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Selected Topics: Toxicology

DEXTROMETHORPHAN- AND PSEUDOEPHEDRINE-INDUCED AGITATED PSYCHOSIS AND ATAXIA: CASE REPORT

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□ **Abstract**—Pseudoephedrine and dextromethorphan are therapeutic constituents of numerous commonly used, over-the-counter cough and cold preparations. Although this drug combination is generally considered quite safe if utilized in recommended doses, overmedication or overdose can result in serious neurologic and cardiovascular abnormalities that occasionally can be life-threatening. We present a case of a 2-year-old child who developed hyperirritability, psychosis, and ataxia after being overmedicated with a pseudoephedrine/dextromethorphan combination cough preparation, and discuss probable mechanisms of toxicity and risk factors for adverse events. © 1999 Elsevier Science Inc.

□ **Keywords**—dextromethorphan; pseudoephedrine; toxicity; pediatric

INTRODUCTION

Pseudoephedrine (PE) and dextromethorphan (DM) are the principal therapeutic agents in a number of over-the-counter cough and cold preparations in widespread use. Overall, these agents are generally considered quite safe by health professionals and parents alike (1). Improper dosing, abuse, or intentional overdosage can result in severe neurologic and cardiovascular adverse effects. We present a case of PE/DM overmedication in a 2-year-old child resulting in hyperirritability, psychosis, and ataxia.

CASE REPORT

A 2-year-old, 10.8-kg male child, with no significant prior medical history, was brought to our Emergency Department (ED) by his mother and baby-sitter with complaints that the child was acting bizarrely and “walking like he’s drunk.” The child had experienced upper respiratory symptoms the prior 2 days and received three doses of one and a half teaspoonsful of Robitussin CF[®] cough preparation (pseudoephedrine [15 mg] with dextromethorphan [7.5 mg]/5 mL) spaced 6 h apart on the day of admission only. After the last dose (3 h before presentation), the child slept for 1 h but awoke in a state of hyperexcitability, irritability, incoherent babbling, and difficulty maintaining his balance. The physical examination was remarkable for hyperactivity, ataxia, dilated (4 mm) reactive pupils, and an initial tachycardia of 180 beats per minute (bpm). A 12-lead cardiogram 30 min after ED arrival demonstrated a heart rate of 130 bpm without evidence of ischemia or dysrhythmia, and blood pressure was 100 mmHg systolic. At this point, his speech seemed normal, and his mother corroborated this improvement over his earlier altered speech pattern, but the ataxia and hyperactivity persisted. A computed tomography (CT) scan of the head was normal. Urinalysis was unremarkable (urine pH 6.0). Toxicologic testing on blood drawn approximately 3.5 h after the last medication

dose reported serum dextromethorphan ($240 \times 10^{-6} \mu\text{g}/\text{mL}$) and pseudoephedrine levels ($2.2 \times 10^{-3} \mu\text{g}/\text{mL}$) (2–4). The child's status normalized over an observation period of 4 h in the ED, and he was discharged uneventfully. As per existing regulations, Institutional Review Board approval was not required for this case report.

DISCUSSION

Pseudoephedrine, a stereoisomer of ephedrine demonstrating both alpha- and beta-sympathomimetic effects, directly stimulates adrenergic receptors and causes the release of stored norepinephrine from neurons, resulting in enhanced sympathetic tone and central nervous system (CNS) stimulation (5). Clinically, the vasoconstrictive properties of PE are employed for its decongestive effects on nasal mucous membranes (4). The volume of distribution of PE is 2.0 to 3.0 liters (6), and the average half-life ($t_{1/2}$) of 7 h, impacted significantly by urinary pH, decreases to 1.6 h at a pH of 5.6 (5). It undergoes mainly renal excretion with minor hepatic metabolism (6). The usual adult dose is 60 mg four times daily, and 4 mg/kg/day in four divided doses for children (7,8). The drug is well-tolerated by most adults, with tachycardia and elevated blood pressure generally noted only in daily doses > 180 mg (5). Children may be especially susceptible to adverse effects of PE, and although most such events in the pediatric literature deal with combination drugs (e.g., PE with dextromethorphan, triprolidine, etc.), making it difficult to allocate the adverse effects of individual constituent agents, PE alone has been associated with hallucinations, behavioral abnormalities, and seizures (9,10). Overdose, overmedication, or enhanced susceptibility to PE may result in significant cardiovascular (tachycardia, hypertension, dysrhythmias, myocardial infarction) or CNS (agitation, psychosis, paranoia, hallucinations, seizures, intracranial hemorrhage) adverse effects (5,10,11). Serum PE levels are rarely reported, and toxic serum levels have not been identified, but a serum level of $1.42 \times 10^{-3} \text{mg}/\text{mL}$ was noted in a hemodialysis patient with a toxic psychosis who had been taking PE for 2 weeks (6). Some potential risk factors for PE toxicity include renal failure, concomitant use of herbal preparations containing ephedrine or ephedrine-like substances (e.g., ma huang, ginseng, khat, etc.), thyrotoxicosis, underlying behavioral disorders, uncontrolled hypertension, and concomitant monoamine-oxidase inhibitor use (5,12–15).

