

# Toxicity of Over-the-Counter Cough and Cold Medications

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**ABSTRACT.** Over-the-counter (OTC) cough and cold medications are marketed widely for relief of common cold symptoms, and yet studies have failed to demonstrate a benefit of these medications for young children. In addition, OTC medications can be associated with significant morbidity and even mortality in both acute overdoses and when administered in correct doses for chronic periods of time. Physicians often do not inquire about OTC medication use, and parents (or other caregivers) often do not perceive OTCs as medications. We present 3 cases of adverse outcomes over a 13-month period—including 1 death—as a result of OTC cough and cold medication use. We explore the toxicities of OTC cough and cold medications, discuss mechanisms of dosing errors, and suggest why physicians should be more vigilant in specifically inquiring about OTCs when evaluating an ill child. *Pediatrics* 2001;108(3). URL: <http://www.pediatrics.org/cgi/content/full/108/3/e52>; over-the-counter medications, cough and cold preparations, morbidity, mortality, phenylpropanolamine.

ABBREVIATIONS. OTC, over-the-counter; PPA, phenylpropanolamine; ED, emergency department; PICU, pediatric intensive care unit; CBC, complete blood (cell) count; WBC, white blood cell (count); bpm, beats per minute; AAP, American Academy of Pediatrics; CNS, central nervous system; FDA, Food and Drug Administration.

Colds, coughs, and upper respiratory infections are common childhood illnesses. The average child suffers from 6 to 10 colds per year, and each cold can last from 10 to 14 days, providing several days and nights of discomfort for the child as well as for his/her caregiver.<sup>1</sup> Many times parents will turn to one of many hundreds of cough and cold preparations for relief. However, over-the-counter (OTC) cough and cold preparations—although generally safe—have no demonstrated benefit. No studies have proven the efficacy of cough and cold preparations in facilitating recovery from these illnesses,<sup>2-6</sup> and most children will eventually improve on their own. However, a small number of children may suffer significant adverse effects from the administration of the very cough and cold formulations they were given in an attempt to relieve their symptoms. For example, the Food and Drug Administration recently issued an advisory to re-

move phenylpropanolamine (PPA)—a common constituent of OTC decongestants—from those products because of concern for increased risk of hemorrhagic stroke.<sup>7,8</sup> We present 3 cases of children who suffered significant morbidity from OTC cough and cold preparations requiring admission and treatment in a tertiary care hospital during a 13-month period; they ranged from a self-limited reaction requiring an intensive care unit admission to death in 1 patient. Because no cases of death or heart failure attributable to OTC cough and cold preparations have been reported in recent literature, these cases are presented to serve as points for additional discussion on the risks of OTC cough and cold preparations in children.

## CASE REPORTS

### Case 1

A 36-month-old boy was transferred to the pediatric emergency department (ED) from an outside hospital for lethargy and vomiting. Several hours earlier, the child's mother had given her son an unspecified amount of Dimetapp (Whitehall-Robins, Madison, NJ) cold syrup containing PPA (12.5 mg/5 mL) and brompheniramine (2 mg/5 mL). His past medical history was remarkable for prematurity and hydrocephalus with ventriculoperitoneal shunt placement as a result of child abuse.

On arrival to the ED, the patient was lethargic, bradycardic, tachypneic, and hypertensive. Physical examination revealed equal, but sluggishly reactive pupils, and slightly increased tone. Shunt survey showed no evidence of shunt disruption, and computerized tomography scan of the head was within normal limits. A pediatric neurosurgeon evaluated the patient, and determined—without tapping his shunt—that shunt malfunction was not the source of the child's altered mental status. Urine toxicology testing demonstrated the presence of brompheniramine, while all other laboratory investigations were normal.

He was admitted to the pediatric intensive care unit (PICU) for additional observation, where he was given intravenous fluids and close monitoring. His activity level and mental status improved spontaneously over the next several hours. He was discharged from the hospital from the PICU with a diagnosis of mental status change secondary to antihistamine and sympathomimetic ingestion.

### Case 2

A 35-month-old boy was seen at a community ED with a chief complaint of fever to 104°F. A complete blood (cell) count (CBC) revealed a white blood cell (WBC) count of 8400 with 33% bands and 27% neutrophils. A blood culture was sent, and a chest radiograph obtained, which was read as findings consistent with a left lobe infiltrate and cardiomegaly. He was treated with intramuscular ceftriaxone and discharged from the hospital with instructions to follow-up with his pediatrician the next day.

