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Extreme Hyperpyrexia Associated with Central Anticholinergic Syndrome

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Central anticholinergic syndrome is a complication that for many years has been known to occur with the administration of a variety of drugs, most notably the anticholinergics atropine and scopolamine. Fever of a relatively mild degree has been reported in association with central anticholinergic syndrome with clinical doses of anticholinergics.

I present a case of potentially harmful hyperpyrexia associated with central anticholinergic syndrome after the administration of intramuscular scopolamine in a patient presenting for posterior spine fusion.

CASE REPORT

A 23-yr-old woman, weighing 60 kg, with a history of kyphoscoliosis presented for posterior spine fusion.

Although in good health, the patient had received extensive workup in the past for her kyphoscoliosis, including magnetic resonance imaging of the brain and spine, myelogram, and muscle biopsies, all of which showed no significant abnormalities except extreme thoracolumbar scoliosis. She had also been evaluated by psychiatrists on numerous occasions for the diagnosis and treatment of severe anxiety attacks. These were accompanied by shortness of breath, hyperventilation, tachycardia, diaphoresis, blurred vision, and mild temperature elevation, with peaks from 38.1 to 38.5° C recorded by nursing staff. The attacks were usually precipitated by venipuncture for blood drawing, medication administration, or intravenous catheter insertion. On the psychiatrist's recommendation, she was treated with alprazolam for the attacks and seemed to respond well to this regimen. Her other medications included ketorolac for back pain, albuterol inhaler for mobilization of secretions, and diphenhydramine as needed for sleep. She had no significant allergies.

At 5:10 on the morning of surgery, the patient was noted to be having an anxiety attack and was given alprazolam 0.25 mg orally. She was tachypneic and had slight perioral cyanosis. Her vital signs were as follows: temperature 37.1°C (measured sublingually with an electronic Datex 500 unit (American Hospital Supply, McGaw Park, IL)), blood pressure 125/75 mmHg, pulse 88 beats/min, and respiration 40 breaths/min. At 5:35 AM her scheduled preoperative medications of morphine 6 mg and scopolamine 0.4 mg were given intramuscularly. Approximately 5–10 min later the patient was again noted to be agitated with symptoms similar to her previous attack. Because of the cyanosis, oxygen was administered by nasal cannula at 4 l/min. Hemoglobin oxygen saturation by pulse oximetry (Sp_{O_2}) was not being monitored at the time.

The patient continued to be agitated and became increasingly combative and incoherent. At 6:25 AM her vital signs were: temperature 39.3° C, blood pressure 160/90 mmHg, pulse 200 beats/min, and respiration 48 breaths/min. At this time the anesthesiology service was notified. On arrival, the anesthesiologist noted that the patient was totally incoherent and combative. Physical examination showed the patient to have widely dilated pupils; hot, dry skin; and perioral cyanosis. Her lungs were clear to auscultation bilaterally. Her vital signs were: temperature 41.3° C, blood pressure 155/90 mmHg, pulse 196 beats/min, and respiration 52 breaths/min. An 18-G catheter was inserted in the right saphenous vein, and 500 ml of normal saline was started.

When questioned, the family stated that the patient had had attacks similar to this one, with perioral cyanosis, confusion, tachypnea, and slight temperature elevation, but nothing approaching the severity of this attack. An arterial blood gas sample was drawn while the patient was receiving oxygen *via* nasal cannula at 4 l/min, with the following results: *p*H 7.45, Pa_{CO_2} 27, and Pa_{O_2} 50. Sp_{O_2} was 92%. Oxygen was then administered at 40% by face mask, and Sp_{O_2} increased to 100%. A 12-lead ECG showed sinus tachycardia with a rate of approximately 200 beats per min. Vital signs at this point were: temperature 42° C, blood pressure 150/90 mmHg, pulse 200 beats/min, and respiration 42 breaths/min. A cooling blanket was placed under the patient, and ice packs were applied to her head.

We were then informed that the patient had recently received her preoperative medication of morphine and scopolamine. Because her symptoms, except for markedly elevated temperature, were consistent with central anticholinergic syndrome, this tentative diagnosis was made. We believed that an exaggerated episode of her usual anxiety attacks, infection, unrecognized malignant hyperthermia or pheochromocytoma, use of illicit drugs, or scopolamine dosage error were unlikely. Physostigmine 3 mg was administered intravenously in three divided doses every 5 min with almost immediate resolution of the patient's confusion after the third dose. The patient's vital signs were normal within 0.5 h, and her temperature was normal 1 h later. Because of the immediate resolution of symptoms, we believed that the diagnosis of central anticholinergic syndrome was confirmed. We did not obtain further drug screening or cultures. Her operation was postponed but proceeded uneventfully the following day.

