

Review articles

Treatment of Myoclonus

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Abstract

Myoclonus is a clinical term meaning a sudden, quick, involuntary muscle jerk, irregular or rhythmic, arising in the central nervous system. The most important initial step in the treatment of myoclonus is to try to subclassify the type of myoclonus and identify the underlying disease process. Metabolic derangements or other underlying conditions, if found, need to be treated. Offending drugs causing myoclonus should be removed. A number of different drugs have been used for the symptomatic control of myoclonus. They include sodium valproate, clonazepam, some other antiepileptic drugs, piracetam, and levetiracetam.

Key words : Myoclonus ; sodium valproate ; clonazepam ; piracetam ; levetiracetam.

Introduction

Myoclonus is a clinical term meaning a sudden, quick, involuntary muscle jerk, irregular or rhythmic, caused by muscular contraction (positive myoclonus) or inhibition (negative myoclonus), usually arising from the central nervous system. Myoclonus can be classified according to clinical type, aetiology, and pathophysiology. The clinical classification is based on two distinguishing features : the myoclonus may be arrhythmic or rhythmic, and it may be focal, multifocal or generalised. The aetiological classification of myoclonus is based on the presence of other symptoms, the evolution of the disease and, when known, the cause. There are four major categories : physiological myoclonus, essential myoclonus, epileptic myoclonus, and symptomatic myoclonus. Finally, the pathophysiological classification of myoclonus is based on the origin of myoclonus in the central nervous system. It distinguishes cortical from subcortical (brainstem and spinal) myoclonus. Rare cases of peripheral myoclonus, due to irritation of a root, plexus or peripheral nerve, have also been reported (Abbasi *et al.*, 2001).

In 1996, we reviewed the use of piracetam in the treatment of myoclonus (Van Vleyen and Van Zandijcke). Now, we present an update on the therapeutic approaches to myoclonus.

General considerations

The most important initial step in the treatment of myoclonus is to try to subclassify the type of myoclonus and identify the underlying disease process. Metabolic derangements or other underlying conditions, if found, need to be treated. Offending drugs causing myoclonus should be removed. Drugs inducing myoclonus include anticonvulsants, levodopa, lithium, monoamine oxidase inhibitors and bismuth subsalicylate (Gordon *et al.*, 1995). Propofol (Hughes and Lyons, 1995) and fentanyl (Bruera and Pereira, 1997) may cause myoclonus. Tricyclic antidepressants may cause an encephalopathy and myoclonus with EEG changes, resulting in confusion with Creutzfeldt-Jakob disease (Foerstl *et al.*, 1989). Trazodone also has been implicated in the generation of myoclonus. (Bodner *et al.*, 1995) Amantadine has been described to cause cortical myoclonus with EEG changes (Matsunaga *et al.*, 2001). Tardive myoclonus has been described following exposure to long term neuroleptics (Little and Jankovic 1987). Clozapine (Bak *et al.*, 1995) also may cause myoclonus. Antiepileptic drugs, such as valproic acid (Aguglia *et al.*, 1995), vigabatrin (Neufeld and Vishnevskaya, 1995), lamotrigine (Janszky *et al.*, 2000), and gabapentin (Asconape *et al.*, 2000), and the beta-blocker carvedilol (Fernandez and Friedman 1999), have been reported to induce myoclonus. Paradoxically, some drugs used to treat myoclonus can also provoke myoclonus.

Treatment

The treatment of myoclonus is largely empirical, because the understanding of its biochemical basis is very limited. Monotherapy should be the starting point. However, polytherapy is likely to be required in most cases. Drugs used to treat myoclonus usually enhance GABA inhibitory activity.

A number of different drugs have been used for the symptomatic control of myoclonus.

Sodium valproate is the drug of first choice to control epileptic seizures and decrease myoclonus in cortical myoclonus. The efficacy in the treatment

of myoclonic jerks is based on clinical observations and open studies (Iivainen and Himberg, 1982). It is mostly well tolerated. Side effects are tiredness, weight gain, tremor, hair loss, and amenorrhea. Sodium valproate is used in doses from 250 mg to 4500 mg per day.

