COCHRANE COMMENTARIES

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Balancing risks and benefits still the key to anti-epileptic prescribing for benign epilepsy with centro temporal spikes

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Cochrane: Tan HJ et al. Comparison of antiepileptic drugs, no treatment or placebo for children with benign epilepsy with centro temporal spikes.
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What is this review about?

What is the best treatment for children with Benign Epilepsy with Centro Temporal Spikes (BECTS), also known as Benign Rolandic Epilepsy? What are the effects of treatment on cognition? What are the adverse effects of treatment?

What are the findings?

- A higher proportion of children taking sulthiame (Ospolot®) (90%) were seizure free in the short term (up to six months) compared to placebo (40%). No other anti-epileptic drug (AED) was compared to placebo.
- It is not clear which AED is the best treatment. There were no difference between seizure free outcomes for three different comparisons (levetiracetam v oxcarbazepine; topiramate v carbamazepine; clobazam v carbamazepine) with outcomes measured at up to 12 months of medication.
- The effects of seizure control and AEDs on cognition in children with BECTS are unclear.
- When AEDs were compared the main adverse event was rash from carbamazepine (14.8%) compared with topiramate (1.7%).

What are the findings based on?

Four trials of children aged 3-15 years (N=262). All children had more than one known seizure and some studies required frequent seizures or daytime seizures or parental anxiety/parental choice to consider AEDs for inclusion. Studies differed with respect to

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design, AEDs and outcome measures (Table 1). The only trial with low risk of bias compared sulthiame to placebo [2]. Additional data extraction and analysis conducted by the systematic review authors found that children on sulthiame were more likely to be seizure free at three to six months. However, the sample size of this study was small and thus the “effect estimate” may be inaccurate.

The three other studies, with comparisons made as listed above, all had a high risk of bias. Furthermore, the relative estimates for seizure freedom were imprecise, due to the small sample size of each trial and there were also differences in duration of follow-up. Only two studies included cognitive outcomes but these had minimal clinically noticeable effects (See Table 1). Low numbers prohibit interpretation of adverse event data.

Implications for practice

Due to insufficient evidence, the routine use of AEDs for children with typical BECTS is not recommended. There is evidence from a single trial that the short-term use of low dose sulthiame increased the proportion of children who were seizure free but with a non-statistically significant trend to a higher proportion of children experiencing adverse events. If AEDs are considered, then clinicians should be cautious of the adverse effect of rash with carbamazepine.

Clinical perspective

BECTS is one of the most common childhood seizure disorders and is the best known of the Benign Focal Epilepsies of Childhood. Seizure onset is between the ages of four and ten years with the majority of patients growing out of their epilepsy by age 12 years (92%) and 99.8% seizure free by 18 years[3], with or without AED treatment. Seizures are usually brief nocturnal or early morning events, all of focal origin, but may become generalized secondarily[4]. Seizure frequency is low: 20% of children have only a single seizure whereas another 20% have frequent seizures, meaning three or more seizures in one month or more than two generalised seizures in three months[5]. The characteristic EEG usually shows a normal background with centro temporal spikes from the left or right or bilaterally, particularly during sleep. Neuroimaging is generally not required in the presence of a typical history and EEG appearance. Children with BECTS usually have normal development and no neurological deficits. However, there is an increasing awareness of subtle cognitive, language or fine motor skill deficits in some children. It is uncertain whether the cognitive or language deficits, when present, arise secondary to the AED or the seizures, or are a co-morbidity of the underlying aetiology. It is also unclear whether BECTS is the mildest end of a spectrum of focal epilepsy syndromes which may include Landau-Kleffner syndrome, pseudo-Lennox syndrome and Electrical Status Epilepticus in slow wave Sleep (ESES) [6, 7].

Treatment for BECTS remains controversial in the absence of definitive evidence, with most children becoming seizure free and no apparent risk in Sudden Unexplained Death in Epilepsy (SUDEP)[8]. In Australia and New Zealand, sulthiame would not usually be first line treatment for focal seizures, rather other AEDs such as sodium valproate or carbamazepine are usually prescribed[9]. Regular use of AEDs has side effects, some of

which would not be identified in short-term trials. It is unclear whether AEDs control the focal component of the seizure or only reduce the risk of secondary generalisation. Therefore, careful risk-benefit assessment on an individual basis should be undertaken. AEDs should be considered if seizures occur during the daytime (therefore potentially leading to injury) or are perceived to significantly impact on a child's or family's life, what the authors of this Cochrane review refer to as the "intrusiveness of seizures". This is clearly a grey area, but informed discussion with parents prior to considering the use of AEDs is required to explain that AEDs do not "cure" the epilepsy, do not reduce the risk of progression to a more severe form of epilepsy, do not lower the age of seizure remission, or improve the developmental or cognitive outcome. The potential for AEDs to cause both systemic and cognitive and behavioural side effects, albeit rare, should be clearly stated. In summary, in the absence of definitive evidence, decision making for the treatment of BECTS must incorporate the risk-benefit of the child's profile of seizures, their environment and family values.

Table 1 Characteristics of included Studies

Study	Trial Design	N	Intervention	Seizure freedom	Cognition	Adverse events
Rating, 2000[2], Multicentre: 26 centres Europe	Double blinded randomised- placebo controlled	66	sulthamine versus placebo	3 months: RR 2.26, 95% CI 1.48 - 3.44 6 months: RR 2.63, 95% CI 1.43 - 4.86 Added for Cochrane review; time to first seizure after randomisation: Hazard ratio: 7.8, 95%CI 2.66 – 22.87	Not assessed	Not significant
Coppola, 2007[11], Multicentre: 3 centres Italy	Unblinded open label randomised prospective	39	levetiracetam versus oxcarbazepine	Added for Cochrane review; 3 months: RR 1.13, 95% CI 0.93 - 1.36 12 months: RR of 1.29 with 95% CI 0.89 - 1.86	Not assessed	Not significant
Kang, 2007[12], Multicentre: 12 centres Korea	Single observer blinded, open label randomised, parallel group	112	topiramate versus carbamazepine	28 weeks: RR 1.02 with 95% CI of 0.8 - 1.3	28 weeks: topiramate - worsening on arithmetic subtest : p=0.037; 95% CI 0.07-2.12 carbamazepine – improvement on maze subtest p=0.026; 95% CI 0.20- 3.10 On minimum target dose, topiramate - improvement on object assembly, carbamazepine – worsening on object assembly p=0.006; 95% CI:0.20 - 4.10	Rash with carbamazepine
Andrade, 2009[13], Single centre	Unblinded, open label, randomised- controlled	43	clobazam versus carbamazepine	4-40 weeks: RR of 1.04, 95% CI of 0.67 - 1.62 Freedom 9 months: RR of 1.06 with	Neuropsychometric scores not reported. Children were categorised into mild,	Not significant

Cuba	95% CI of 0.84, 1.34	moderate and severe learning difficulties by WISC. There were no differences between the groups but at the end of the study less were in the severe group for both clobazam and carbamazepine
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