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BRIEF COMMUNICATION

Severe myoclonic epilepsy in infancy: A systematic review and a meta-analysis of individual patient data

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SUMMARY

Severe myoclonic epilepsy in infancy (SMEI) is a rare, but severe disorder with seizures typically resistant to conventional antiepileptic drugs. The objective of the present study was to systematically review the literature on the available treatments for SMEI.

Databases searched included Medline, Embase, and Cochrane. We used a fixed effect model to summarize the odds ratio of seizures rates and a logistic model to evaluate the influence of patient characteristics on treatment effect.

We found 23 uncontrolled studies and 2 randomized controlled trials (RCTs) that compared stiripentol with placebo. Overall, 64 children aged between 3 and 20 years were included in the two RCTs. The odds ratio of responding to stiripentol relative to placebo was 32 (CI: 6.2, 161) and stiripentol reduced seizure rate by 70% (93%; 47%). The multivariate analysis does not suggest any differences within subgroups of participants and cotherapy.

Results of uncontrolled studies in children with SMEI are potentially biased and do not provide valid information on the benefits and harms of treatments. The two RCTs identified, however, were performed with the same objectives and design and showed that seizure frequency is greatly reduced by stiripentol in children with SMEI after 2 months of treatment.

KEY WORDS: Meta-analysis, Severe myoclonic epilepsy, Pediatrics.

Severe myoclonic epilepsy in infancy (SMEI), first described by Dravet (Dravet, 1978; Dravet et al., 1992), is a rare disorder with an incidence ranging between 1 per 20,000 (Yakoub et al., 1992) to 1 per 40,000 children (Hurst, 1990), and affects males twice as often as females. SMEI, also called Dravet syndrome, has been recognized as an independent epilepsy syndrome since 1988 (Commission on Classification and Terminology of the International League against Epilepsy, 1989). It is characterized by febrile or afebrile generalized tonic–clonic, and often prolonged unilateral or generalized clonic seizures, occurring from the first year of life in an otherwise normal infant (Commission on Classification and Terminology of the International League against Epilepsy, 1989). Later on, myoclonus, absence, and partial seizures may appear. In its typical form, patients carry a high risk of mental retardation and behavioral disorders after age 2. Long-term follow-up of a series of patients (Dravet et al., 2005) suggests that seizures have a deleterious effect on cognitive development. Some patients with a borderline variant of Dravet syndrome, however, may retain normal development skills (Oguni et al., 2005). Sodium channel *SCN1A* gene mutations have been found in 40–70% of patients with typical SMEI (Claes et al., 2001; Nabbout et al., 2003; Oguni et al., 2005).

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In SMEI, seizures are typically resistant to antiepileptic drugs (AEDs) and may even be worsened by some of them. However, studies evaluating most AEDs in SMEI have been uncontrolled and included few participants, leading to potentially biased estimates of treatment effect. Because SMEI is an epileptic encephalopathy wherein seizures cause cognitive deterioration, and also carries a high risk of sudden death (15% vs. 5% other epilepsies), treating seizures as early as possible is crucial to improve overall prognosis.

The limited number of patients and the severity of this syndrome justify the best use of current knowledge. Meta-analysis is a valuable tool used to quantify treatment efficacy. Meta-analysis of individual patient data, however, is more powerful when investigating patient characteristics that might influence treatment efficacy. We systematically reviewed the literature on the available treatments for SMEI and specifically evaluated the pooled estimate for efficacy of stiripentol in SMEI using meta-analysis of individual patient data.

Methods

We performed a systematic review of the literature. Databases searched included Medline from 1966 to 2007, Embase from 1974 to 2007, and the Cochrane database. The following search terms were used in multiple search strategies with Boolean terms in order to find relevant articles in Medline: anticonvulsants, epilepsy, severe myoclonic, myoclonic epilepsy, Dravet, seizure, polymorphic, stiripentol, clinical trials, and randomized controlled trials (RCTs). Two authors (BK, SA) blindly reviewed all abstracts. Differences were resolved by consensus. We contacted BIOCODEX (Gentilly, France), the manufacturer of stiripentol, to identify any unpublished trials.

Only randomized controlled trials were eligible for measuring the treatment effect using meta-analytic techniques. A narrative review of uncontrolled trials has been also presented.

