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Acute Mental Status Changes, Hypotension, and Bradycardia in a 15-Year-Old-Boy

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CASE PRESENTATION

Initial Presentation and History

A 15-year-old boy with slurred speech, pallor, unsteady gait, confusion, and headache was transferred from a community hospital to the emergency department (ED) of a tertiary care center. His past medical history was significant for bipolar disorder, attention-deficit/hyperactivity disorder (ADHD), oppositional defiant disorder, obsessive-compulsive disorder, constipation, gastroesophageal reflux, and headaches. Prior brain magnetic resonance imaging studies demonstrated ventriculomegaly. Although the ventriculomegaly had been stable, there was concern that he may have developed hydrocephalus and increased intracranial pressure (ICP), thus causing his headaches. For this reason, the patient recently had been hospitalized for ICP monitoring. The patient underwent intraparenchymal ICP monitoring, which showed normal pressures. The monitor was removed prior to discharge from the hospital. On the day following discharge, he was unsteady and complained of a new mild headache, which persisted for the next 2 days. On the day of this current presentation, he awoke with slurred speech and dizziness. His mother reported that he appeared to be confused and pale upon awakening.

The patient's medications were as follows: extended-release clonidine 2.25 mg/night, lansoprazole 30 mg/day, lithium 600 mg twice daily, modafinil (a central nervous system stimulant) 100 mg/day, olanzapine (an atypical antipsychotic) 10 mg/night, and polyethylene glycol 17 g/day. His adoptive mother initially denied any recent medication changes. He had no known drug allergies. His biological father had bipolar disorder and adult-onset hydrocephalus requiring a shunt. Both biological parents had a history of substance abuse. The patient lives with his adoptive parents, and his adoptive mother administered his medications.

Physical Examination

In the ED, the patient's confusion and slurred speech had improved from earlier in the day when he had been evaluated at the community hospital's ED. The patient's vital signs were as follows: temperature, 35.8°C (96.5°F); heart rate, 47 to 57 bpm (normal, 55–85 bpm); respiratory rate, 20 breaths/min (normal, 14–20 breaths/min); blood pressure, 81/41 mm Hg (normal, 110–135/65–85 mm Hg); and oxygen saturation on room air, 99% (normal, 95%–100%).[1,2] There were no signs of infection at the site where the ICP monitoring device had been inserted.

On neurologic examination, the patient was somewhat sleepy but was able to follow commands. The patient's speech was not clear due to slurring; however, the content of his speech was lucid. He had tremor on finger-nose testing with mild dysmetria. He walked with a wide-based, ataxic gait and was unable to walk unassisted. The remainder of the examination was unremarkable. The patient was admitted due to persistent mental status changes and abnormal vital signs.

- **What is the differential diagnosis for acute mental status changes in children?**
- **What diagnostic evaluations are indicated?**

APPROACH TO EVALUATION OF ACUTE MENTAL STATUS CHANGES

The differential diagnosis for acute mental status changes in children is broad (**Table 1**). Common causes of acute mental status changes in pediatric patients include infections, toxic ingestions (**Table 2**),

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Table 1. Differential Diagnosis for Acute Mental Status Changes in Children

Central nervous system disorders
Cerebral degenerative disease
Head trauma
Increased intracranial pressure due to abscess, edema, hydrocephalus, tumor, hemorrhage
Migraine
Seizures
Drugs and toxins (see Table 2)
Hypoxia-ischemia
Cardiac disease
Hypotension
Near-drowning
Infections
Acute systemic infections (eg, bacterial sepsis, pneumonia, pyelonephritis)
Central nervous system infections (eg, meningitis, encephalitis)
Less common infections (eg, malaria, rabies, Rocky Mountain spotted fever, syphilis)
Metabolic derangements
Electrolyte or acid-base disturbances
Endocrine disorders (eg, diabetic ketoacidosis, thyroid disorders)
Hypoglycemia
Hyponatremia
Inborn error of metabolism
Miscellaneous causes
Heat stroke
Hepatic encephalopathy
Hypothermia
Insect or spider bites
Renal disease
Psychological (eg, psychosis)
Vascular
Congestive heart failure
Hypertensive encephalopathy
Vasculitis

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Table 2. Drugs and Toxins That Can Cause Mental Status Changes

