



An unusual case of 4-aminopyridine toxicity in a multiple sclerosis patient : epileptic disorder or toxic encephalopathy ?

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Abstract

We report the case of a 45-year old female multiple sclerosis patient, who accidentally was overdosed with 4-aminopyridine which resulted in dystonic, choreathetoid type abnormal movements in the four limbs, motoric distress, confusion and opisthotonus.

There is little known about 4-aminopyridine toxicity. There are only a few reported cases ranging from mild paresthesias to tonic-clonic seizures.

4-aminopyridine enhances neuronal conduction at neuromuscular synapses and is indicated in the treatment of selected neurological disorders including multiple sclerosis (MS) and myasthenia gravis, among others.

Key words : 4-aminopyridine ; neurotoxicity ; confusion ; epilepsy ; multiple sclerosis.

Introduction

We describe a 45-year old woman with a 19 year history of secondary progressive MS. She had no other remarkable medical or surgical history except for a cholecystectomy. She never suffered from epileptic disorder nor had she known allergies. MS was diagnosed in 1989 following a bilateral optic neuritis. She is treated with interferon β -1a since 2000.

Current medication consisted of escitalopram (Sipralexa[®]) 10 mg 1dd, tetrazepam (Epsipam[®]) 50 mg 1dd, tizanidine (Sirdalud[®]) 4 mg max. 4dd, trazodonhydrochloride (Trazolan[®]) 100 mg 1dd, oxybutyninehydrochloride (Ditropan[®]) 5 mg 1dd, terazosine (Hytrin[®]) 5 mg 1dd, interferon β -1a 30 ug IM (Avonex[®]) and 4-aminopyridine. 10-10-7.5 mg.

On the day of admission the patient ingested 35 mg of 4-aminopyridine in three doses roughly within a time span of ten hours. The patient's daughter found her at home. She reported that her mother was acting very strange : she was shaking and had involuntary movements of her extremities. She was

unresponsive and had a fixed stare. Speech was slurred and she was confabulating. There was no urinary or fecal incontinence.

On arrival at the emergency department, the patient was very restless. Choreathetoid movements of the four limbs were noticed. Two milligrams of lorazepam (Temesta[®]) IV had no beneficial effect. Vital signs were as follows : blood pressure 120/75 mmHg, heart rate 135/min, respiratory rate 35/min, tympanic temperature 36.9°C and pulse oximetry 98%. Glasgow coma scale was 12/15.

On physical examination, she was unresponsive to external stimuli. She had equal reactive pupils ; cranial nerve examination was normal. Bilateral extensor plantar reflexes were present. A diffuse tremor was present. Cardiac, respiratory and abdominal findings were normal. ECG was normal. Results of urine analysis and assays on blood were all within normal limits. Arterial blood gas analysis revealed a metabolic acidosis with a pH at 7.22.

Cerebrospinal fluid analysis was within normal limits, excluding encephalitis.

Electroencephalography showed symmetric, slow waves at 5 Hz without features of epileptic activity. Brain MRI showed no signs of bleeding nor recent ischemic pathology. Gadolinium enhanced white matter lesions could not be detected, excluding a new MS lesion.

The patient was admitted to the intensive care unit (ICU). Current medications were stopped ; during observation at the ICU, the patient only received clorazepate (Tranxene[®]) 100 mg IV/24 h. Initially the patient was also administered IV valproate (Depakine[®]) because an underlying epileptic disorder was suspected. She developed however a thrombopenia, so that the anticonvulsant treatment was ceased.

Re-intake of 4-aminopyridine caused the symptoms to reappear instantaneously (with confusion, opisthotonus, risus sardonicus, motoric distress and

head tremor). We decided therefore to withhold 4-aminopyridine permanently. The patient remained without complaints since then.

Discussion

4-aminopyridine is a K(+) channel blocker and enhances nerve conduction in demyelinated nerve fibers at the neuromuscular junction. It crosses the blood-brain barrier. 4-aminopyridine also stimulates the release of excitatory neurotransmitters in the spinal cord. Therefore, its use in demyelinating diseases, e.g. multiple sclerosis, is common. Its benefit in multiple sclerosis, however, is not fully proven. Studies have shown a positive effect on muscle strength, ambulation and EDSS-score. No improvement was seen in neuropsychological tests. However, a thorough evaluation of the available studies, shows that no confident estimate of effectiveness in the management of multiple sclerosis symptoms is possible, due to limited power of available studies and publication bias (Solari *et al.*, 2003).

4-aminopyridine enhances synaptic transmission and induces epileptiform activity in the hippocampus. This epileptic activity can be abolished by valproate (Martin & Pozzo, 2003).

The toxicity of 4-aminopyridine reported in literature has been limited to central nervous system hyperexcitation, cardiac disease and gastrointestinal upset.

Central nervous system side-effects include confusion, epilepsy, involuntary movements, choreoathetoid movements, opisthotonic posturing, nystagmus, cerebrovascular accident. Seizures can be induced by (accidental) overdose (e.g. compounding errors), but can also occur at the recommended dose.

Cardiac features reported are cardiac arrhythmias (tachycardia), cardiac conduction disorders and hypertension. Other clinical signs are tachypnea and respiratory failure (Spyker *et al.*, 1980 ; Stork & Hoffman, 1994 ; Smeets & Kunst, 1995 ; Pickett & Enns, 1996 ; Velez *et al.*, 2003 ; Johnson & Morgan, 2006 ; Burton *et al.*, 2008).

In our patient the clinical syndrome was very similar to a paediatric case reported in the literature (Velez *et al.*, 2003). In both cases an electroencephalogram, while the patient still had opisthotonus, nystagmus, confusion and involuntary movements of head and limbs, failed to show evidence of seizure activity. In our case the background EEG activity was slowed to 5-6 Hz activity, compatible with encephalopathy. In another report the EEG was also interpreted as normal, but it was performed only at day 4 of the hospital stay (Spyker *et al.*, 1980). In 4 patients who developed status epilepti-

cus, the EEG failed to demonstrate epileptic activity in 3 of them (Burton *et al.*, 2008).

In contrast with experimental findings in animals, the epileptic nature of 4-aminopyridine toxicity is not well documented in the clinical setting. Velez *et al.*'s and our case suggest that the motor symptoms are most likely not caused by epileptogenic activity in the brain but by neuromuscular junction hyperactivity. Dysfunction of the basal ganglia, due to an altered acetylcholine release induced by 4-aminopyridine, could explain the abnormal involuntary, choreoathetoid movements in our patient. Velez suggests that these patients are experiencing dystonic activity (Velez *et al.*, 2003).

In conclusion, the exact pathophysiology of 4-aminopyridine toxicity remains to be elucidated. The epileptic nature of the 4-aminopyridine-induced toxic side effects is not sufficiently proven.

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