We used a fixed-effects model to summarize the odds ratio (OR) of seizures. The following covariates were analyzed using logistic regression techniques, with a fixed effect for trial: the country of the study, age at enrollment, sex, weight, and nature of cotherapy. Data are presented as ORs for dichotomous outcomes, with 95% confidence intervals (CIs). Heterogeneity was assessed and quantified using the Q statistic. In multivariate analyses, interaction between age and country of study was also explored. All analyses were intention-to-treat.

Results

A total of 2,629 citations and abstracts were reviewed, of which 114 initially seemed relevant to our study. Twenty-four articles were potentially eligible. We found a total of 23 articles reporting uncontrolled studies of various interventions in children with SMEI (see Table 1). Four articles were case reports on efficacy or adverse events (Minakawa, 1995; Molina-Carballo et al., 1997; Saito et al., 2001; Goldsmith et al., 2004). Nine studies, one with carbamazepine (Horn et al., 1986), two with bromide (Ernst et al., 1988), one with ketogenic diet (Caraballo et al., 1998), one with barbiturate anesthesia (Rantala et al., 1999), three with topiramate (Mikaeloff et al., 2003; Grosso et al., 2005a, 2005b; Kroll-Seger et al., 2006), and one with leviracetam (Labate et al., 2006) enrolled only subgroups of patients with SMEI. Three were retrospective studies of stiripentol (Thanh et al., 2002), ketogenic diet (Fejerman et al., 2005), and topiramate (Kroll-Seger et al., 2006); five were prospective before–after studies in children with SMEI (Oguni et al., 1994; Guerrini et al., 1998; Nieto-Barrera et al., 2000; Ceulemans et al., 2004; Caraballo et al., 2005). Table 1 summarizes the design and results of uncontrolled studies.

Only one published article (STICLO France) and one unpublished study (STICLO Italy) were RCTs. They compared STP to placebo as an add-on therapy (Chiron et al., 2000; Guerrini and Pons, 2000). For these two studies, we were able to obtain individual patient data (Table 2). Responders on stiripentol and on placebo were defined in both studies as having experienced at least a 50% reduction of clonic (or tonic–clonic) seizure frequency during the second month of the double-blind period compared with baseline.

Overall, 64 children aged between 3 and 20 years were included in the analysis of the treatment effect on seizure rate. STP resulted in an overall OR of responding of 32 (CI: 6.2, 161): 47 (5.1, 438) in the STICLO France study (Chiron et al., 2000) and 20 (1.85, 216) in the STICLO Italy study (Guerrini and Pons, 2000) (Fig. 1). No heterogeneity was detected between these studies ($p = 0.63$). The overall seizure rate was reduced by 70% (95% CI: 93%; 47%): by 62% ($p < 0.05$) in the STICLO France study, and by 74% in the STICLO Italy study ($p < 0.05$).

The multivariate analysis does not suggest any interaction between the treatment effect and country of the study, that is, the treatment seems beneficial in both Italian and French studies. After adjustment for sex, weight, age, and nature of cotherapy, stiripentol still exhibited a highly significant effect (Table 3).

Discussion

Results obtained from any systematic review can be misleading if publication bias is present. A comprehensive review of the literature of computerized databases as well as searches to find unpublished studies was performed to minimize publication bias.

