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Selected Topics: Toxicology

SEVERE ACCIDENTAL OVERDOSE OF 4-AMINOPYRIDINE DUE TO A COMPOUNDING PHARMACY ERROR

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□ **Abstract—Background: 4-Aminopyridine (4-AP) is a potassium channel-blocking drug used to ameliorate symptoms of multiple sclerosis and spinal cord injury by facilitating neural impulse conduction. It is not Food and Drug Administration (FDA) approved, but information about it is disseminated via the Internet, and it is currently available from compounding pharmacies with a physician's prescription. Dose-related toxicity is frequent and includes dizziness, insomnia, paresthesia, asthenia, headache, tremor, delirium, choreoathetosis, and seizures. Objectives: To report a case of life-threatening accidental overdose of 4-AP resulting from a pharmacy error. Case Report: A 42-year-old man with a history of C3 spinal cord injury with residual left-sided weakness and anesthesia, taking 4-AP, presented to the Emergency Department with the sudden onset of abdominal pain, vertigo, anxiety, profuse diaphoresis, hypersalivation, hypertension, bradycardia, agitation, and choreoathetosis, followed by status epilepticus. Toxicity due to 4-AP was suspected and the patient was treated symptomatically. He recovered with permanent short-term memory loss after a prolonged and complicated hospital course. Analysis of the pills, which had been prescribed for him by a physician and specially compounded by a pharmacist, showed that they contained approximately 10 times the dose indicated on the label, a dose that reliably produces severe toxicity. Conclusion: Emergency physicians should be familiar with the signs of 4-AP toxicity. Additionally, they should be aware that 4-AP and other non-FDA-approved medications may be available to patients from compounding pharmacies, and that quality control of made-to-order drug compounding may not be up to the standard that is expected with mass-produced pharmaceuticals.**

□ **Keywords—4-aminopyridine; toxicity; compounding; pharmacist; error; fampridine**

INTRODUCTION

4-Aminopyridine (4-AP) is an orphan drug used to ameliorate symptoms of multiple sclerosis and spinal cord injury by facilitating neural impulse conduction (1). It is not Food and Drug Administration (FDA) approved, but information about it is disseminated via the Internet, and it is currently available from both brick-and-mortar and Internet compounding pharmacies with a physician's prescription (2,3). Typical doses are 10–50 mg/day. A slow-release formulation of 4-AP (Fampridine SR 25 mg) has recently undergone phase 3 clinical trials (4). It is also marketed for agricultural use as Avitrol, which is used for repelling and killing bird pests (5). 4-AP selectively blocks voltage-gated potassium channels in nerve and other excitable tissues, prolonging the action potential, increasing presynaptic calcium influx, thus facilitating both interneuronal and neuromuscular transmission (6). Dose-related toxicity is frequent and includes dizziness, insomnia, paresthesia, asthenia, headache, diaphoresis, hypersalivation, tremor, delirium, choreoathetosis, and seizures (7). Despite the fact that 4-AP blocks potassium

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channels in experimental animal cardiac muscle preparations, it does not prolong the QT interval in therapeutic doses, nor has it yet been reported to produce torsade de pointes in overdose (8,9). I report here a case of life-threatening accidental overdose of 4-AP resulting from a pharmacy error.

CASE REPORT

A 42-year-old man weighing 132 kg, with a history of C3 spinal cord injury with residual left-sided weakness and anesthesia, presented to the Emergency Department via ambulance in 2001 with the sudden onset of abdominal pain, vertigo, and anxiety. His only medication was "F.A.P." On arrival, he quickly became agitated, incoherent, and combative. Blood pressure was 200/100 mm Hg, heart rate 47 beats/min, oral temperature 36.2°C (97.2°F), respiratory rate 32 breaths/min, and pulse oximetry was 100% on room air. Initially, he was shouting that he could not see, but pupils were equal, mid-sized, and reactive. He was profusely diaphoretic and producing frothy saliva. The neck was supple, the lungs were clear, and the heart rate was slow and irregular. There was left arm weakness and chronic contracture. Wild choreoathetotic movements developed and he struck and injured a nurse who was attempting intravenous access. Five staff members were required to restrain him before a central line could be placed in the femoral vein. Lorazepam, atropine, lidocaine, etomidate, and succinylcholine were given i.v., and the patient was endotracheally intubated. Ceftriaxone, vecuronium, and acyclovir were also given. All routine laboratory assessments, urine toxicology, spinal tap, and computed tomography of the head, were unremarkable except for the spinal fluid opening pressure of 280 cm of water. About 2 h after arrival, when the effects of the paralytic agents had worn off, generalized convulsive status epilepticus became apparent. This was terminated by the administration of additional i.v. lorazepam and phenytoin. Sinus tachycardia with ventricular bigeminy developed. The QT interval was normal. The patient's wife arrived and related that he had been taking 4-AP (10-mg capsules, two by mouth three times a day) for 6 months, and that shortly before symptom onset, he had taken the second dose of a new refill, which had been prescribed by his physician and compounded for him by a local pharmacy. There was no depression or suicidal ideation, and a pill count of his current medication bottle did not disclose any discrepancies. He was admitted to the intensive care unit (ICU), where his course was prolonged and complicated. He was given charcoal via nasogastric tube, and his hypertension was treated with i.v. metoprolol, with resolution of his hypertension within a few hours. On the second hospital day, his troponin-I was 10 ng/mL and his creatinine phosphokinase was 387, but the electrocardiogram showed no ischemic changes. Subcutaneous enoxaparin was started. Fifteen days later, partial seizures developed and a magnetic resonance imaging study showed a large left parietal intracerebral hemorrhage, originating in the subcortical white matter with mass effect and midline shift. This resolved with discontinuation of the anticoagulation. Other events of note included a prolonged period of encephalopathy, as documented by two electroencephalograms 7 days apart, lobar lung collapse requiring bronchoscopic clearing of mucoid impaction, recurrent respiratory failure requiring tracheal reintubation, central line sepsis, upper gastrointestinal bleeding, and possible pulmonary embolism, which resulted in the placement of an inferior vena caval filter. After a 25-day acute care hospitalization and a 43-day rehabilitation facility stay, he was discharged home, with persistent anterograde short-term memory loss as his only long-term sequela, which the patient continues to experience 7 years later. Laboratory analysis of the remaining pills revealed that individual capsules each contained approximately 100 mg of 4-AP instead of the labeled 10 mg. A civil suit brought against the pharmacy was settled out of court.

DISCUSSION

Most emergency physicians are unfamiliar with the clinical effects of 4-AP. Initially, the specific etiology of this patient's symptoms seemed inexplicable despite a full neurological work-up. When the medication history was provided by his wife, it became immediately apparent that he was experiencing typical symptoms of 4-AP overdose. The cerebral hemorrhage was associated with the use of enoxaparin and occurred some 2 weeks after the overdose. All symptoms ultimately resolved with supportive therapy, except for the short-term memory loss. The patient and his wife report that he repeatedly forgets conversations and other recent events, including the multiple contacts with the author, both over the phone and in person. Persistent memory loss has not previously been associated with 4-AP toxicity. Additionally, the cerebral hemorrhage cannot be excluded as a possible cause. Thus, 4-AP toxicity cannot be definitively implicated as the cause of the memory loss.

Compounding pharmacy is the long-standing practice of mixing drugs by a pharmacist to fit the unique needs of a patient, by customizing the dose, vehicle, flavor, or binders, etc. For example, a child might require a medication that is available only in adult-sized tablets, so a compounding pharmacist could prepare an appropriate dose in suspension form, adding an appealing flavor.