Cold Medications
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Özet
Soğuk Algınlığı İlaçları

Anahtar kelimeler: Soğuk algınlığı ilaçları, pseudoefedrin, öksürük

Abstract
Colds, coughs, and upper respiratory infections are common childhood illnesses. Cough and cold medications are marketed widely for relief of common cold symptoms. However, minimal data exist to support their effectiveness. Studies have failed to demonstrate a benefit of these medications for young children. In addition, adverse effects and over-dosage associated with the administration of cough and cold preparations in children have been reported. We explore the toxicities of cold medications, and suggest why physicians should be more vigilant about these drugs. Education of patients and parents about the potential risks of these products is needed.

Key words: Cold medications, pseudoephedrine, cough

Introduction
Based on concerns about safety and efficacy, international authorities have either advised against the use of cough and cold medication or considering such action. We aimed to systematically review the evidence for the effectiveness and safety of cough and cold medicines in children.

Colds, coughs and cold medicines in children
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 parents (1). Respiratory tract infections are the most common diseases in children, but their home treatment is often far from proper (2,3). Without basic knowledge of the ailments concerning children, parents may worry unnecessarily and also may be easily influenced in how they care for their sick children (4,5). 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 (6,7) and most children will eventually improve on their own.

Total consultation rates in general practice for acute respiratory infections in children under the age of 4 were over 13 000 per 10 000 patient years in 1991/92 in the UK (8) and a survey in the USA reported that almost 40% of preschool children had been given one or more OTC cold medications during the preceding month (9). The NHS direct healthcare guide recommends simple cough medicines for dry cough (10). By 2002, all National Health Service (NHS) direct sites nationally will be able to refer callers to their local pharmacy, where appropriate, for advice on OTC medications (11). Every week %10 of American children will use OTC medications.
Children 2 to 5 years of age are the most common users of such preparations, followed by children younger than 2 years of age (12). The current interest in restricting cough and cold medicines began with a ‘citizen petition’ to the US Food and Drug Authority (FDA) in 2007. The citizens were mainly academic paediatricians and health administrators. While the FDA is yet to rule on the petition, major drug companies have voluntarily withdrawn cough and cold medicines for children under 4 years old. Currently available cough and cold pharmaceuticals for children contain an antitussive, an antihistamine a decongestant or an expectorant, or combinations of these (Table 1).

<table>
<thead>
<tr>
<th>Table</th>
<th>Drugs used in cough and cold medicines for children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihistamines</td>
<td>Brompheniramine maleate, chlorpheniramine maleate, dexchlorpheniramine maleate, diphenhydramine hydrochloride, doxylamine succinate, pheniramine maleate, promethazine hydrochloride, promethazine hydrochloride, triprolidine hydrochloride</td>
</tr>
<tr>
<td>Antitussives</td>
<td>Codeine phosphate, dextromethorphan hydrobromide, dihydrocodeine tartrate, pentooxyverine citrate, pholcodine</td>
</tr>
<tr>
<td>Mucolitics</td>
<td>Ammonium chloride, bromhexine hydrochloride, guaifenesin, ipecacuanha</td>
</tr>
<tr>
<td>Decongestants</td>
<td>Phenylephrine hydrochloride, pseudoephedrine hydrochloride, oxymetazoline hydrochloride, xylometazoline hydrochloride</td>
</tr>
</tbody>
</table>

The three main components of most cough and cold medications are antihistamines, decongestants, and antitussives.

**Antihistamines**

Antihistamines are used for the treatment of the symptoms of the common cold, acute cough, nasal congestion and allergic rhinitis. A cochrane review of antihistamines for the common cold concludes that antihistamine monotherapy did not improve nasal congestion, rhinorrhoea, sneezing or the subjective symptoms of the common cold in children and adults. The Cochrane review concluded that first-generation antihistamines cause more side effects than placebo, particularly an increase in sedation for patients with the common cold (13,14). Diphenhydramine, the most cardiotoxic of the antihistamines reported in children and numerous deaths from it have been reported in children (15). Adverse effects of antihistamines are arrhythmia, blurred vision, dizziness, dry mouth, hallucinations, heart block, paradoxic excitability, respiratory depression, sedation, tachycardia and urinary retention (16).

**Antitussives**

Antitussives are a class of medication that reduce coughing by acting on the cough center in the brain. They are used to treat non-productive or dry, hacking non-productive coughs that prevent you from sleeping or resting adequately. Narcotic antitussives, which may contain codeine, dihydrocodeine, hydrocodone or hydromorphone, reduce coughing by suppressing your central nervous system. Codeine appears to cause more adverse effects than other opioid-type antitussives and reports of fatal cases because of respiratory depression and cyanosis (14,17).

Antitussive side effects that need immediate medical attention and must be reported to your doctor immediately include difficulty breathing or swallowing, fast heartbeats, pounding heartbeats or irregular heartbeats, rashes, itching, hives, changes in vision and seizures. Adverse effects in babies are difficulty nursing, increased sleepiness, limpness and difficulty breathing (18).

**Mucolitics**

There are no studies of ipecacuanha, ammonium chloride or bromhexine for acute cough in children (14,16).

