

Treatment of myoclonic epilepsies

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Despite the fact that there are many descriptions of the pathophysiology of myoclonic seizures, and some clear descriptions of the different myoclonic epilepsy syndromes, relatively little has been written on their treatment. However, when reviewing clinical data, the limitations of such in the treatment of myoclonus have to be considered. Myoclonus is often not the only seizure type within an epilepsy syndrome. Not all antimyoclonic drugs are antiepileptic, and only some antiepileptic drugs are antimyoclonic. In addition, not only are many of the myoclonic epilepsies refractory to drug treatment, some antiepileptic drugs may exacerbate or even induce myoclonus. In addition, in a situation where many of the seizure syndromes involving myoclonus are age related and seen in childhood, very few randomised controlled trials have been performed.

Some randomised controlled trials report on the effect on myoclonic seizures of the respective medication. An early review of the use of lamotrigine reported 36% individuals with myoclonic seizures achieving at least 50% seizure reduction.¹ In RCTs of the use of Topiramate in enox Gastaut syndrome there were 14% of those with myoclonic seizures seizure free², and in the generalised tonic clonic seizure study, 33%.³ More informative however at present is to review the possible benefit of individual epilepsy syndromes to various medications and for this we have to go to reviews of treatment in unselected cohorts .

Benign myoclonic epilepsy of infancy has been reported to be highly sensitive to treatment with sodium valproate with up to 70% seizure free.⁴ In contrast, the early myoclonic encephalopathies are highly resistant to medication and show an extremely poor prognosis, although there is some anecdotal evidence that lamotrigine and topiramate may be of some limited benefit.⁵ There are few reports of the treatment of myoclonic atstatic epilepsy (Doose Syndrome); Oguni and colleagues reported a retrospective review of 81 patients and showed most but limited response to ACTH and ethosuximide, with relatively poor response to sodium valproate and benzodiazepines.⁶ Of note in this study however was 58% showing at least 90% improvement in

seizures on the ketogenic diet, in this study the medium chain triglyceride diet.

Severe myoclonic epilepsy of infancy (Dravet Syndrome) has been shown to be highly resistant to many medications; sodium valproate and the benzodiazepines, particularly clobazam have been the drugs of choice. Stiripentol is a cytochrome P450 inhibitor shown to be effective in several types of epilepsy. It is not known whether it acts as a direct anticonvulsant or by inhibition of metabolism of concomitant medication. Certainly most side effects can be related to the latter. A recent randomised controlled trial of stiripentol added to clobazam and sodium valproate showed significant short term benefit in seizure control, particularly control of status epilepticus when compared to placebo,⁷ Sustained benefit has been reported in a later study. The syndromes of epilepsy with myoclonic absence and eyelid myoclonia with absences appear to respond to sodium valproate, ethosuximide, benzodiazepines or lamotrigine, wither individually or particularly in combination although most reports are case study based.⁵ As these are historical many report on use of the older medications; a recent pragmatic study examining the use of topiramate showed benefit in severe myoclonic epilepsy of infancy and myoclonic atstatic epilepsy although numbers were small.⁸

Juvenile myoclonic epilepsy is known to be highly responsive to sodium valproate.⁵ There has emerged an issue however with regard to choice of long term treatment, particularly in women. There has been debate as to the possible association with polycystic ovaries, although a causal relationship between this medication and polycystic ovary syndrome has not been proven. Of more concern is the evidence of a higher incidence of congenital malformations in children born to mothers on sodium valproate; as well as a possible higher risk of children with a lower IQ. The results of studies suggest so far that valproate treatment should be avoided where possible at conception. Although lamotrigine may appear safer in current data available to date, response in JME is variable- it appears less effective on myoclonus and has been reported to aggravate

seizures in this syndrome. Newer medications may be effective but data on their use in pregnancy remain limited. Individuals therefore require counselling and full discussion of the issues involved on prescribing of treatment. Data are being accumulated from pregnancy registers around the world.

Resistance to treatment in JME, or indeed apparent aggravation or deterioration in seizures may imply that this is not the diagnosis, and one of the progressive myoclonic epilepsies may need consideration. In these syndromes the myoclonus can be extremely difficult to eradicate. Sodium valproate remains the first line medication. Piracetam, has been shown to be effective in cortical myoclonus, regardless of the cause, and may be particularly useful in PME. There is some evidence that some of the newer antiepileptic agents may also be beneficial. In particular levetiracetam and zonisamide.⁹ Authors have reported a significant reduction in the myoclonus with both drugs although a note of caution is reported with regard to deterioration seen with abrupt withdrawal of piracetam in patients who were already on levetiracetam, despite the medications being closely related.¹⁰ Zonisamide, has also been shown to improve cognition and functioning, not likely to be secondary to the antimyoclonic effect alone.¹¹

Of major importance remains avoidance of medication that may aggravate seizures. Carbamazepine, phenytoin and vigabatrin have all been reported to do this, and to a limited degree lamotrigine.¹² The detrimental effect of lamotrigine is unpredictable, and has been most notably reported in SMEI. Induction of myoclonic seizures may be seen with carbamazepine in benign epilepsy with centrotemporal spikes demonstrated to be epileptic negative myoclonus

Surgery may have a role, particularly where myoclonic seizures are seen as part of a symptomatic focal epilepsy, and seizures are demonstrated to be coming from a clear focus that can be resected. However, some syndromes may be age related in association with negative myoclonus and show spontaneous remission; this has been demonstrated in association with the onset of continuous spike wave of slow sleep in children with hemipolymicrogyria and has shown spontaneous remission in teenage years. Caution should therefore be shown in considering them for surgical treatment. Corpus callosotomy may be very beneficial in the treatment of children with drop attacks causing injury as the result of myoclonus. Although vagal nerve stimulation

has been used in a wide variety of different types of epilepsy, there is a paucity of long term follow up data on its use in the myoclonic epilepsies.

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