Table 1. Population and study characteristics of uncontrolled trials

Treatment	Author	Population	Study design	Results
Carbamazepine	Horn et al. (1986)	Subgroup of patients with SMEI	Retrospective	Not quantified
Bromide	Ernst et al. (1988)	Subgroup of patients with SMEI	Retrospective	Not quantified
	Steinhoff and Kruse (1992)	Subgroup of patients with SMEI	Retrospective	Not quantified
	Oguni et al. (1994)	Patients with SMEI and SMEB	Prospective, before–after study	8 of 22 patients with general seizure and 2 of 10 patients with partial and myoclonic/absence seizures had >50% reduction of seizure frequency at 1 year
	Diener et al. (1998)	3 patients with SMEI	Case report of adverse events	3 cases of necrotizing panniculitis
Midazolam	Minakawa (1995)	SMEI with status epilepticus	Case report	Not quantified
Melatonin	Molina-Carballo et al. (1997)	SMEI	Case report	Not quantified, after melatonin withdrawal seizures resumed and restabilized after restoring melatonin
Ketogenic diet	Caraballo et al. (1998)	Subgroup of patients with SMEI	Prospective, before–after study	Not quantified
	Caraballo et al. (2005)	SMEI	Prospective, before–after study	20 of 52 participants were included and placed on diet. 13 participants under diet after 1 year had >50% reduction of seizure frequency. 4 remained under diet for 2 years, 1 seizure-free, 1 relapse, 2 not quantified
	Fejerman et al. (2005)	SMEI	Retrospective study	>50% decrease of seizure frequency in 8 of 17 patients on diet for mean follow-up of 24 month
Lamotrigine	Guerrini et al. (1998)	SMEI	Prospective, before–after study	>50% increase of seizure frequency in 8 of 20 patients with convulsive seizure and in 6 of 18 patients with myoclonic seizure
Barbiturate anesthesia	Rantala et al. (1999)	Subgroup of 1 patient with SMEI	Prospective, before–after study	Not quantified
Phenytoin	Saito et al. (2001)	3 patients with SMEI	Case report of adverse events	Report of 3 cases of dose-related choreoathetosis
Topiramate	Nieto-Barrera et al. (2000)	SMEI	Prospective, before–after study	>50% decrease of seizure frequency in 10 of 18 patients
	Mikaeloff et al. (2003)	Subgroup of 1 patient with SMEI	Prospective, before–after study	Not quantified
	Grosso et al. (2005a, 2005b)	Subgroup of 6 patients with SMEI	Prospective, before–after study	>50% decrease of seizure frequency in 2 of 6 patients
	Grosso et al. (2005a)	Subgroup of 10 patients with SMEI	Retrospective study	>50% decrease of seizure frequency in 5 after mean of 9 months
	Ceulemans et al. (2004)	SMEI	Prospective, traditional AEDs vs. valproate + topiramate	Not quantified
	Kroll-Seger et al. (2006)	SMEI	Retrospective study	28 of 36 patients had >50% decrease of seizure frequency
Stiripentol	Thanh et al. (2002)	SMEI	Retrospective study	>50% decrease of seizure frequency in 10 of 46 patients after median treatment duration of 2.9 year
Miconazole and clobazam	Goldsmith et al. (2004)	SMEI	Case report	Not quantified
Levetiracetam	Labate et al. (2006)	Subgroup of 4 children with SMEI	Prospective before–after study	3 of 4 had >50% decrease of seizure frequency

Table 2. Population and study characteristics of randomized trials

Study	Year	Population	RCT follow-up	Treatment
STICLO France (Chiron 2000)	Oct 1996 to Aug 1998	41 children: 65.9% boys/34.1% girls, mean age: 9.35 years (range 3–20.7)	2 months	STP vs. placebo co medication: clobazam+ valproate
STICLO Italy	Apr 1999 to Oct 2000	23 children: 56.1% boys/43.9% girls, mean age: 8.95 years (range 3.47–18.9)	2 months	STP vs. placebo co medication: clobazam + valproate

We were able to find one published and one unpublished trial using STP in SMEI. Individual patient data were provided by the principal investigators and Biocodex for these two trials. Summary data obtained from published articles are useful for estimating the pooled treatment effect, and metaregression techniques can be used to explore the influence of study-level patients characteristics on treatment effects (Greenland, 1998). Individual patient data, however, are more powerful than study-level data and potentially less biased (Gueyffier et al., 1995; Berlin et al., 2002; Lambert et al., 2002). Meta-analysis is an appropriate tool in estimating the treatment benefit in rare diseases where clinical trials are generally underpowered. Moreover, empirical evidence shows that compared to observational studies (Ioannidis et al., 2001), small well-performed RCTs do not overestimate the treatment benefit (Kjaergard et al., 2001). Two RCTs included in our meta-analysis were performed with the same objectives and design. Our results show that in children with SMEI, when STP is added to clobazam and valproate, seizure frequency is greatly reduced after 2 months of treatment. We were not able to show any interactions between gender, weight, cotherapies, age, and the treatment effect. The number of children included in these studies was small, however, and our analysis lacked power as indicated by the large CIs of the estimated OR. However, the observed treatment effect is beneficial and consistent across studies.