The dextro-rotatory isomer of the synthetic opioid levorphanol, DM was developed as a CNS antitussive agent (16). It acts at CNS sigma opiate receptors and both enhances release and prevents reuptake of serotonin, as well as antagonizing *N*-methyl-D-aspartate recep-

tors (17). It is metabolized by the P-450 2D6 enzyme to its active metabolite, dextrorphan, which is generally acknowledged to account for most of DM's effects (18,19). Dextrorphan binding of phencyclidine (PCP) receptors accounts, in part, for its abuse potential as a hallucinogen as well as its toxic effects (e.g., hallucinations, tachycardia, hypertension, ataxia, nystagmus) (19). Abusers of DM have reported that its effects are reminiscent of LSD or PCP experiences, and epidemics of DM abuse have been reported in the U.S. and abroad (19–22). The pharmacological $t_{1/2}$ of 2 to 4 h is less than the duration of effect (3 to 6 h), and serum levels after a single 20-mg oral dose of DM are < 2 ng/mL but may be upward of 8 ng/mL in individuals who are slow metabolizers of the drug (2,18). One case of respiratory depression due to DM was associated with a serum level of $100 \times 10^{-6} \text{mg}/\text{dL}$ (2). The usual oral dose for children is 1 mg/kg/24 h in four divided doses (23). Risk factors for adverse effects with DM include use of long-acting DM preparations and concomitant MAO-inhibitor or serotonin-reuptake inhibitor drug use (17,24,25). An additional risk factor is altered DM metabolism in some individuals due to recognized P-450 2D6 enzyme genetically determined polymorphism (26).

Utilizing weight-based dosing recommendations, our patient should have been receiving 1/3 teaspoonful of DM (0.25 mg/kg) and 3/4 teaspoonful of PE (1 mg/kg) every 6 h, but was receiving one and a half teaspoonsful of a combination preparation (8,23). This amount of drug equilibrated to doses 450% and 225% above recommendations for DM and PE, respectively, with subsequent overmedication and resultant toxicity. Significant overlap in clinical effects of both drugs precludes allocation of symptomatology of the individual agents, save for ataxia, which has been reported with DM but not PE. Some of the signs and symptoms noted in our patient are also observed in the serotonin syndrome associated with both DM and PE (27). However, the lack of febrile response and muscular rigidity, as well as the rapid return to baseline status, mitigate against the serotonin syndrome in this patient (25).

Toxic serum DM and PE levels have not been determined, and there seems to be great individual variability in response to these drugs. Fortunately, their relatively short $t_{1/2}$ makes most toxicity short-lived, and good supportive care is the mainstay of therapy (15). Nonetheless, PE and DM overdoses have resulted in toxic manifestations for periods of 24 h or more, and one pediatric PE overdose required a 2-day hospitalization (10,19). Naloxone has been successfully employed to reverse ataxia and respiratory depression in cases of DM toxicity and, although its ultimate role remains uncertain, warrants consideration (2,16,18). We elected not to use naloxone because of theoretical concerns that, in the face of on-

going PE toxicity, blockade of endogenous opioids that modulate blood pressure might result in CNS excitability and precipitate a hypertensive crisis (28). Severe hypertension following PE ingestion has been treated successfully with both a combination alpha/beta-blocker (labetalol) and beta-blocker (propranolol) alone (29,30). Labetalol's alpha-blocking effects are significantly less than its beta-blocking properties, and, theoretically, unopposed alpha effects could still occur with this drug. Both DM and PE are rapidly absorbed, and gastric lavage is unwarranted more than 60 min after a toxic ingestion (4,18,31). Insufficient data exist to support or exclude the use of charcoal, though administration more than 60 min after toxic ingestion is likely to be less efficacious than early administration (32). Urinary acidification, while theoretically sound, is generally not employed in PE toxicity because the urine is generally somewhat acidic, and associated rhabdomyolysis is possible (15). However, at urine pH > 7.0, the rate of PE excretion is dependent upon urine flow, making it important that the clinician ensure adequate urinary flow in toxic states (5).

Experience over the past decade with DM- and PE-containing preparations suggests that adverse effects to over-the-counter cough and cold medications may be considerably higher than previously entertained (9,33). Clearly, education of parents or other caretakers in appropriate dispensing of medications can lead to reduced treatment failures and drug toxicity, and should be a priority for prescribing physicians and pharmacists dispensing these drugs (34). Methods for minimizing the potential for toxicity from these products include use of single agents rather than combination ingredients to diminish possible adverse drug interactions and toxicity. Also, as highlighted in the present case, the different medication volumes for individual drug components, based on accepted weight-based dosing regimens (i.e., 1/3 teaspoonful of DM and 3/4 teaspoonful of PE for our patient), make accurate dosing of combination preparations especially difficult and may result in over-administration of individual components. Parental or caretaker instruction in appropriate indications for administration, the use of calibrated dispensing instruments (e.g., syringes) for accurate dosimetry, and careful weight-based dosing rather than use of age-based dosages utilizing relatively wide age categories (e.g., 2 to 6 years) are additional measures to enhance safety (1,34). Perhaps a more important issue revolves around the use of these products in the face of increasing reports of toxicity in children and a lack of supportive data on efficacy (1). Since other symptom-relieving measures (e.g., nasal suction, humidification, increased fluid intake, etc.) are safer and less expensive, perhaps the medical community should endeavor to promote these therapies as alternatives to the all-too-frequent use of cough and cold prepa-

arations (1). Emergency physicians, many of whom serve as the sole medical providers for the underprivileged and uninsured, should recognize the potential for toxicity from these agents and, as advocates for preventive health measures, join our pediatric colleagues in educating the public to the dangers of these largely unproven therapies as well as suggesting alternate methods for symptom relief.

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