In his primary care clinic the next day, his parents reported that he had had intermittent fevers for 3 weeks, along with cough and rhinorrhea, prompting the ED visit. He had been eating and drinking well. When asked about medications, his parents said he was only taking Tylenol (McNeil Consumer Healthcare, Fort Washington, PA) as instructed for fever. His vital signs were: temperature, 37.3°C axillary; pulse, 150 beats per minute (bpm);

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and respirations, 40 breaths per minute. He was tired-appearing, but cooperative. His physical examination was notable for mild yellow rhinorrhea and tachycardia on heart examination without murmurs, gallops, or rubs.

A chest radiograph was repeated because of the report of cardiomegaly. His heart size was within normal limits and there was no evidence of a focal infiltrate. An electrocardiogram was obtained for persistent tachycardia in the absence of fever, and demonstrated only sinus tachycardia. An echocardiogram was performed to further evaluate the etiology of tachycardia, and it revealed a mildly dilated left ventricle and moderate left ventricular dysfunction. He was admitted to the cardiology service for additional evaluation of possible myocarditis or cardiomyopathy, and was scheduled for cardiac catheterization.

The patient continued to have persistent tachycardia in the hospital. His parents repeatedly denied administering any medications other than Children's Tylenol (McNeil Consumer Healthcare, Fort Washington, PA), and also denied the possibility of ingestion of any other preparations. However, when his parents produced the bottle of Tylenol, which they had been using for fever, the bottle was labeled Children's Tylenol: Cold, which contains acetaminophen (160mg/5 mL), chlorpheniramine (1mg/5 mL), dextromethorphan (5mg/5 mL), and pseudoephedrine (15mg/5 mL). His urine toxicology screen revealed 2 metabolites of chlorpheniramine. His tachycardia slowly resolved before discharge on hospital day 3. His left ventricular function as determined by echocardiogram improved during the hospitalization, and had returned to within normal range 2 weeks after discharge.

### Case 3

A 9-month-old boy was referred to the ED by his primary care physician for evaluation of persistent crying and fever. His mother stated that the symptoms had started 6 days previously with a fever to 102°F, although the child had had a cough without rhinorrhea for several weeks. Throughout the week, the child had been fussy and nonconsolable, according to the mother, and had not slept at all for the 3 nights before being seen in the ED. His mother denied diarrhea, but reported emesis 3 times per day. His mother reported only giving him ¼ dropper of Motrin (Pharmacia Upjohn, Peapack, NJ).

Vital signs on arrival in the ED were: temperature, 39.5°C; pulse, 208 bpm; respirations, 40 breaths per minute; and blood pressure, 121/78 mm Hg. Physical examination was notable for a screaming infant, immobile, erythematous tympanic membranes, tachycardia without murmur, and brisk capillary refill. Because of his persistent irritability and fever, an evaluation for meningitis/sepsis was performed, and was normal (WBC of 7600, urine analysis with 3–5 WBCs and cerebrospinal fluid with 8 WBC per high-power field and negative Gram stain). Several hours after presentation, the infant was noted to be alert, active, and playful, and tolerating oral liquids. He was given intramuscular ceftriaxone and was discharged from the hospital with instructions to return to the ED the following day for reevaluation.

Approximately 12 hours after discharge, the infant was brought back to the ED in full cardiopulmonary arrest. By report he had gone to bed at 4 am, and had been sleeping with his grandmother. When the grandmother awakened at 11:30 am, the child was blue and apneic. The paramedics were called and he was brought to the ED with cardiopulmonary resuscitation in progress. On arrival, the child was cyanotic, cold, and slightly stiff. Initial temperature was 35°C rectally; no other vital signs could be obtained. Blood pH was 6.35; glucose, 20 mg/dL; serum sodium, 167 mEq/L; and potassium, 10.5 mEq/L. Advanced life support was conducted for approximately 20 minutes, but was unsuccessful, and the child was pronounced dead.

