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Selected Topics: Toxicology

AN UNUSUAL CASE OF 4-AMINOPYRIDINE TOXICITY

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□ **Abstract—4-aminopyridine (4-AP) is an orphan drug in the United States. It enhances neuronal conduction at synapses and is indicated in the treatment of selected neuromuscular disorders, including multiple sclerosis and myasthenia gravis, among others. Its documented toxicity generally has been limited to central nervous system (CNS) hyperexcitation and gastrointestinal upset. In this case, a 56-year-old man accidentally overdosed on an unknown amount of generic 4-AP. This history was unknown by his family and unavailable to initial providers. Approximately 1 h after ingestion, his son found him diaphoretic, vomiting, and having unintelligible speech. In the ensuing 2–3 h, the patient became moderately hypothermic (32.8°C; 91°F), developed atrial fibrillation with a rapid ventricular response, and had neurological changes that were confused with an acute cerebrovascular accident. After a 36-h stay in the intensive care unit that included mechanical ventilation, cardioversion, passive rewarming, and an extensive medical workup, the patient recovered without sequelae. After extubation he stated that he thought he may have ingested too much 4-AP after rubbing a large amount of it against a sore tooth to take advantage of its local analgesic properties. This case of 4-AP overdose resulting in atrial fibrillation with rapid ventricular response, hypothermia, and acute neurological changes mistaken for an acute cerebrovascular accident is an unusual one. This case shows that overdose of 4-AP can cause or mimic several serious medical conditions, and that a detailed history and physical examination are essential for uncovering unusual diagnoses.** **© 2006 Elsevier Inc.**

□ **Keywords—neuromuscular disorders; 4-aminopyridine; toxicity**

INTRODUCTION

4-aminopyridine (4-AP) was originally developed by Phillips Petroleum (Houston, Texas) in the 1960s and marketed as an avicide and bird repellant under the name of "Avitrol." Avitrol's toxicity lies in its enhancement of transmission at neuromuscular junction and neuronal synapses, which causes the birds to become disoriented and let out a distress cry that signals the rest of the flock to flee (1). 4-AP has since become an orphan drug in the United States that has been indicated as a treatment in selected cases of a number of neuromuscular disorders including multiple sclerosis, botulism, spinal cord injury, Alzheimer's disease, myasthenia gravis, and Eaton-Lambert syndrome, as well as reversal of neuromuscular blockade in anesthesia, and verapamil overdose (2–7). The drug also has been used in cardiovascular research to block the transient outward potassium channel affecting phase 1 of the action potential (8). It is marketed under the name Fampridine-SR® (Acorda Therapeutics, Hawthorne, New York), and is pending FDA approval. We found little documentation in the medical literature regarding side effects and toxicity related to 4-AP ingestion and overdose. Most reports have centered on acute confusional states and gastrointestinal upset.

CASE REPORT

A 56-year-old man was brought to the Emergency Department (ED) at an urban level one trauma center for

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altered mental status. According to the family, he had been in his usual state of health until he began complaining of a toothache a few hours before his arrival in the ED. He was found by his son on the bathroom floor, 1 h before presentation, diaphoretic, vomiting, and having unintelligible speech.

Upon presentation, the vital signs were: blood pressure 147/59 torr, pulse 90 beats/min, respiratory rate 28 breaths/min, temperature 35°C (95°F), O_2 100% on room air. He was very diaphoretic, lying in bed, and repeating a single unintelligible word. Neurologic examination was difficult secondary to the patient's mental status, but showed a left facial droop. He did not appear to move the left eye medially, nor did he move the upper extremity on the left. Reflexes were symmetrical; all other cranial nerves appeared intact. Both of the patient's feet were wrapped with gauze that was removed and showed ulcerated lesions with greenish drainage. The rest of the physical examination was unremarkable.

The patient's past medical history was remarkable for a 35-year history of insulin-dependent diabetes mellitus, peripheral vascular disease requiring amputation of a number of toes bilaterally, and a subarachnoid hemorrhage 1 year previously. He worked as a pharmacist.

During the ED course, a normal head computed tomography (CT) scan was obtained. Laboratory tests showed a normal urinalysis, complete blood count, electrolytes, coagulation studies, cardiac enzymes, and thyroid-stimulating hormone level. The lactate was mildly elevated at 3.4 mmol/L. An initial electrocardiogram (EKG) showed normal sinus rhythm without signs of ischemia. Due to the lateralized neurologic findings on physical examination, the neurointerventional radiologist was called, and the patient was prepared for cerebral angiography. Just before leaving the ED, the patient's cardiac rhythm changed to atrial fibrillation with rapid ventricular response. A repeat set of vital signs were significant for a heart rate of 150 beats/min, and temperature of 32.8°C (91°F).

Cerebral angiography was normal, but in the angiography suite the patient became more combative and was intubated. He was then transferred to the medical intensive care unit (ICU). Shortly after arrival in the ICU, the patient was cardioverted at 200 J and his rhythm converted to normal sinus. He was still hypothermic, but quickly normalized with passive rewarming using a Bair hugger. At this point, the etiology of the patient's symptoms still carried a wide differential. A carotid ultrasound and echocardiogram were both normal. Blood, urine, and sputum cultures, as well as cerebrospinal fluid analysis were done looking for infectious etiologies. These were normal. Urine toxicology screen was positive only for benzodiazepines and opiates, both of which were used in the angiography suite. Approximately 6 h after ICU admission, the patient's sedation was held, and he remained very confused and combative, although he did move all extremities, and gaze appeared normal.

