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A randomised open-label study of tiagabine given two or three times daily in refractory epilepsy

S. Arroyo[a], B.R. Boothman[b], M.J. Brodie[c], J.S. Duncan[d], R. Duncan[e], M. Nieto[f], E. Pita Calandre[g], I. Forcadas[h], P.M. Crawford[i,*]

[a]*Hospital Clinico de Barcelona, Servicio de Neurologia, C/Villarroel 170, 08036 Barcelona, Spain*
[b]*Preston Acute Hospital, NHS Trust, Fulwood, Preston PR2 9HT, UK*
[c]*Epilepsy Research Unit, University Department of Medicine, Western Infirmary, Glasgow G11 6NT, UK*
[d]*Chalfont Centre of Epilepsy, Chalfont St. Peter, Gerrards Cross, Bucks SL9 0RJ, UK*
[e]*Institute of Neurological Sciences, Southern General Hospital, Glasgow G51 4TF, UK*
[f]*Hospital Virgen del Rocio, Consultas Externas de Neuropediatria, Avda Manuel Siurot, s/n 41013 Sevilla, Spain*
[g]*Facultad de Medicina, Catedra de Farmacologia, Avda Madrid, 18012 Granada, Spain*
[h]*Hospital de Cruces, Department de Neurologia, Pl. de Cruces, s/n 48903 Baracaldo, Vizcaya, Spain*
[i]*York District Hospital, Department of Neuroscience, Wigginton Road, York YO31 7HE, N. Yorkshire, UK*

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Summary Efficacy and tolerability of tiagabine was evaluated in patients with non-controlled partial seizures in a multicentre, open-label, parallel group study. Tiagabine was administered either two (b.i.d.) or three times daily (t.i.d.) as adjunctive therapy and titrated stepwise to a target of 40 mg/day during a 12-week, fixed-schedule titration period; this was followed by a 12-week flexible continuation period. The primary efficacy endpoint was the proportion of patients completing the fixed-schedule titration period. A total of 243 patients were randomised and received treatment, 123 to b.i.d. and 120 to t.i.d. dosing. Fewer patients in the b.i.d. (76 and 62%) than in the t.i.d. (87 and 72%) group completed the fixed-schedule titration period (OR: 0.562; 95% CI: 0.309–1.008; $P = 0.0532$). The median percentage decrease in all types of seizure (excluding status epilepticus) during the fixed schedule titration period was 33.4% for the b.i.d. and 23.8% for the t.i.d. groups ($P = 0.9634$; Van Elteren's test). The proportion of responders was similar for the b.i.d. and t.i.d. groups. There were no significant differences between dosage regimens in the change in median seizure rates from baseline. Adverse events were more frequent during the titration than the continuation period. Most events were mild and related to the central nervous system. Although their incidence was similar between treatment groups, severity was more frequent in the b.i.d. group. Our results suggest that during titration tiagabine is better tolerated with t.i.d. dosing,

* Corresponding author. Tel.: +44 1904 725754; fax: +44 1904 726374.
E-mail address: pcrawford@doctors.org.uk (P.M. Crawford).

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but during long-term maintenance, a t.i.d. schedule is as effective and well tolerated as b.i.d.

Introduction

Tiagabine inhibits seizures by increasing the synaptosomal concentrations of the inhibitory neurotransmitter γ-aminobutyric acid (GABA). After rapid absorption following oral administration, the drug undergoes extensive metabolism in the liver.[1] Its half-life is 7—9 h in non-enzyme induced patients and about 3 h in induced patients. Thus, frequent daily dosing has been advocated. Several randomised, double-blind trials have shown that three times daily (t.i.d.) dosing is adequate for use and this dosing has been recommended in the tiagabine label.[2] However, broad clinical experience has suggested that a two times daily (b.i.d.) tiagabine regimen may also be effective and well tolerated. This study represents a prospective assessment of the efficacy and tolerability of two tiagabine dosing regimens (b.i.d. and t.i.d.) in patients with epilepsy from 31 centres in the UK and Spain.

