Blepharospasm - successful treatment with baclofen and sodium valproate

A case report

R. SANDYK

Summary

In a patient with idiopathic blepharospasm treatment with the gamma-aminobutyric acid (GABA)-mimetic combination of baclofen and sodium valproate resulted in complete and sustained remission of symptoms and signs. It is suggested that blepharospasm results from a relative deficiency of GABA-ergic neurons and dopamine predominance in the striatum, and that treatment with the GABA-mimetic agents (baclofen and sodium valproate) represents a more physiological means of reducing dopaminergic predominance in the striatum. This report, together with previous reports, suggests that the combination of these two agents should be tried in the initial management of this syndrome.

Blepharospasm is a chronic, disabling neurological condition in adults characterized by involuntary eye closure that may be brief, episodic, or sustained. The disorder had not been associated with drug reactions and is not a sequel to postencephalitic parkinsonism. The symptoms range from clonic involuntary contractions of the eyelids to persistent tonic spasms of eye closure. Patients often complain of an inability to open their eyes for minutes at a time. The eye closure is always bilateral and may be accompanied by involuntary contractions of other muscles innervated by all except the 4th and 6th cranial nerves. In severe cases the condition may progress to involve the face, tongue, pharyngeal muscles, shoulders, hands, and sometimes the trunk. The involvement of involuntary contractions spreads in a cranial-to-caudal direction with progression of the disease. The symptoms range from clonic involuntary contractions of the eyelids to persistent tonic spasms of eye closure. Patients often complain of an inability to open their eyes for minutes at a time. The eye closure is always bilateral and may be accompanied by involuntary contractions of other muscles innervated by all except the 4th and 6th cranial nerves. In severe cases the condition may progress to involve the face, tongue, pharyngeal muscles, shoulders, hands, and sometimes the trunk. The involvement of involuntary contractions spreads in a cranial-to-caudal direction with progression of the disease.

Eyelid movements are always bilaterally symmetrical and, as with most movement disorders, are increased by emotional upset, decreased with relaxation, and absent during sleep. The onset may be sudden, frequently after a major illness or insidious, beginning with movements suggestive of habit spasms or tics. The involvement of involuntary contractions spreads in a cranial-to-caudal direction with progression of the disease.

In the initial management of this syndrome, the combination of baclofen and sodium valproate has been successful in many cases. The treatment of choice in the past has been with anticholinergic drugs such as benztropine mesylate. Precursors and blockers of dopamine, serotonin and acetylcholine have all been tried without notable success. The following case provides evidence that blepharospasm may result from relative gamma-aminobutyric acid (GABA)-deficiency and dopamine predominance in the striatum.

Department of Medicine, Hillbrow Hospital, Johannesburg
R. SANDYK, M.D. (BONN). (Present address: Department of Clinical and Experimental Pharmacology, University of the Witwatersrand, Johannesburg)
Case report

A 42-year-old Black woman presented with an 18-month history of involuntary eye closure, grinning of the mouth, retraction of the head on the neck, and tongue spasms. She further complained of frontovertical headaches, most severe in the late afternoon and evening. Personal and family history were non-contributory. There was no history of treatment with antipsychotic or antidepressant drugs or of toxic exposure. The following types of spasm were observed: severe bilateral blepharospasm, eyebrow elevation and frowning, mild spasms of the orbicularis oris resulting in lip pursing and tightening, and occasionally spasms of the extrinsic ocular muscles producing transient disturbances of gaze. Spasms were not observed during sleep. The rest of the neurological examination was negative and there was no evidence of dementia or psychiatric disorder. All other investigations were negative.

The patient had been treated without benefit with a host of drugs including haloperidol, diazepam, clonazepam, phenytoin, L-dopa, amantadine, reserpine and carbamazepine. Treatment with the GABA-mimetic combination of baclofen and sodium valproate was started, initially at 30 mg and 600 mg respectively in three divided doses daily. Over a period of a week the daily doses were increased to 60 mg and 1 200 mg respectively. The patient reported improvement within 2 weeks; 1 month later the dystonic spasms were no longer present and the condition remained in total remission over a 6-month period without adverse drug effects. To test the efficacy of this drug combination, both were then discontinued for 1 month. Within 2 weeks the symptoms had returned; re-introduction of the drugs led to improvement as before. The patient is now being maintained on baclofen 30 mg daily and sodium valproate 1 200 mg daily. She does not appear to feel drowsy, but occasional lightheadedness has been a persistent though tolerable side-effect.

Discussion

Blepharospasm is a rare, slowly progressive condition, usually occurring in middle-aged or elderly women. It has been suggested that the condition represents a form of local dystonia. Treatment has been unsatisfactory so far. Anticholinergics and benzodiazepines have been shown in some patients to provide some relief; others obtained benefit from tetrabenazine or dopamine-receptor antagonists. Recently, Neophytides et al. found lowered GABA levels in the CSF of patients with adult-onset dystonia, possibly reflecting a reduction in central GABA-mediated inhibition secondary to a striatal dopaminergic pre-dominance. Sodium valproate has been shown to act by increasing the synaptic concentration of GABA in the brain; baclofen has been shown to be a selective agonist for GABA receptors present on central nerve terminals through which the release of several neurotransmitters, including dopamine, seems to be inhibited. A combination of both drugs could therefore be expected to act synergistically, reducing activity in the nigrostriatal dopaminergic pathways and inhibiting release of dopamine from dopaminergic terminals in the striatum. Such a combination might represent a more physiological means of reducing dopaminergic predominance in the striatum than direct blockade of dopamine receptors. Recently Brennan et al. and Sandyk have reported a good clinical response in a severely affected patient with focal dystonia (Meige's disease) and in a patient with writer's cramp treated with a combination of sodium valproate and baclofen. In both cases, as in the present one, the movement disorder was extremely disabling and resistant to a variety of drug combinations. The combination of sodium valproate and baclofen was extremely beneficial, leading to a total remission of symptoms within a relatively short time. Toxic side-effects have not been observed so far.

Although it is difficult to predict the long-term efficacy of this drug combination, it is suggested that a more extensive and prolonged trial is warranted in this distressing and often intractable disorder. It is further suggested that this group of movement disorders results from a relative deficiency of GABA-ergic neurons and dopamine predominance in the striatum. Measurement of CSF GABA levels in these patients before and after treatment with this combination would be of further value in assessing this assumption.

REFERENCES