Alcohols (eg, ethanol, ethylene glycol, methanol)
Amantadine
Amphetamines
Anticholinergics (eg, antihistamines, atropine, phenothiazines)
Antidepressants (eg, tricyclic antidepressants, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors)
Antiepileptics
Antipsychotics
Barbiturates
Benzodiazepines
Caffeine
Carbon monoxide
Cholinergics (eg, carbamates, organophosphates)
Cocaine
Cyanide
Dextromorphan
Drug withdrawal states
γ-Hydroxybutyrate
Glucocorticoids
Hallucinogens (eg, ketamine, lysergic acid diethylamide, mescaline, phencyclidine, psilocybin)
Heavy metals (eg, arsenic, lead, mercury)
Hypoglycemic agents
Imidazolines (eg, tetrahydrozoline)
Inhalants (eg, hydrocarbons)
Lidocaine
Lithium
Mushrooms
Opiates
Phenylpropanolamine
Plants
Salicylates
Skeletal muscle relaxants
Sympatholytics (eg, β-blockers, calcium channel blockers, clonidine)
Theophylline

Data from Fenichel GM. Clinical pediatric neurology: a signs and symptoms approach. 5th ed. Philadelphia: Saunders; 2005:49; *and* Rodgers GC, Matyunas NJ. Poisonings: drugs, chemicals and plants. In: Behrman RE, Kliegman RM, Jenson HB, editors. Nelson textbook of pediatrics. 17th ed. Philadelphia: Saunders; 2004:2363–74.

electrolyte disturbances, shock, hypoglycemia, and hypoxia.[3,4] Because of the wide differential, a history and physical examination should be used to guide further work-up after initial stabilization. If the diagnosis is not immediately clear from the history or physical examination, initial laboratory studies should include a complete blood count; coagulation studies; electrolyte panel; arterial blood gases; and measurement of calcium, magnesium, phosphate, glucose, blood urea nitrogen, creatinine, bilirubin, liver enzymes, and ammonia.[5] Blood, urine, and cerebrospinal fluid cultures can be obtained to exclude infection. Drug screening should be performed on blood and urine for suspected intoxications. Routine urine toxicology screening can only detect a few

substances, which vary by institution; substances commonly tested for include amphetamines, benzodiazepines, barbiturates, cannabinoids, cocaine, and opiates. Comprehensive urine drug screening using immunoassay and thin-layer chromatography and gas chromatography-mass spectroscopy can detect thousands of drugs, although this is not available at all institutions. Computed tomography or magnetic resonance imaging of the head can be performed to identify abnormalities (eg, hemorrhage, stroke, hydrocephalus, tumor) that may be responsible for neurologic symptoms.

Key Point

Common causes of acute mental status changes in pediatric patients include infections, toxic ingestions, electrolyte disturbances, shock, hypoglycemia, and hypoxia. A thorough history and physical examination should be used to narrow the broad differential diagnosis.

CASE PATIENT: LABORATORY AND IMAGING STUDIES

Initial diagnostic considerations for this patient included central nervous system infection as a complication of his recent ICP monitoring, hydrocephalus, toxic exposure, and adverse reaction to medications. A computed tomography scan of the head showed stable ventriculomegaly with no interval change. Analysis of cerebrospinal fluid showed no white blood cells (normal, 0–5 cells/μL), 40 red blood cells (normal, 0 cells/μL), a glucose level of 64 mg/dL (normal, 15–60 mg/dL), and a protein level of 38 mg/dL (normal, 45–80 mg/dL). Although the patient's results were slightly outside reported normal limits, the medical team felt that the abnormalities were not clinically significant. The patient's lithium level was 0.84 mEq/L (therapeutic range, 0.6–1.2 mEq/L). Laboratory studies included electrolytes, blood urea nitrogen, creatinine, glucose, complete blood count with differential, and liver function tests, all of which were normal. Routine urine drug screening, which included amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, and opiates, was negative. Based on the acute onset of his symptoms, normal laboratory results, and abnormal vital signs, toxic exposure was suspected.

- **What is the prevalence of toxic exposures in children?**

TOXIC EXPOSURE

In 2004, there were approximately 2.4 million toxic exposures reported to the 62 participating poison centers in the United States.[6] Of these exposures, 65% occurred in persons younger than age 20 years and 7.2% occurred in adolescents aged 13 to 19 years. A male predominance was found in those younger than 13 years, but the sex distribution was reversed in teenagers and adults. The majority (84.1%) of poison exposures in adults and children were unintentional; however, only 48.3% of reported exposures were unintentional in teenagers. Therapeutic errors accounted for 9.1% of all cases.[6]

