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Retention rate of Clobazam, Topiramate and Lamotrigine in children with intractable epilepsies at 1 year

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ABSTRACT

Clobazam (CLB), Topiramate (TOP) and Lamotrigine (LAM) are newer second-line antiepileptic drugs (AEDs) used in children. This is a single-centre retrospective observational study of the efficacy, tolerability and retention rate in 224 separate treatment episodes in 194 children, aged 0.1–16.7 years (median 9.4) over an 8 year period. The median age of epilepsy onset was 3.3 years (range 0–15.1). 79% started CLB, TOP or LAM as at least the 3rd AED, with 39% having been withdrawn from at least 2 AEDs. 53% had generalised and 37% idiopathic epilepsies. The maintenance doses for CLB ranged 0.12–3.50 mg/kg/day (mean 0.7); for TOP 0.45–32.0 mg/kg/day (mean 7.1) and for LAM 1.13–16.0 mg/kg/day (mean 5.6). The study comprised 75 person-treatment years for CLB, 56 for TOP, 124 for LAM.

Results: CLB, TOP and LAM were well tolerated with 51%, 37% and 69% remaining on treatment beyond 1 year respectfully. 1 serious adverse event for CLB (inducing seizures) and 2 for LAM (rashes) were reported, and 60%, 47% and 39% had possibly and probably related adverse events for CLB, TOP and LAM respectively. Beyond 12 months seizure improvement (<50% seizure frequency compared to baseline) was reported in 43%, 35% and 44% on CLB, TOP and LAM, including 5% and 8% remaining seizure free on CLB and LAM respectively.

Conclusion: Our results demonstrate the efficacy and tolerability of CLB, TOP and LAM in children with difficult to treat epilepsies and a good response in CLB and LAM, and a reasonable response in TOP beyond 12 months.

1. Introduction

About 30% of children and young people with epilepsies do not respond to the first two appropriate antiepileptic drugs (AEDs), and can be considered to have "intractable" or "difficult to treat" epilepsies.[1,2] Clobazam (CLB), Topiramate (TOP) and Lamotrigine (LAM) are antiepileptic drugs with different pharmacological actions, with proven efficacy in treating generalised and partial seizures.[3,4] However, there are few studies of these drugs in children.[5] CLB is marketed for use in children over 3 years, whilst TOP and LAM are both marketed for children over 2 years with difficult to treat epilepsies. This study reports on the use of CLB, TOP and LAM in 224 separate treatment episodes in 194 paediatric patients with difficult to treat epilepsies over an 8 year period.

2. Methods

Children under 18 years of age starting treatment with CLB, TOP or LAM from September 2000 to April 2008 were ascertained retrospectively from hospital pharmacy and paediatric neurology databases in a tertiary referral paediatric neurology department. CLB, TOP and LAM were prescribed as "adjunctive therapy" for controlling difficult to treat focal or generalised epilepsies by two Consultant paediatric neurologists.

A retrospective chart review using a standard pro forma to capture demographic data, aetiology, epilepsy syndrome, seizure frequency, medication dosage, concomitant AEDs, efficacy and adverse events was recorded at more than 2, 6 and 12 months from starting that AED. Efficacy data was analysed using SPSS 18.0 on an intention to treat basis. As this was not a prospective trial with allocation of treatments, but an observational study of recent local practice, the "intention to treat" analysis of perceived efficacy used the complete data set including all patients who had started the AED, including those in whom it had been withdrawn. A few patients were omitted from the perceived efficacy analyses at some time windows if they had not been withdrawn but were not observed during that time window.

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Statistical tests included simple mean, median and range, ANOVA for difference in age of starting an AED, Chi-Squared for differences in aetiology and seizure type, and Kaplan–Meier survival plot for time on the AED. This was an observational non-intervention study, registered as a clinical audit by the Nottingham University Hospital's NHS Trust.

3. Results

224 treatment episodes in 194 children (52% female) were ascertained. 73 treatment episodes for CLB, 60 for TOP, and 91 for LAM. 29 patients had been on of two of the AEDs and 1 patient on CLB, TOP and LAM during the study period. There were no differences in their use with respect to gender.

Patients starting each drug had similar age ranges: 0.5–16.7 years (median 7.6) for CLB; 0.3–16.2 years (median 9.9) for TOP; and 1.1–16.2 years (median 10.6) for LAM. However, the age of starting CLB was younger compared to LAM following ANOVA statistical analysis, with Bonferroni correction applied to account for Type 1 error ($p = 0.015$, 95% CI [−3.91 to −0.32 years]). There was no difference in mean age of starting TOP, compared to LAM and CLB.

The population had mostly early onset of seizures, with a median age of onset of 3 years 3 months (range 0–15 years). CLB, TOP and LAM were used in epilepsies with a variety of aetiologies and locations of epileptic seizure origin and spread. TOP and LAM were used slightly more in idiopathic than symptomatic epilepsies, whilst CLB was used slightly more in symptomatic epilepsies. However these differences were not statistically significant. CLB and TOP were used in similar numbers for generalised and focal epilepsies, with LAM being used slightly more in generalised epilepsies, however this trend was also not statistically significant. 37% of cases had idiopathic, and 53% generalised epilepsies.