DISCUSSION

To this author's knowledge, this is the first case of extreme hyperpyrexia associated with clinical doses of scopolamine. Mild fever has been known to occur with central anticholinergic syndrome, but this case illustrates a rare and potentially fatal complication.[1]

Central anticholinergic syndrome may present to the clinician in several forms, ranging from an agitated or excitatory state to a state of extreme depression with decreased respiratory drive and coma, or with fluctuations between the two (although coma is unusual with clinical doses of anticholinergics).[2] These states may be accompanied by a centrally induced hyperpyrexia; however, this occurs in only approximately 25% of patients with central anticholinergic syndrome.[3] The depressed state may be

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the more common of the two and may be unrecognized in many patients, especially in the perioperative period when patients have received numerous drugs that have central or sedative actions. In fact, the occurrence of this syndrome in the perioperative period has been estimated to be between 1 and 40% and is believed to occur more often in patients who have received multiple drugs.[1,4,5] The agitated state as illustrated by this case may be more readily recognized. It is characterized by excitation, disorientation, anxiety, photophobia, hyperalgesia, hallucinations, restlessness, seizures, tachycardia, hypertension, mydriasis, and dry skin.

Because these symptoms may have any one of several etiologies, the clinician must first have a high index of suspicion that central anticholinergic syndrome is the underlying cause. The diagnosis is often presumptive and might be confirmed after prompt resolution of symptoms with treatment. If resolution of symptoms does not occur, the clinician should consider the following differential diagnosis: relative anesthetic or opioid overdose, disorders of glucose and electrolyte metabolism, hypoxia, pheochromocytoma, hypercarbia, hypothermia, dehydration, renal and hepatic disorders, neurologic disorders, including intraoperative cerebral hypoxia, stroke, surgical injury, and brain swelling or hemorrhage. If hyperpyrexia is noted, as in my patient, malignant hyperthermia, infection, thyrotoxicosis, neurolept malignant syndrome, and extreme anticholinergic overdose must be included. If the patient is seen in an emergency setting or has a history of illicit drug use, acute intoxication with cocaine, amphetamines, or other centrally acting drugs should be considered.

Treatment of central anticholinergic syndrome is with the cholinesterase inhibitor physostigmine. The recommended doses and routes of administration vary slightly between sources, but the dose generally recommended is 0.04 mg/kg or 2–3 mg in adults.[4] Onset time after administration is rapid, with resolution of symptoms occurring within 2–20 min. This, in fact, occurred in my patient, with immediate resolution of confusion within several minutes and prompt defervescence over 1 h without the administration of any other antipyretics. The drug should be administered slowly to prevent peripheral evidence of cholinergic stimulation, and it should probably be administered at the rate of 1 mg/min. Side effects include bradycardia, profuse perspiration, salivation, nausea, and hyperperistalsis. There are two reported cases of asystole with the administration of physostigmine.[6] However, in these cases, while the bradycardia that ensued after the administration of physostigmine was being treated, small doses (0.5–1 mg) of atropine were given with subsequent asystole. It is possible that the small doses of atropine caused a paradoxical response in heart rate, and asystole followed.

The diagnosis of central anticholinergic syndrome was more difficult in this case because of the patient's presentation with extremely high fever and her previous history of mild temperature elevation, tachycardia, and hypertension with her anxiety attacks. We believed that, in light of the recent administration of scopolamine and the patient's toleration of her other medications for several days, a presumptive diagnosis of central anticholinergic syndrome could be made. It is unlikely that any of the drugs except a massive overdose of diphenhydramine could have caused her symptoms. The chance of a massive overdose of scopolamine is unlikely, because the patient received 0.4 mg, the unit dose that is packaged in vials in our institution. The nursing staff would have had to open numerous vials of scopolamine to give a massive overdose. Illicit drug use is not likely, as the patient had no history of drug use and had been hospitalized for 1 week prior to her operation. Her family also denied any drug use by the patient. Also, this patient's symptoms, if associated with recreational drugs, should not have been alleviated almost immediately with physostigmine, as in this case.

In summary, this case illustrates extreme fever with central anticholinergic syndrome in association with a clinical dose of scopolamine. Because of the remarkable variability in presentation, the differential diagnosis that can be generated by the symptoms, and a low index of suspicion by many clinicians, it is probably underdiagnosed. When a physician is presented with a patient with temperature elevation in a setting where drugs with anticholinergic properties have been administered, central anticholinergic syndrome needs to be part of the differential diagnosis.

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