Clonazepam is a benzodiazepine with anti-epileptic properties. Case reports indicate an effect in myoclonus, but there are no controlled studies. Clinical trials in epilepsy have shown that side effects such as drowsiness, ataxia, and behavioural changes are frequent requiring discontinuation in 9-26% (Chadwick *et al.*, 1977). However, these side effects are often transient and can be largely overcome by gradually increasing the dosage. The usual dosage of clonazepam is 4 mg to 10 (15) mg per day.

Other antiepileptic drugs, such as phenytoin, and carbamazepine (Obeso *et al.*, 1989) are of limited benefit in controlling myoclonus. Phenytoin may even be contra-indicated in patients with progressive myoclonus epilepsy because these patients appear to be unusually susceptible to phenytoin intoxication, leading to worsening ataxia, decreased mobility, reduced alertness and shortened survival. (Iivainen and Himberg, 1982 ; Eldridge *et al.*, 1983). Barbiturates have shown their utility by widespread use but are now avoided due to their side effects.

Several cases of myoclonus treated with **serotonin precursors** (e.g. 5-hydroxy-tryptophan) have been reported. However, serotonin precursors are poorly tolerated ; nowadays they are only used as last resort. Anorexia, nausea, diarrhoea, and mental stimulation often require discontinuation of therapy (Magnussen *et al.*, 1977 ; Van Woert *et al.*, 1977).

The **pyrrolidone** (2-oxopyrrolidine) family of chemicals has been the subject of research for more than three decades (Shorvon, 2001). Experimental and clinical work first focused on their so-called nootropic effects ; later came the possibilities for neuroprotection after stroke and use as antiepileptic agents. Unfortunately the consistent findings from animal experimentation proved difficult to replicate clinically (Flicker and Grimley Evans, 1999). Piracetam, the first of the class, was developed by pioneering research by C. Giurgea in the late 1960s ; it was he who coined the term "nootropic", to mean enhancement of learning and memory. The term is sometimes extended to include other actions such as neuroprotection. These properties, together with the lack of other generally adverse psychopharmacological actions (e.g. sedation, analgesia, or motor or behavioural changes), distinguish the pyrrolidones from other psychoactive drug classes.

The mechanisms of action of these drugs are still not fully established ; indeed, different compounds in this class may have different modes of action. Interest in this drug class has recently been reawa-

kened by the licensing of levetiracetam as a major new antiepileptic drug and of piracetam for its anti-myoclonic action and effects after stroke and in mild cognitive impairment.

An overview of the treatment of myoclonus with **piracetam** in 62 case reports, 3 open trials and 2 double blind trials, covering 171 patients was reported in 1996 (Van Vleymen and Van Zandijcke). Efficacy was noted in 2 placebo-controlled, double blind cross-over studies, covering 41 patients. If neurophysiological examinations support a cortical origin of the myoclonus, the likelihood of responding to piracetam is higher (Brown *et al.*, 1993 ; Giroud *et al.*, 2001). The starting dose is 7.2 g per day, increasing every three or four days by 4.8 g per day to a maximum dose of 24 g per day or until stable clinical benefit is evident. Piracetam is well tolerated. The only prerequisite to be taken into account is renal function, since piracetam is not metabolised and excreted unchanged by the kidneys.

Recently, **levetiracetam** has been reported to alleviate post-hypoxic and postencephalitic myoclonus (Genton and Gelisse, 2000 ; Genton and Gelisse, 2001 ; Krauss *et al.*, 2001 ; Schauer *et al.*, 2002). Unverricht-Lundborg disease myoclonus, progressive myoclonic epilepsy, myoclonus dystonia, spinal myoclonus and paraneoplastic myoclonus have been successfully treated with levetiracetam in a few patients (Frucht *et al.*, 2001). Bourdain *et al.* (2002) conducted an open-label trial of levetiracetam in eight men and eleven women, of average age 47.4 ± 23.4 years. Seventeen received levetiracetam for myoclonus refractory to at least one treatment. Levetiracetam was administered from 500 to 2,000 mg per day, over a period from four weeks to eleven months. Levetiracetam was well tolerated in all cases, except in two patients who had to stop treatment because of sedation. Three patients felt dramatic improvement within the first week of treatment, but the improvement then completely disappeared at the same dose. Two patients had good and two others mild improvement. Two of these seven patients had evidence for cortical involvement in myoclonus. Twelve patients reported no efficacy, including one patient with cortical myoclonus. The authors conclude that levetiracetam is a well tolerated medication. Because of the poor efficacy of other medications, levetiracetam can safely be proposed to most patients with myoclonus. Nevertheless, its efficacy is unconstant, even when cortex is involved. In summary, these results provide support for a larger, placebo-controlled trial of levetiracetam in cortical myoclonus.