**Decongestants**

The three most commonly used oral decongestants are pseudoephedrine, phenylephrine, and phenylpropanolamine. These agents cause direct presynaptic catecholamine release and also may block catecholamine reuptake and influence enzymes slowing catecholamine breakdown. Blood pressure elevation often is accompanied by a reflex bradycardia caused by the baroreceptors and results in postural hypotension. Clinical manifestations result from a direct effect on adrenergic receptors in muscles and glands and stimulation of the respiratory center and CNS. They are absorbed readily from the gastrointestinal tract (except for phenylephrine because of irregular absorption and first pass metabolism by the liver) and attain a high concentration in the CNS. Peak plasma concentrations are achieved within 1-2 hours after oral administration. Cochrane review concluded that there was insufficient evidence for the use of nasal decongestants in children (14,19). There is limited data on safety of phenylephrine also a review found no support for phenylephrine usage in common cold (14, 20).
In general

There is a little evidence for the effectiveness of OTC cough medicines in children with acute upper respiratory tract infections. Two previous reviews on this topic, which did not show OTC products to be better than placebo in relieving symptoms of acute cough in children (6-12, 21). There are some significant adverse effects from the administration of the very cough and cold formulations. For example, the Food and Drug Administration recently issued an advisory to remove phenylpropanolamine (PPA) - a common constituent of OTC decongestants - from those products because of concern for increased risk of hemorrhagic stroke (22,23).

Most cough and cold suppressant preparations are marketed as mixtures of dextromethorphan and codeine with antihistamines, decongestants, expectorants, and/or antipyretics. Some nonprescription preparations subside diphenhydramine or eucalyptus oil in place of codeine or dextromethorphan. These preparations are nearly ubiquitous, and are marketed for the relief of those most symptoms of the common cold. Studies in children of the immediate (24), short-term (25) (within 48 hours), and long-term (26) (after 72 hours) effects of cough and cold preparations showed no significant difference between OTC medications and placebo in the reduction of cough. OTC cough and cold medications are associated with serious side effects (22-27).

The potential toxicities of cough and cold medications vary with their composition. Clinical toxicity presents with central nervous system (CNS) stimulation, hypertension, and tachycardia with ephedrine or pseudoephedrine ingestion, and bradycardia with PPA ingestion (28,29). CNS stimulation can manifest as extreme agitation, restlessness, insomnia, psychosis, and seizures.

Other complications after decongestant ingestions and/or overdoses include hypertension, tachycardia, bradycardia, seizures, stroke, and cerebral hemorrhage (28-30). Dysrhythmias, myocardial infarction, and ischemic bowel infarction have also been reported (29,32-35). One study about OTC medicine, presented three cases of adverse outcomes over a 13-month period-including 1 death-as a result of OTC cough and cold medication use (36). That literature revealed reports of heart failure or death attributable to such medications. Cough and cold medicines, therefore, are not administered without risk. In one 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 (37).

In addition to side effects of the various ingredients, OTC cough and cold preparations also present potential hazards due to dosing errors. Parents can misunderstand the recommended dose, frequency or length of therapy, use an incorrect measuring device, or even give the wrong preparation (38,39). Additionally, many parents may be unaware of the potentially serious side effects of OTC cough and cold medications (40). 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 (41).

American Academy of Pediatrics (AAP), guidelines state that physicians have a responsibility to educate parents about the lack of benefit and known risks of OTC cough and cold preparations. Let one study suggested 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 (36).

Health care providers educate parents about the use of OTC cough and cold medications as recommended by the AAP (7).

The number of studies suggesting OTC have played a role in pediatric morbidity and mortality should provide evidence there is a real risk in using these preparations in children. More recent data regarding OTC and pediatric deaths were published in 2009 (42). They found that of 189 cases, 118 were judged to be possibly, likely, or definitely related to OTC ingredients. Of the 118 cases, 103 involved nonprescription drugs, with 88 involving overdose. The authors found several factors associated with the fatalities: age younger than 2 years, use of the medication for sedation, combining 2 or more medications containing the same ingredient, failure to use a measuring device, product misidentification, and use of products intended for adults.

In the fall of 2008, Health Canada and the FDA released separate statements regarding the use of cold and cough medications in children. Citing a lack of evidence of efficacy and growing concerns about adverse reactions, Health Canada advised against the use of all OTC formulations in children younger than 6 years of age and suggested caution be exercised when these formulations were used in children older than 6 years of age. For similar reasons, the FDA is advising against the use of OTC in children younger than 4 years of age (43-47).
Conclusion

This review has found little support for the effectiveness of cough and cold medications for acute cough and cold medicines for acute cough or the common cold in children. However, the majority of these medicines do not appear to be highly toxic in children and is not a major cause of severe effects following unintentional poisoning. We cannot support the suggestion that in common usage, these agents are responsible for increased deaths in young children. Many cases of toxicity from cough and cold medications in young children are a result of therapeutic error, so education and restriction will play a role in the supply of these medications (42). Particular medications including diphenhydramine and codeine appear to be associated with a much higher frequency of severe adverse effects and toxicity, and their use should be reviewed given the availability of less toxic alternatives.

Further restriction of cough and cold medicines in children is supported by currently available evidence. Restriction is accompanied not only by risk (of what will be used instead) but also the opportunity of re-evaluating the phenomenon of ‘social medication’ and the best care of children with common illnesses. Both require far more study. The use of these drugs should decline, but there remains an unfilled need for proven, effective and safe medicines for acute cough and colds in children.

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