Brain imaging (MRI) and electroencephalography (EEG) results were retrieved in 88% and 70% of cases respectfully. In those patients whose MRI reports were available, MRI was abnormal in 52% (29/56) of patients on CLB; 50% (18/36) of patients on TOP; and in 31% (20/64) of patients on LAM. Of EEG reports available, 75% (54/72) were abnormal for patients on CLB, 65% (39/60) for patients on TOP and 77% (51/66) for patients on LAM.

The intractable nature of this study population's epilepsies is demonstrated by the number of previously withdrawn (Table 1) and concomitant AEDs (Table 2).

No patients were on CLB as a first line treatment, 6/73 had either 1 previously withdrawn or 1 concomitant AED, with 67/73 receiving CLB as the 3rd to 10th choice of AED. No patients were on TOP as the 1st choice of treatment, with 10/60 on TOP having either 1 previously withdrawn or 1 concomitant AED, with 50/60 receiving TOP as the 3rd to 6th choice of AED. 4/91 patients had received LAM as the 1st choice, 26/91 patients on LAM had either 1 previously withdrawn or 1 concomitant AED, and 61/91 were receiving LAM as the 3rd to 6th choice of AED.

Table 1
Number of AEDs previously withdrawn.

Drug	Number of AEDs withdrawn	%
CLB	0–1	50
	2–4	39
	>4	11
TOP	0–1	47
	2–4	49
	>4	4
LAM	0–1	80
	2–4	18
	>4	2

Table 2
Number of AEDs concomitantly prescribed.

Drug	Number of concomitant drugs	%
CLB	0–1	47
	2–4	50
	>4	3
TOP	0–1	53
	2–4	47
	>4	0
LAM	0–1	56
	2–4	44
	>4	0

This study comprised 74.5 person-treatment-years for CLB; 56.1 for TOP; and 124.4 for LAM. Mean maximum dosage was 0.7 mg/kg/day (range 0.12–3.50) for CLB; 7.1 mg/kg/day (range 0.45–32.0) for TOP; and 5.6 mg/kg/day (range 1.13–16.0) for LAM.

2 patients on CLB; 3 on TOP; and 1 on LAM achieved monotherapy. Of these patients, 1 on each of CLB, TOP and LAM had Idiopathic Generalised Epilepsies, 1 patient on CLB had Symptomatic Focal Epilepsy, and 2 on TOP had Symptomatic Generalised Epilepsies. Both CLB patients and the patient on LAM had a considerable improvement in seizure frequency by the last follow up. 2 of the 3 patients on TOP had a significant improvement with the other 1 demonstrating a lack of efficacy by the last follow up. The majority of these patients had at least 2 previous AEDs (range 0–4).

Possibly and probably related adverse events were reported in 60% on CLB; 47% on TOP; and 39% on LAM. The most frequent adverse events involved excessive sleepiness with 27% of all CLB patients reporting this, behavioural problems and excessive weight loss on TOP with 15% and 12% respectively reporting these. Sleeping problems (difficulties getting to sleep) followed by rash were the most common complaints with 12% and 10% of LAM patients respectively reporting these. Table 3 shows the different reported adverse events for each AED.

Most adverse events appeared within the first 3 months of treatment. The adverse events seen were often at the lower-end of the recommended dosage ranges. Whilst most adverse events were mild and predictable from the pharmacology, 1 serious CLB and 2 serious LAM reactions occurred, resulting in hospitalisation. The chart note suggested that CLB had induced an increase in seizures. The 2 LAM patients that had severe rashes that resulted in hospitalisation were on 0.8 mg/kg/day and 1.5 mg/kg/day. No fatalities occurred as a result of treatment. Most adverse events resolved without requiring withdrawal of medication, however 8/73 (11%) on CLB; 9/60 (15%) on TOP; and 11/91 (12%) LAM patients were withdrawn from their medication as a consequence of adverse reactions.

31/73 (42%) children withdrew from CLB: 8 because of adverse events, 19 lack of efficacy, 1 poor concordance (adherence), and 3 being seizure free. 29/60 (48%) were withdrawn from TOP: 9 because of adverse events, and 20 due to lack of efficacy. 35/91 (38%) were withdrawn from LAM: 11 because of adverse events, 19

Table 3
Adverse effects associated with each AED.

Drug	None reported	Behavioural problems	Sleeping problems	Rash	Others[a]
CLB ($n = 73$)	22 (30)	13 (18)	20 (27)	0	18 (25)
TOP ($n = 60$)	28 (47)	9 (15)	3 (5)	0	20 (33)
LAM ($n = 91$)	48 (53)	8 (9)	11 (12)	9 (10)	15 (16)

CLB = Clobazam, TOP = Topiramate, LAM = Lamotrigine. Percentages in brackets.
[a] Others: speech problems, incoordination of movements, weight gain, weight/appetite loss, vomiting/headache/dizziness, developmental problems, worsening seizures, concordance problems.