On day 2, approximately 36 h after initial presentation, the patient's mental status cleared enough to be extubated. A few hours later, he was questioned about the preceding evening's events, and he stated that he had accidentally ingested an unknown quantity of 4-aminopyridine just before being found by his son.

Upon further discussion with the patient, it was uncovered that he had been prescribed 4-AP by his neurologist for his diabetic neuropathy. He obtained the drug from a local pharmaceutical distributor, which came in "rock" form in a vial. He normally took the medication two to three times a week, but said the dosage was variable. He would scrape off small "flakes" of medicine from the rock, place them on his tongue, and quickly swallow a glass of water. He stated he was never quite sure how much he was taking but it usually was "one or two flakes." He had noted previously that these flakes made both his finger and his tongue go numb where they were placed, and therefore attempted to numb his sore tooth by massaging the large rock of 4-AP on his tooth. His assumption is that he ingested some flakes of medicine while doing this, thus causing an overdose.

DISCUSSION

4-AP has been shown to be efficacious in treatment of neuromuscular disorders by increasing transmission at neuronal junctions. The mechanism of action is a potassium channel blockade at the presynaptic neuron, which causes an increase in intracellular calcium concentration. This influx of calcium into the cell enhances the release of acetylcholine (ACh) into the synapse (3).

In multiple sclerosis (MS), this increased ACh release is proposed to improve neuronal conduction in demyelinated nerve fibers, and therefore, motor functioning (2). 4-AP has been shown in numerous studies to improve motor function in those suffering from certain neuromuscular disorders. Although the results have been promising, most of these studies have been small, and methodologically flawed, and the drug is currently awaiting FDA approval (4).

The drug has many reported side effects. Gastrointestinal side effects of the drug are common, and included nausea, abdominal pain, and obstipation (5). More pertinent to the current case are the side effects from studies on 4-AP that have centered around central nervous system (CNS) dysfunction, including paresthesias, dizziness, anxiety, fatigue, tremor, gait instability, and tonic-clonic seizure. Acute confusional episodes also have been reported (6). Our patient

likely fit into this categorization, however, his presentation was confounded by the disparity in spontaneous movement between the right and left sides coupled with a profound aphasia leading to the provisional diagnosis of stroke. The observation of the disparity in movement was likely biased by the relatively short time the patient spent with us (given the hindsight of a more plausible explanation, a negative cerebral angiogram, and the patient's complete recovery).

Cardiovascular side effects that have been documented include increased mean arterial pressure and sinus tachycardia (in patients presenting with seizure) (3,7). There is also a single reported case of a transient right bundle branch block and later an accelerated idioventricular rhythm in a bodybuilder who took the drug due to the 'amino' in the name (9). Our patient developed rapid atrial fibrillation in the ED. There are several possible explanations for the association of the development of atrial fibrillation with 4-AP toxicity. In a patient with pre-existing structural cardiac disease (or even without), the adrenergic stimulation could precipitate atrial fibrillation. The patient was also hypothermic, at least upon initiation of the dysrhythmia. This could have contributed to irritability of the myocardium. A third possibility comes from research done in Hungary. 4-AP was found to prolong the action potential in atrial fibrillation (and thus possibly contribute to its amelioration) but to shorten the action potential in sinus rhythm, and thus possibly be dysrhythmogenic in this setting (10).

Our patient was also found to be hypothermic. There is a previously reported case of hypothermia with 4-AP toxicity (11). In this case the authors felt that the measurement may have been falsely low due to oral measurement in a hyperventilating patient. Our patient had his temperature measured rectally and was more profoundly hypothermic. One possible explanation is profound diaphoresis contributing to evaporative heat loss. This explanation is most plausible given the ease with which the patient was warmed with passive measures. An alternative explanation would be a central action of the drug. If a less profound hypothermia were a consistent effect of the drug (not documented to our knowledge), this could be a contributing factor to its efficacy in temperature-sensitive MS.

As with many toxicologic ingestions, treatment of 4-aminopyradine is largely supportive (e.g., treatment of seizures with benzodiazepines, protection of the airway). This is fortunate in our case because the ingestion was not known or suspected. If the ingestion is suspected, it has been suggested that repeated administration of activated charcoal should be effective in preventing adsorption. Additionally, based on the fact that active tubular secretion of the drug is thought to be important in elimination of the drug, forced diuresis may be useful. Hemoperfusion also has been suggested as a method of elimination (12).

To summarize, we present an unusual case of a patient with 4-AP toxicity. The patient presented with altered mental status, hypothermia, and rapid atrial fibrillation. Also unusual was the reason for the patient's use of the drug (initially for neuropathy associated with diabetes and then for a toothache) and its method of administration (rock form). For these reasons it is difficult to speculate as to the amount taken and to compare it to previously studied doses and their safety. This case undoubtedly lends some credence to the admonition "take as directed." It also highlights the fact that a detailed history and physical examination are essential for uncovering unusual diagnoses.

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