- **How should pediatric patients be assessed for toxic exposure?**

When a toxic exposure is suspected, the toxic profiles of substances that may have been ingested should be reviewed. Side effects and toxic effects of medications can be found in many medical references. Pharmacists and poison control centers also can be of assistance. Key elements of the history include obtaining a list of the patient's medications and doses (including any recent changes or refills) and determining the patient's access to alcohol, illegal drugs, and other medications in the home (eg, over-the-counter medications, herbal supplements). When toxic exposure is suspected in an adolescent, the patient should be interviewed alone, if possible. Adolescents should be asked about past and present psychiatric symptoms and suicidality to determine whether the ingestion may have been purposeful. The level of adult supervision also should be verified. The parents of this patient reported a high level of supervision, including administration of his medications. He had not been unsupervised since his hospital discharge 2 days prior.

Key Point

Toxic exposures are a common cause of mental status changes, requiring a thorough history taking that includes assessing the patient's access to medications and drugs, level of supervision, and suicidality. When a toxic exposure is suspected, the toxic profiles of substances that may have been ingested should be reviewed.

CASE PATIENT: DIAGNOSIS AND HOSPITAL COURSE

The patient's medications and their side effects were reviewed (**Table 3**). Olanzapine and clonidine were held because they were suspected as possible causes of the patient's symptoms. Over the course of hospital day 1, the patient continued to improve. On further questioning, the patient's mother reported that she had refilled his medications 2 days prior to presentation and that his psychiatrist had recently changed the patient's clonidine dosing schedule from 3 times daily to once nightly. The patient had originally been prescribed 1 75-μg clonidine tablet 3 times daily (total, 225 μg/day). To simplify the patient's regimen, his

Table 3. Toxic Effects of the Case Patient's Medications

Drug	Most Common Toxic Effects
Clonidine	Early hypertension followed by hypotension, bradycardia, respiratory depression, hypothermia, drowsiness, decreased or absent reflexes, weakness, irritability, miosis
Lansoprazole	No documented symptoms from overdose; side effects include abdominal pain, nausea, diarrhea, constipation
Lithium	Fine hand tremor, polyuria, thirst, diarrhea, vomiting, drowsiness, muscular weakness, decreased coordination, ataxia, giddiness, tinnitus, blurred vision
Modafinil	Agitation, insomnia, tachycardia, hypertension, anxiety, irritability, aggressiveness, confusion, nervousness, tremor, palpitations, sleep disturbances, nausea, diarrhea, decreased prothrombin time
Olanzapine	Altered level of consciousness (ranging from sedation to coma), drowsiness, slurred speech, agitation/aggressiveness, dysarthria, tachycardia, extrapyramidal symptoms
Polyethylene glycol	No documented symptoms from overdose; diarrhea and possibly dehydration expected; side effects include nausea, vomiting, abdominal fullness

Data from 2007 Physicians' desk reference. 61st ed. Montvale (NJ): Thomson Healthcare; 2006: 843–4, 988–92, 1025–6, 1692–4, 1830–8, 3271–7.

Table 4. Clinical Manifestations in 6042 Symptomatic Pediatric Clonidine Exposures

Symptom/Sign	Cases (*N*)	Symptomatic Patients (%)
Drowsiness/lethargy	4858	80.4
Bradycardia	1045	17.3
Hypotension	886	14.7
Respiratory depression	218	4.7
Miosis	195	3.2
Dizziness/vertigo	151	2.5
Coma	148	2.4
Agitation/irritability	134	2.2
Ataxia	115	1.9
Hypertension	91	1.5
Respiratory failure	23	0.4
Death	1	< 0.1

Adapted with permission from Klein-Schwartz W. Trends and toxic effects from pediatric clonidine exposures. Arch Pediatr Adolesc Med 2002;156:394. Copyright © 2002, American Medical Association. All rights reserved.

physician had consolidated the 3 doses into 1 daily dose given once nightly as an extended-release tablet. The patient's new prescription for an oral extended-release formulation of clonidine was compounded by his pharmacist because this formulation is currently not commercially available in the United States. The pharmacist confirmed that all medications were filled as written. On further inspection, however, the pharmacist noticed that the clonidine dose had been written incorrectly: 2.25 mg/night of clonidine was ordered instead of 225 μg/night. The pharmacist filled the prescription as written, resulting in the patient receiving a daily dose that was 10 times greater than the intended dose. This prescription error had escaped the notice of the ordering physician, filling pharmacist, physicians in 2 EDs, and admitting team. Based on this new information, no further studies were necessary. The patient was observed until his vital signs and neurologic symptoms normalized, and he was discharged.