Methods

Patients

Male and female patients aged ≥12 years who were diagnosed with partial seizures, with or without secondary generalisation, at least 6 months prior to study entry were enrolled. Additional criteria included at least four partial seizures during an 8-week period before study start. Patients gave written informed consent to participate and the study was approved under local ethics legislation and in accordance with GCP and the Declaration of Helsinki.

Design

This open-label, randomised, parallel-group study involved 31 centres in the UK and Spain and comprised an initial 12-week fixed schedule titration period of add-on tiagabine, followed by a 12-week, open-continuation period.

Eligible patients were randomised to receive tiagabine either b.i.d. or t.i.d., titrated after the first dose of 10 mg/day, in increments, to a target daily dose of 40 mg/day within 6 weeks (Fig. 1). If a dose increase step was not tolerated, patients were maintained on the highest tolerated dose level at that dosing frequency. The dose could be altered by the investigator within the range 30—70 mg/day during the flexible continuation phase.

Statistical analysis

The primary endpoint was the proportion of patients completing the fixed-schedule titration period (intent-to-treat (ITT) population) and results are presented as odds ratios (OR) with associated confidence intervals (CI) [an $OR > 1$ means more patients completing in the BID group]. A secondary variable, the median percentage change in seizure rate (per 28 days) from baseline to 12 weeks in the 'patients with seizure data' population (an ITT subset that provided seizure data for the fixed-schedule titration period), was assessed using Van Elteren's method.[3] The number of responders with ≥50% reduction in seizures was analysed by Fisher's Exact Test. All statistical tests were two-sided with a significance level of 0.05.

Results

Patient disposition

The ITT population comprised 243 patients receiving tiagabine (123 b.i.d., 120 t.i.d.). Of these, 80 had incomplete seizure data for the duration of the fixed-schedule titration period. Thus, 163 patients comprised the 'patients with seizure data' subset (76 b.i.d., 87 t.i.d.). The treatment groups were well matched for baseline characteristics. The most frequent type of seizure was complex partial (102/123 b.i.d., 101/120 t.i.d.).

Efficacy

Fewer patients in the b.i.d. group than in the t.i.d. group completed the fixed-schedule titration period, 76 (61.8%) and 87 (72.5%), respectively (OR: 0.562; 95% CI: 0.309, 1.008; $P = 0.0532$).

The median percentage decrease in the rate of all types of seizure (excluding status epilepticus) during the 12-week fixed-schedule titration period ('patients with seizure data' population) was 33.4% for the b.i.d. and 23.8% for the t.i.d. groups ($P = 0.9634$ for Van Elteren's test).

The proportion of responders was similar for b.i.d. and t.i.d. groups in both the fixed-schedule titration and continuation phases (Fig. 2).