The major weakness of the identified RCTs was the short-term follow-up duration. Consequently, although the seizure rate appears to be a clinically relevant end point, its relationship with developmental delay, cognitive impairment, and behavioral disorders has not been unequivocally established. Long-term follow-up is also necessary to evaluate survival (Tomson & Forsgren, 2005) and adverse events related to epilepsy and its treatment (Reynolds, 2005).

Evaluation of a homogeneous subgroup of patients with a high probability of responding to treatment is an interesting strategy in evaluating drugs for rare diseases. The definition of a subgroup, however, is problematic. In children with epilepsy, misclassification could occur because of differential diagnostics or nosological heterogeneity in SMEI. More important, the assumption that the subgroups with a characterized syndrome such as SMEI and/or with some genetic factors will respond consistently to a given treatment needs to be evaluated in longer-term RCTs (Senn, 2004).

It has been argued that the efficacy of stiripentol, an inhibitor of CYP450, might be explained by an increased concentration of valproate and clobazam (or active

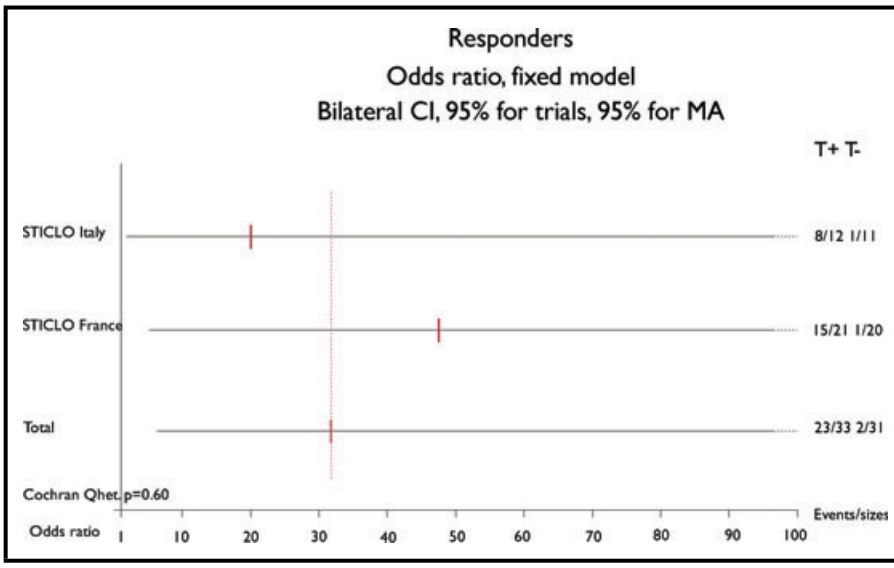

Figure 1.
Odds ratio of responders in STP group compared to placebo.
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Table 3. Treatment benefit (odds ratio) after adjustment for patient characteristics

	OR	95% confidence interval
Treatment effect	32	(6, 161)
Treatment effect adjusted for sex, age, and weight	35	(7, 186)
Treatment effect adjusted for cotherapy (diazepam vs. others)	29	(6, 147)
Treatment effect adjusted for cotherapy (progabide vs. others)	32	(7, 162)

metabolite of clobazam) (Tran et al., 1997; Trevathan, 2000; Giraud et al., 2004). However, STP enhances central GABA transmission (at least in vitro) by a barbiturate-like effect, suggesting that STP does possess antiepileptic properties (Quilichini et al., 2006).

We found 23 uncontrolled studies in children with SMEI. The results of these studies are potentially biased and do not provide valid information on the benefits and harms of treatments (Caldwell et al., 2004) and are as a result unethical (Freedman, 1987). To find out whether a new treatment can replace conventional AEDs, randomized controlled monotherapy trials are required. Because many conventional AEDs have not been compared to placebo and long-term AED treatment is potentially harmful (Marson & Ramaratnam, 2003), withdrawal design trials with replacement of conventional drugs by new treatments seem an appropriate and ethical alternative to monotherapy. A double placebo should be systematically used in such trials to ensure adequate blinding.

Acknowledgment

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Conflict of interest: Drs. Kassaï, Cucherat, and Gueyffier have independently evaluated the individual patient data and have no ties with BIOCODEX, the maker of stiripentol.

Drs. Chiron, Pons, Dulac, and Guerini have been investigators in stripentol RCTs, but have no financial ties with BIOCODEX.

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