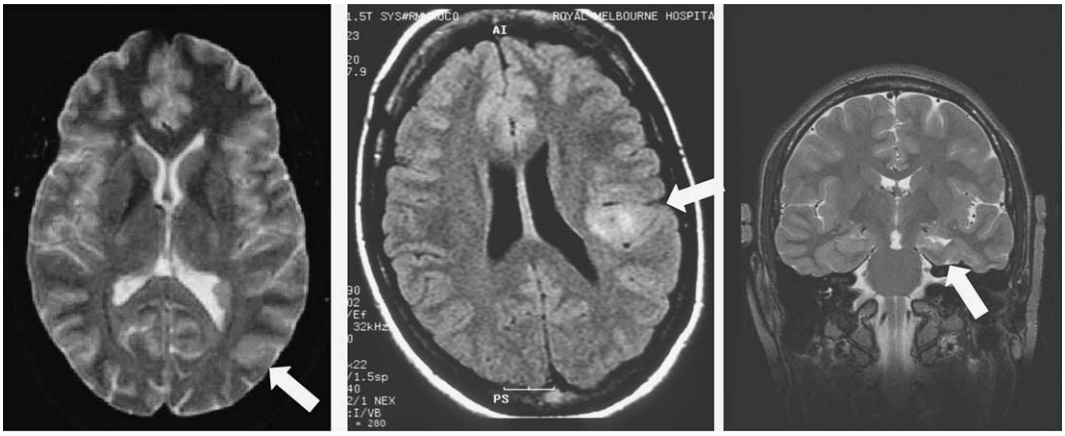

Fig. 1 MRI images from the three cases: (A) demonstrated a region of focal malformation of cortical development in the left parietal and posterior temporal region (case 1); (B) demonstrated a focal malformation of cortical development in the left frontal operculum (case 2); (C) demonstrated changes consistent with left mesial temporal sclerosis (case 3).

RESULTS

Case one

A 39-year old woman diagnosed with epilepsy since age four presented with complex partial seizures (CPS) and generalised tonic-clonic seizures (GTCS) occurring at least weekly despite trials of multiple different anticonvulsant medications. Her MRI revealed a focal malformation of cortical development, with a closed lip schizencephaly and polymicrogyria in the left parietal and posterior temporal region (Fig. 1(A)). Interictal EEG recordings had demonstrated epileptiform spikes in the left parietotemporal region. Tiagabine 10 mg daily was commenced as monotherapy and gradually increased to 30 mg daily. Two weeks later she was admitted to hospital with confusion, poor responsiveness and intermittent myoclonic jerks.

EEG recording revealed continuous generalised high amplitude 2–4 Hz delta activity with intermingled spike and wave activity (Fig. 2). A diagnosis of NCSE was made and 1 mg of intravenous clonazepam administered. This resulted in immediate normalisation of her EEG and complete resolution of the confusion. The tiagabine was ceased and she was commenced on sodium valproate and lamotrigine in combination. No further episodes of NCSE have occurred.

Case two

A 29-year-old woman with epilepsy since three months age presented with poor seizure control having failed multiple anticonvulsant medications. Her MRI revealed focal cortical dysplasia in the left frontal operculum (Fig. 1(B)). Interictal EEG demonstrated focal epileptiform spikes in the left anterior temporal region. Seizures were predominantly CPS with secondary generalisation and were occurring three times per week despite various combinations of AEDs. She was commenced on 10 mg tiagabine as an adjunct to carbamazepine and lamotrigine. At a dose of 30 mg daily there was no improvement in seizure control and the dose was then escalated to 60 mg daily. Following this she was admitted to hospital with frequent periods of confusion and unresponsiveness lasting hours in duration.

EEG recording during a 4 h period of unresponsiveness revealed continuous generalised high amplitude 2–4 Hz delta activity with intermingled spike and wave activity, (Fig. 3) consistent with a diagnosis of NCSE. She was treated with intravenous clonazepam and her clinical state and EEG rapidly improved. The tiagabine dose was reduced to 30 mg daily and she has had no further episodes of NCSE.

Case three

A 16-year-old girl with long standing CPS presented with frequent secondary generalisation. She had a past history of mycoplasma pneumoniae encephalitis at age 11 with subsequent development of left mesial temporal sclerosis (MTS) on MRI (Fig. 1(C)). Interictal EEG demonstrated focal epileptiform spikes in the left temporal region. Multiple different AEDs had been trialed without achieving satisfactory seizure control. Tiagabine was introduced in addition to her baseline topiramate and the dose gradually escalated to 30 mg daily. The topiramate was gradually weaned. She continued to have occasional CPS and the tiagabine dose was increased to 40 mg daily. Within a few days she was admitted to hospital with bouts of confusion lasting up to several hours.

Ambulatory EEG monitoring revealed generalised spike and slow wave activity during the episodes of confusion with normalisation during periods of clinical normality. A diagnosis of intermittent NCSE was made and she was treated with intravenous clonazepam and a reduction of her tiagabine dose to 30 mg daily. The episodes of confusion completely resolved and the EEG pattern normalised (Fig. 4).

A trial of an increased dose of tiagabine was again associated with recurrence of the NCSE. This recurrence resolved with reduction of the dose. Clobazam was added to tiagabine and there has been no further recurrence of the NCSE.

Literature review

The demographic and clinical details of three patients and those of the 11 previously reported cases are summarised in Table 1. The patients reported are all aged under 40, the youngest patient documented aged only 4 years.[10] All have well documented focal epilepsy and a variety of corresponding lesions on brain imaging. None of the patients had generalised epileptic activity on the routine interictal EEG to suggest a generalised epilepsy syndrome. Many of the patients had a history of refractory focal seizures with frequent secondary generalisation, for which tiagabine was instituted.[7,9,10] The doses at which NCSE was induced was variable, but all patients had tiagabine administered in the therapeutic range (25–60 mg daily). The presence of concomitant AEDs was