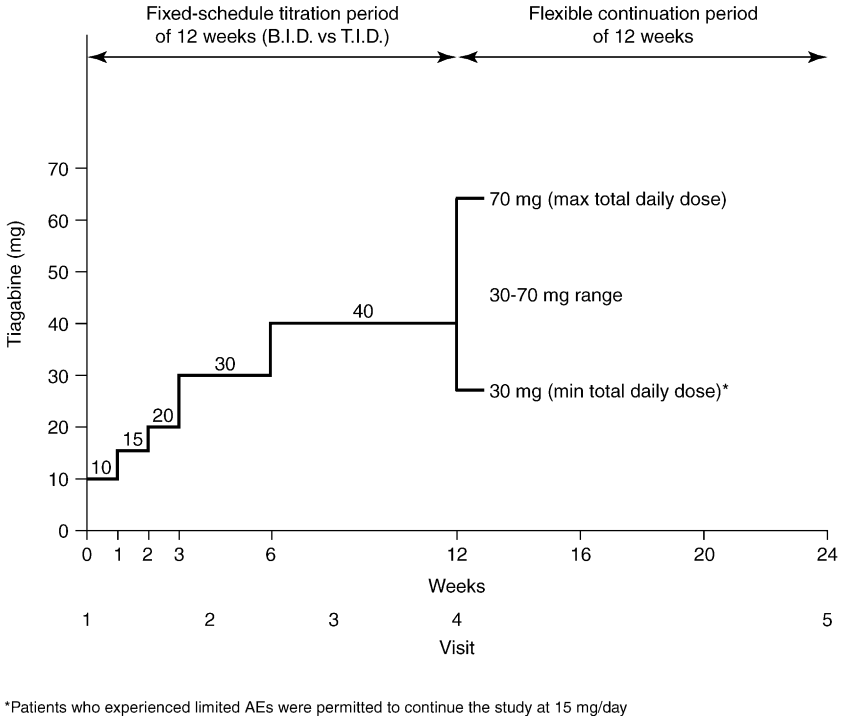

Figure 1 Study dosing schedule.

Safety

A comparable number of patients reported at least one AE during the fixed schedule titration period in each group (102 b.i.d., 94 t.i.d.). The corresponding numbers in the continuation phase for b.i.d. and t.i.d. groups were 31 and 36, respectively. The occurrence of AEs during the titration (Table 1) and continuation periods (not shown) was mostly balanced between the treatment groups and most AEs were related to the central nervous system (CNS). There were nine serious adverse events possibly or probably related to tiagabine in the b.i.d. group and two in the t.i.d. group. All except one occurred during the fixed schedule phase. No clinically significant changes in clinical chemistry, haematology values or vital signs were observed during the study.

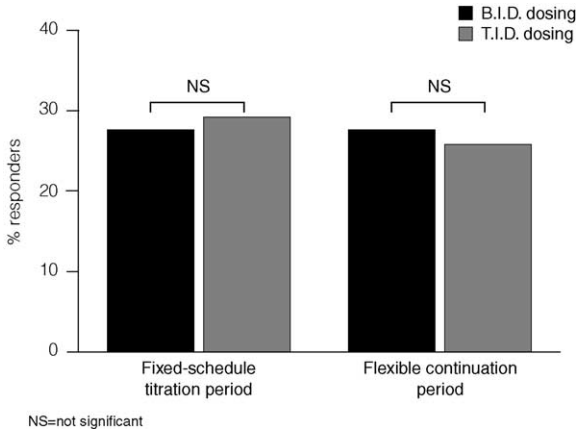

Figure 2 Percentage of responders in all seizure types in the ITT population during the final 4 weeks of the fixed titration period and during the last 8 weeks of the flexible continuation phase.

Table 1 Frequently occurring (≥5% incidence) treatment-emergent adverse events that started in the fixed-schedule titration period.

Adverse event	Patients dosed with tiagabine b.i.d. *n* (%)	Patients dosed with tiagabine t.i.d. *n* (%)
Total patients	123	120
Dizziness	38 (31)	27 (23)
Somnolence	21 (17)	24 (20)
Headache	27 (22)	14 (12)
Tremor	14 (11)	16 (13)
Asthenia	10 (8)	15 (13)
Ataxia	13 (11)	11 (9)
Confusion	10 (8)	10 (8)
Nausea	12 (10)	4 (3)
Pharyngitis	6 (5)	10 (8)
Infection	7 (6)	6 (5)
Depression	8 (7)	2 (2)
Myoclonus	8 (7)	1 (1)
Amblyopia	6 (5)	2 (2)
Amnesia	2 (2)	6 (5)

Discussion

Administering tiagabine b.i.d. provides a similar level of efficacy to t.i.d. dosing, without markedly affecting the proportion of patients tolerating the drug during the fixed-schedule titration period. The proportion of responders in both treatment groups during the fixed schedule titration and flexible continuation phases was similar. Our results support those of a previously published comparison of tiagabine regimens.[4]

There were limited differences between the treatment regimens in terms of safety findings and tolerability. Central nervous system related events such as dizziness and headache were the most reported symptoms in both dosing groups and were predominantly of mild intensity. The presence of a higher number of adverse events during the fixed-schedule titration period and more frequent severe adverse events with b.i.d. dosing during this period suggest that during titration t.i.d. is better tolerated. However, our results also suggest that patients with partial seizures who were previously maintained on a t.i.d. tiagabine dosing schedule may benefit from the use of a more convenient b.i.d. regimen.

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