An autopsy by the medical examiner revealed no gross abnormalities of any organs including the brain and heart, and no evidence of traumatic injuries. Postmortem urine toxicology testing revealed acetaminophen, pseudoephedrine, chlorpheniramine, dextromethorphan, and PPA. Postmortem blood analysis from the heart revealed markedly elevated levels of several substances. The level of pseudoephedrine was 10.0 mg/L; PPA, 1.4 mg/L; and dextromethorphan, 0.6 mg/L. Postmortem liver analysis showed a concentration of pseudoephedrine of 14.0 mg/L and PPA of 0.5 mg/L. After review of the autopsy findings and tests, the medical examiner determined the cause of death as mixed drug intoxication secondary to ingestion of these drugs.

Additional investigation and questioning of the caretakers revealed numerous doses of OTC cough and cold preparations had been given to the infant. A criminal investigation ensued; however, it was determined that the OTC cough and cold medicines were not intentionally given in toxic doses.

### DISCUSSION

OTC cough and cold preparations are nearly ubiquitous, and are marketed for the relief of those most irritating symptoms of the common cold: rhinorrhea and cough. Although they may alleviate some symptoms in adolescents and adults,<sup>2</sup> many studies have demonstrated that OTC cough and cold preparations do not achieve such claims in the younger pediatric population.<sup>2–6</sup> In fact, studies in children of the immediate,<sup>5</sup> short-term<sup>4</sup> (within 48 hours), and long-term<sup>3</sup> (after 72 hours) effects of cough and cold preparations showed no significant difference between OTC medications and placebo in the reduction of cough. In addition, OTC cough and cold medications are associated with potentially serious side effects.<sup>7–20</sup>

In 1997, the American Academy of Pediatrics (AAP) issued a statement on the use of codeine- and dextromethorphan-containing cough remedies in children, concluding that physicians should clearly educate parents about the known risks and lack of benefits of these medications.<sup>6</sup> We chose to report these cases because they represent the range of severity of adverse outcomes that can be seen with OTC cough and cold preparations. In addition, a review of the recent literature does not reveal reports of heart failure or death attributable to such medications. Finally, our case reports from a single institution reflect 3 episodes in just over 1 year that required admission, and most likely only represent the “tip of the iceberg” of adverse outcomes attributable to OTC cough and cold preparations.

The potential toxicities of cough and cold medicines vary with their composition. Many products contain multiple substances including a decongestant, cough suppressant, antihistamine, and/or antipyretic/analgesic. Pseudoephedrine and PPA are sympathomimetics that reduce nasal congestion by stimulating the  $\alpha$ -adrenergic receptors on vascular smooth muscles. Clinical toxicity presents with central nervous system (CNS) stimulation, hypertension, and tachycardia with ephedrine or pseudoephedrine ingestion, and bradycardia with PPA ingestion.<sup>10–12</sup> CNS stimulation can manifest as extreme agitation, restlessness, insomnia, psychosis, and seizures. Serious complications after decongestant ingestions and/or overdoses include hypertension, tachycardia, bradycardia, seizures, stroke, and cerebral hemorrhage.<sup>10,13–14</sup> Dysrhythmias, myocardial infarction, and ischemic bowel infarction have also been reported.<sup>9,11,12,16,17</sup>

A comprehensive review of >100 case reports of adverse drug effects involving PPA described 24 cases of intracranial hemorrhage—8 with seizures and 8 fatalities—between 1965 and 1990.<sup>11</sup> PPA toxicity may present with agitation, psychosis, seizures, chest pain, or headache.<sup>12</sup> Hypertension is common after overdose and some patients may also present with confusion and altered mental status as a result

of hypertensive encephalopathy. Many reports of severe hypertension after therapeutic and toxic doses of PPA have been published, some of which resulted in intracranial hemorrhage and death.<sup>7,13,14</sup> Reflex bradycardia may accompany the hypertension, which distinguishes toxicity from this drug and other sympathomimetics. Toddlers may be at increased risk for hypertensive episodes with unintentional ingestions because of the relatively significant mg/kg dose ingested. Recently, the Food and Drug Administration (FDA) started taking steps to remove PPA from all drug products and has requested that all drug companies discontinue marketing products containing PPA,<sup>8</sup> after results of a study found an increased association between PPA use and hemorrhagic stroke in women.<sup>7</sup> Although this risk of stroke is very low, the FDA has significant concerns resulting from the seriousness of this adverse event and the inability to currently predict who is at risk for this complication.