CLONIDINE

In recent years, clonidine has become increasingly popular as an adjunct therapy for ADHD, although it is not currently approved by the US Food and Drug Administration for this indication. Its effects on blood pressure are believed to result from stimulation of noradrenergic activity in the locus ceruleus, which causes changes in dopaminergic tone.[7] Clonidine is an α-adrenergic agent with both central and peripheral actions. After oral administration, it is absorbed rapidly with 95% bioavailability. A decrease in blood pressure occurs within 30 to 60 minutes after administration, with a peak effect occurring within 1 to 3 hours. The elimination half-life ranges from 6 to 24 hours.[8] Because clonidine has a short therapeutic duration, dosing 2 to 4 times daily is typically required.[7] Side effects include dry mouth, drowsiness, dizziness, constipation, and sedation. The side-effect profile of clonidine differs greatly from that of stimulant medications (eg, methylphenidate, modafinil) typically used for ADHD. Because stimulants and clonidine both have cardiovascular side effects and are often used together, the patient's vital signs should be monitored regularly.[7]

As pediatric clonidine prescriptions have increased, so have toxic exposures to clonidine. Between 1993 and 1999, 10,060 pediatric clonidine poisonings were reported to the American Association of Poison Control Centers. During this time, the yearly rate of pediatric toxic exposures to clonidine increased dramatically, with roughly 2.5 times as many exposures in 1999 as compared with 1993. Of the cases reported, 6042 (60%) were symptomatic.[9] The most common symptoms observed are summarized in **Table 4**.[9]

This patient exhibited bradycardia, hypotension,

and ataxia. Interestingly, his first presenting symptom was a mild headache starting 2 days before admission. Suchard and Graeme[10] reported 2 cases of clonidine overdose in older children who both had an initial complaint of headache. Although this side effect has not been reported in larger case series of pediatric clonidine overdoses,[11] headache may be a presenting symptom of clonidine toxicity.

Key Point

Clonidine is an antihypertensive medication increasingly used in children with ADHD. As prescriptions of clonidine have increased, so have toxic exposures.

In this patient, the medication error could have been fatal if clonidine administration had been continued and cardiorespiratory collapse had occurred. Although few clonidine-related fatalities have been reported, a report on 16 episodes of pediatric clonidine overdose in 15 patients revealed that 50% of patients required intensive care unit admission and 12% required intubation.[12] Knowing that clonidine was the cause of this patient's symptoms may not have changed this patient's management, given that care is supportive. Supportive care can include atropine for bradycardia, vasopressors for hypotension, and naloxone for reversal of central nervous system symptoms,[12] which this patient did not require. However, being aware that the patient had received an overdose of clonidine would have guided monitoring and ensured that the patient was not administered clonidine while hospitalized. Furthermore, preventing the overdose or earlier recognition could have prevented the costs associated with 2 ED visits, an ambulance transfer, and an inpatient admission.

Key Point

The most common symptoms of clonidine poisoning are drowsiness, lethargy, bradycardia, and hypotension. Although clonidine overdoses usually are not severe, they can lead to cardiorespiratory collapse and, rarely, death.

- **What are common sources for medication errors in pediatric patients?**

MEDICATION ERRORS

The Institute of Medicine's 1999 report *To Err is Human* attributed between 44,000 and 98,000 deaths annually to medical mistakes in hospitals.[13] Medication errors were the most frequent type of error identified by the Harvard Medical Practice Study, comprising 19% of all medical errors.[14] Multiple studies have been performed to determine the medication error rates in adult inpatient settings, but few studies have been performed in the pediatric inpatient setting. One large prospective study of pediatric inpatients found that 74% of medication errors were committed by physicians.[15] Many medication errors occur during history taking. In 1 review, 10% to 67% of pediatric patient histories had at least 1 prescription medication error. Barriers to taking an accurate medication history include the time required to take a comprehensive history, patient and parent knowledge, lack of access to physicians' and pharmacists' records, and availability of medication vials.[16] Such barriers become even more significant in patients who have complicated medical conditions requiring multiple prescription medications. There is a direct correlation between the number of drugs administered to hospitalized patients and the frequency and severity of adverse medication reactions.[17] Other frequent causes of medication error include errors in physician order writing, transcription, pharmacy dispensing, and nursing administration.[15]