Treatment of specific syndromes

ESSENTIAL MYOCLONUS

Essential myoclonus often responds to alcohol and may be improved by anticholinergics

(Chokroverty *et al.*, 1987). One report describes a significant reduction of myoclonus and dystonic spasms in a case of alcohol-sensitive myoclonus with dystonia using oral gaba-hydroxybutyric acid, a drug used in the treatment of alcohol withdrawal (Priori *et al.*, 2000).

POST-HYPOXIC MYOCLONUS

In Lance-Adams syndrome and in posttraumatic action myoclonus a combination of 5-hydroxytryptophan (600 mg to 2000 mg per day) and carbido-pa (100 mg to 200 mg per day) can be very effective (Van Woert *et al.* 1977). However, large doses of 5-hydroxytryptophan can cause euphoria or even manic state, whereas discontinuance has sometimes resulted in depression. Piracetam in high doses is now the drug of first choice.

JUVENILE MYOCLONIC EPILEPSY

For idiopathic generalized epilepsies, valproate remains the first choice, whatever the syndrome (de Borchgrave *et al.*, 2002). In syndromes, such as juvenile myoclonic epilepsy, the second choice should be lamotrigine or topiramate (Wheless, 2000). It should be noted that exacerbation of myoclonic seizures by lamotrigine has been described in juvenile myoclonic epilepsy (Biraben *et al.*, 2000). Controlled studies with levetiracetam are ongoing in this indication. Open studies have been published showing good efficacy, but levetiracetam is not yet registered in these epileptic syndromes (Genton and Gelisse, 2000).

PROGRESSIVE MYOCLONUS EPILEPSIES

In mitochondrial cytopathies, different therapeutic strategies have been proposed. However, the rationale for using cytochrome C, flavin mononucleotide or thiamine diphosphate in these cases is not based on controlled studies. In Unverricht-Lundborg disease and in Lafora disease, symptomatic therapy is best focused on the seizure type: valproate, clonazepam, midazolam, zonisamide, piracetam, levetiracetam and chloral hydrate have been used (Berkovic *et al.*, 1986; Obeso *et al.*, 1989; Fedi *et al.*, 2001). A randomised, double blind, crossover study confirmed the therapeutic usefulness of piracetam in progressive myoclonus epilepsy (Koskiniemi *et al.*, 1998). In patients whose seizures persist, vagal nerve stimulation can be a worthwhile therapeutic alternative (McLachlan, 1999).

PALATAL MYOCLONUS OR TREMOR

Palatal myoclonus is usually resistant to therapy. In some cases anticholinergics (Jabbari *et al.*, 1989), 5-hydroxytryptophan (Magnussen *et al.*,

1977) and carbamazepine (Sakai *et al.*, 1981) are helpful. Botulinum toxin injection in the tensor veli palatine muscle has been proposed to suppress the ear click (Deuschl *et al.*, 1991).

SPINAL MYOCLONUS

Spinal myoclonus may respond to removal of compressing lesion (Daniel and Webster, 1984). Effective drugs have included clonazepam and tetrabenazine (Jankovic and Pardo, 1986). Intrathecal baclofen can be used in resistant cases.

NEGATIVE MYOCLONUS

Asterixis results in lapses of maintained postures and is considered a form of negative myoclonus (Young and Shahani, 1986). Negative myoclonus often resolves with the correction of the responsible metabolic derangement. Ethosuximide may be particularly useful in the symptomatic treatment (Shirasaka and Mitsuyoshi, 1999).

Conclusion

Treatment of myoclonus is still unsatisfactory. It is largely empirical, because the understanding of its biochemical basis is very limited. Monotherapy should be the starting point. However, based on clinical experience, polytherapy is likely to be required in most cases. Drugs used to treat myoclonus are sodium valproate, clonazepam, some other antiepileptic drugs, piracetam, and levetiracetam. Levetiracetam seems to have a promising anti-myoclonic effect, especially in cortical myoclonus. Larger, placebo-controlled trials of levetiracetam in this indication are needed. The development of new drugs and of other therapeutic strategies is also warranted.

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