Many cough and cold preparations even include antihistamines such as chlorpheniramine and brompheniramine although histamine has not been shown to contribute to the symptoms seen in the common cold.<sup>15</sup> Adverse effects and clinical toxicity of antihistamines are characterized by a spectrum of anticholinergic symptoms and CNS depression. Tachycardia, blurred vision, agitation, hyperactivity, toxic psychoses, and seizures may be evident. Cardiac dysrhythmias including torsades de pointes have also been reported.<sup>15,18</sup> Dextromethorphan, an antitussive, has also been associated with toxic side effects such as lethargy, stupor, hyperexcitability, ataxia, abnormal limb movements, and coma.<sup>18</sup>

We cannot definitively prove that OTC cough and cold preparations were the cause of the symptoms in all cases. In the first 2 cases, other causes of the patients' symptoms were excluded based on diagnostic testing, repeated clinical evaluations, specialty consultation, and the resolution of symptoms over time without specific interventions. Although the presence of the antihistamines in the urine toxicology test does not establish toxicity, the symptoms and their resolution correlate with adverse effects from the drug and timing of its metabolism. There have been no previous reports of cardiac dysfunction in children specifically with the use of OTC sympathomimetic agents. However, there has been good evidence that demonstrates cardiomyopathy and valvular abnormalities, as well as cardiac dysrhythmias and conduction abnormalities that can result from exposure to amphetamines that are also sympathomimetic agents.<sup>19,20</sup> We hypothesize that the patient in the second case developed left ventricular dysfunction because of sustained tachycardia from the ingested sympathomimetic and antihistamine agents.

In the third case, postmortem drug concentrations from the heart revealed elevated concentrations of pseudoephedrine and PPA. However, therapeutic and toxicity data on serum and postmortem drug concentrations in children is limited. Therapeutic blood concentrations of pseudoephedrine are reported to be between 0.21 and 0.77 mg/L.<sup>21</sup> In 1 report, a 2-year-old child believed to have ingested a

large amount of pseudoephedrine tablets was found dead with a postmortem blood level of 66.0 mg/L.<sup>22</sup> Another fatal overdose demonstrated a pseudoephedrine concentration of 19.0 mg/L in the blood and 33.0 mg/L in the liver.<sup>23</sup> For PPA, therapeutic concentrations in males have been reported to be between 0.11 and 0.40 mg/L.<sup>24</sup> Fatal cases of PPA ingestions have reported postmortem blood concentrations of 2.0 mg/L and 4.6 mg/L.<sup>22</sup> Similarly, for dextromethorphan, therapeutic drug concentrations vary widely and have been reported to average from 2.4  $\mu$ g/L to 207  $\mu$ g/L.<sup>25</sup> Two fatalities in adults reported dextromethorphan concentrations of 3.3–9.2  $\mu$ g/L in blood.<sup>26</sup> Although there are limitations in interpreting postmortem drug concentrations in the blood and determining cause of death—especially in the context of limited data in children—the values in our report are elevated and definitely confirm that multiple substances were present in this infant's body at the time of death. Furthermore, we are unaware of any OTC cough and cold preparation that contains both pseudoephedrine and PPA, again confirming that this infant had been given at least 2 different preparations. Given the child's age, the circumstances of his death, and the finding of significantly elevated levels of these drugs, other diagnoses such as sudden infant death syndrome are unlikely. With evidence of at least 2 cough and cold preparations in his system, it is possible that this infant suffered a dysrhythmia from these drugs, which led to his death.

Cough and cold medicines, therefore, are not administered without risk. In 1 analysis of poison control reports of 249 038 exposures to cough and cold preparations in children <6 years old, there were 72 "major events" and 4 deaths.<sup>27</sup> These numbers are probably falsely low resulting from reliance of this data on voluntary reporting. Other children may have adverse outcomes from cough and cold preparation use, but may not be reported to the poison control centers due to self-limited reactions, failure to recognize the reaction (eg, the child slept through the sedation), lack of reporting by the medical facility, or a lack of acknowledgment that OTC medications had been administered.

