INTRODUCTION

4-aminopyridine (4-AP) is indicated for the improvement of walking speed and motor fatigue in multiple sclerosis (MS). An overdose in 4-AP can produce detrimental side effects. In the majority of cases, overdose is accidental and related to an error in the compounding of the drug. Due to the fact that no commercial preparation for 4-AP is available in Belgium, the medication must be compounded by the pharmacist upon medical prescription. We report a case of sustained encephalopathy following status epilepticus induced by 4-AP overdose.

CASE REPORT

• 58-year-old woman with a history of progressive multiple sclerosis treated by 4-AP (10 mg orally, bid) for more than 3 years (in addition, baclofen, levothyroxine, citiopram and interferon 18.

• A few minutes after the ingestion of a single pill of 4-AP, she started to complain from severe abdominal pain. The pill came from a new box of a pharmacy preparation that was supposed to contain 10 mg of 4-AP per pill. Less than 1 hour after ingestion, rigidity, oculair revulsion, alteration of consciousness and generalized tonic-clonic seizures were noted. Admitted to the ED with GCS 9/15. Recurrence of generalized tonic-clonic seizures treated by i.v. benzodiazepines and valroic acid, in addition to mechanical ventilation. Facial myoclonus was transiently observed. Toxicological screening: no evidence of overdose by baclofen or citiopram. Brain magnetic resonance imaging (MRI): no evidence of new demyelinating lesions.

• First EEG recording (Fig a) performed 12 h after ICU admission: generalized slowing at 6-7 cycles per second, with abundant spike and polyspike-waves on the left fronto-central regions. The epileptiform waves diffused at times to the right fronto-central regions and occasionally became rhythmic during 10-second bursts. On day 3, EEG monitoring showed a discontinuous pattern with bursts of electrical activity characterized by left fronto-central slow spikes at 1-2 Hz on diffusely slowed background. As the sedation was reduced, EEG became gradually continuous with diffusely slow activity at 6-7 cycles/sec, but still showed bursts of delta-waves intermixed with slow spikes on the left-central regions (Fig b).

• Sedative drugs were maintained for 5 days for prevention of recurrent seizures. From day 7: spontaneous eye opening, but no response to verbal command. Day 8 spontaneous movements of the 4 limbs. Day 11: clear motor response to verbal command; day 12, extubation.

• Very slow progression of cognitive and motor status. After 2.5 months of rehabilitation, ability to walk a few meters with bilateral aid, not full recovery of pre-existing cognitive status.

• EEG on day 22: restored reactive structured background rhythm at 8.5-9.5 cycles/sec, with predominant delta waves on the left frontal region, rarely intermixed with isolated slow spikes.

• The box with the pills was brought by the family for toxicological analysis: HPLC coupled to UV detection compared to a standard pill prepared with 10 mg 4-AP. The 4-AP content of the pill that was ingested by the patient was at least 8-times greater (> 80 mg). The pharmacist admitted that each pill was erroneously prepared with a concentration of 100 mg.

DISCUSSION

• 4-AP is a potassium channel-blocking drug. The prolongation of the action potential may facilitate calcium entry into the cell; the increased influx of calcium is thought to enhance neurotransmission by releasing acetylcholine.

• Accidental 4-AP overdose may result in serious neurological events ranging from dystonia to altered consciousness and seizures.

• Seizures have to be clearly separated from other abnormal movements. In a recent review of the literature, King et al. analyzed 19 cases of 4-AP toxicity and found that 5 patients presented isolated seizure and 6 status epilepticus. Intubation was performed in these 11 patients, but also in 3 patients who did not experience seizures. Benzodiazepines were administered to the majority of the patients as well as and anticonvulsants (phenytoin or valproic acid) in reaction to seizures. However, some patients may present with dystonic choreoathetoid movements and altered consciousness. The motor symptoms are most likely not caused by epileptogenic activity in the brain but by neuromuscular junction hyperactivity.

• The interpretation of the EEG may therefore be careful, with a distinction between nonconvulsive status epilepticus and toxic encephalopathy with aspecific electroencephalographic changes. The risk for the patient, if the interpretation of the EEG data is not correct, is that excessive pharmacological treatment could result in prolonged sedation, mechanical ventilation and ICU stay. Our patient presented initial status epilepticus confirmed by initial EEG findings. From day 3 onwards, no further electrical seizures were recorded. EEG was consistent with a prolonged toxic encephalopathy, as also observed in other situations of drug overdose.

• 4-AP overdose has been shown to cause prolonged toxic encephalopathy without initial seizures. This cannot be explained by the kinetics of oral 4-AP. The determination of 4-AP blood concentration is not routinely available in most laboratories, and there is an important overlap of 4-AP concentrations causing seizure or not. The duration of toxic encephalopathy may be several days or even weeks. The neurologic recovery is not complete in all of the patients reported in the literature, as well as in our case. The clinical course is not influenced by any specific treatment.

• In conclusion, for the ICU physicians, it is important to be aware of the clinical and electrophysiological specificities relating to 4-AP overdose, in order to avoid unnecessary treatments for nonconvulsive status epilepticus with as a result prolonged sedation, mechanical ventilation and ICU stay.

REFERENCES