A source of medication error that particularly affects children involves dosing errors. The need for weight-based dosing in pediatric populations provides the opportunity for calculation errors. Given the complexities inherent to prescribing medications to children, it is not surprising that incorrect dosing, including computation errors and incorrect dosing intervals, is the most common type of error in the pediatric population.[15] Dosing errors accounted for 28% of the errors detected in 1 large prospective study of pediatric inpatients.[18] Several studies have also identified errors due to misplaced decimal points as a particularly dangerous problem in pediatric patients.[18]

Likewise, compounding mistakes are another cause of error in pediatric patients. Clonidine is typically used to treat adult hypertension, and pediatric doses can be lower than the preparations used to treat adults. Many medications do not have commercial preparations suitable for children, necessitating manipulation by pharmacies (eg, crushing, splitting, diluting, suspending). Any additional manipulation of a commercial product introduces another opportunity for error.[16] In Suchard and Graeme's[10] report of 2 clonidine poisonings, both patients had recently had their compounded clonidine refilled. Patients may be at higher risk for medication errors immediately after receiving a refill of a compounded medication.[10]

Lack of familiarity with off-label medications used in children also can contribute to error. Clonidine is typically used by physicians who are well versed in the management of ADHD; however, many other physicians

may not be familiar with typical pediatric clonidine dosing or symptoms of overdose. Additionally, care of complicated pediatric patients is often initiated in tertiary care centers but is maintained by community physicians. Because serious disease is relatively rare in children as compared with adults, many physicians have a difficult time remaining current with the latest developments for managing less common or complex diseases.[19]

Key Point

Weight-based dosing, drug compounding, and lack of familiarity with medications all contribute to medication errors in pediatric patients. Other common causes of medication error include errors in history taking, physician order writing, transcription, pharmacy dispensing, and nursing administration.

Adverse Drug Events

For several reasons, pediatric patients are at higher risk (up to 3 times the rate for adults) for potentially dangerous adverse drug events.[15] Relatively few pharmacology studies are performed on pediatric populations, so our understanding of pharmacokinetics, pharmacodynamics, and toxicity profiles in children is often incomplete or absent. Children's limited communication ability and their inability to self-administer prescriptions contribute to increased risk.[18] Finally, medical errors are more likely to have more serious consequences in children than in adults because children may have fewer internal reserves to withstand errors.[15]

- **Why was clonidine overdose missed in this patient?**

Reason's[20] "Swiss cheese" model of human error provides a useful construct for analyzing medical errors. In this model, holes in multiple defensive layers line up to produce a major error, much like lining up holes in a stack of slices of Swiss cheese.[20] A review of this case reveals several holes, or checkpoints, where the error was not detected. The prescribing physician wrote an incorrect dose, which was not detected by the pharmacist filling the prescription. The patient's parent did not understand the change on the medication label. Physicians in 2 EDs as well as the admitting inpatient team failed to check the correct pediatric dose of clonidine as well as common side effects of clonidine overdose.

Recognizing how and why an error occurred in this case highlights how the overdose could have been prevented or recognized earlier. For example, computerized drug programs can help calculate and check dosing, which could have helped detect the prescribing error before administration of the higher dose or upon admission to the ED. Writing out weight-based dosing on prescriptions as well as medication vials can provide an additional checkpoint for physicians and pharmacists.[17] Parents should be educated on the side-effect profiles and potential toxicity of medications that their children take.[12] A more detailed initial medication history might have detected the error earlier. Physicians could receive additional training in taking medication histories.[16] Parents can help the history-taking process by bringing medication vials to the hospital. Medical personnel who work with pediatric populations should always check proper pediatric doses of unfamiliar medications. In cases where a toxic ingestion is suspected, side-effect profiles of all medications should be reviewed. Finally, pharmacists and nurses can review medication orders for appropriate doses and intervals.[17]

Key Point

Medical errors occur when multiple checkpoints are missed. Ensuring that each professional involved carefully reviews medication dosing can reduce medication errors.

CONCLUSION

Acute mental status change in children has a broad differential diagnosis. Evaluation is best guided by a thorough history and physical examination. In patients with complicated medication regimens, medication errors should be considered. This patient presented with drowsiness, hypotension, bradycardia, and ataxia after receiving clonidine at 10 times the intended dose. Clonidine has become increasingly popular as an adjunctive therapy for ADHD, and toxic exposures to clonidine have risen. Medication errors occur when multiple checkpoints are missed. When a toxic exposure is suspected, health care practitioners should confirm pediatric dosing and review the toxic effects of unfamiliar drugs. **HP**

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(continued on page 49)

(from page 44)

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