In addition to side effects of the various ingredients, OTC cough and cold preparations also present potential hazards due to dosing errors. The first and third case reports demonstrate negative outcomes attributable to acute and chronic dosing errors. Little published data exists on levels of OTC cough and cold preparations in infants and children; thus, dosing guidelines historically have been extrapolated from adult data, making them imprecise for children.<sup>6</sup> In 2 studies, caregivers reported that they primarily followed dosing guidelines on the medication package<sup>28,29</sup>; however, this too allows for many potential errors. They can misunderstand the recommended dose, frequency or length of therapy, use an incorrect measuring device, or even give the wrong preparation.<sup>30,31</sup> In our second case report, well-intentioned parents were giving their child what they perceived to be only an antipyretic; however, because of package labeling—the Cold portion of the

name Children's Tylenol: Cold was in much smaller print—they did not realize that what they had actually been giving was a cough and cold preparation.

Some parents may intentionally give children supratherapeutic doses of cough and cold preparations, exceeding either the recommended dose amount or length of therapy. When appropriate doses of pediatric formulations don't achieve the desired outcome, parents may increase the dose, or give adult preparations that may be perceived as stronger.<sup>32</sup> Kapasi et al<sup>28</sup> noted in a study of acetaminophen use, that a significant percentage of poisonings from acetaminophen were secondary to excessive dosing, rather than unintentional ingestion. In the third case report, the child tragically died from an overdose of cough and cold medications that likely had been persistently administered because of continued symptoms in the child.

Other parents, while recognizing that OTC cough and cold medications do not relieve the cold symptoms, may continue to use these medications for 1 of the side effects—sedation.<sup>5,33</sup> Additionally, many parents may simply be unaware of the potentially serious side effects of OTC cough and cold medications.<sup>28</sup>

Despite the risks of OTC cough and cold medicines, many parents believe they should treat their children's cold symptoms with medication.<sup>4</sup> Cold remedies are a formidable industry; in 1990 alone, nearly \$2 billion was spent on OTC cough and cold preparations nationwide.<sup>33</sup> In 1991, Hutton et al<sup>4</sup> conducted a randomized, controlled trial evaluating the efficacy of an antihistamine-decongestant preparation versus placebo, and noted that parents reported greater symptom improvement in children who received medicine even if it was a placebo. This parental observational bias suggests that parents in this study felt the need to treat their children's cold symptoms, and perceived more improvement when they received therapy.

The opportunity for physician-providers to educate parents about OTC medications is tremendous; but it is often missed. Many times, physicians fail to ask specifically about OTC medication use in the evaluation process, presuming that when asked about medicine use parents will include all medicines. However, most parents perceive questions about medications as pertaining to prescription medications only, and not OTC medications. This was evident in the third case report, where the parent revealed antipyretic use, but not the use of a cough and cold medicine, and the issue was not further explored. It is possible that some physicians are concerned that inquiring about OTC medicines and other, alternative therapies, may offend their patients; however, this has not been substantiated. One study of OTC medicine use and provider attitudes concluded that providers should routinely ask their patients about OTC use, and that patients would be appreciative of their providers' inquiries.<sup>34</sup>

Many providers fail to give specific instructions on OTC cough and cold medication use even when they are aware that the patient is using them.<sup>29</sup> In addition, some providers have a lack of knowledge re-

garding the various ingredients in cough and cold preparations. Finally, not only are many physicians unsuccessful in educating parents about the risks of OTC cough and cold preparations, some physicians continue to prescribe them for their patients—despite their lack of demonstrated efficacy. Gadowski and Horton<sup>33</sup> described 2 such cases where a physician-prescribed cough and cold preparation produced an adverse outcome in the patient because of inappropriate dosing by the parents. Although the AAP guidelines do not state that physicians should not prescribe OTC cough and cold preparations, they do clearly state that physicians have a responsibility to educate parents about the lack of benefit and known risks of OTC cough and cold preparations. It is our belief that for those families who insist on using OTC cough and cold preparations, physicians should negotiate to discontinue use in 2 days if there is no appreciated benefit.

## CONCLUSION

Three cases of children experiencing significant adverse effects and toxicity from OTC cough and cold preparations are presented. Health care providers have the opportunity to intervene by inquiring specifically about OTC cough and cold medication use, and by educating parents on the lack of demonstrated benefit and known risks in the pediatric population—as recommended by the AAP.

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