PHARMACY CORNER

E.P.C.M.S.

Why Are Cough and Cold OTC Medications Being Pulled of the Shelves?

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BACKGROUND

On October 19, 2007, the Food & Drug Administration (FDA) announced that all over-the-counter (OTC) cough and cold medications would be relabeled to exclude dosing for children aged 0-2 years.[1] This decision came about after the FDA became aware of the risk of toxicity that arose from the use of these medications, the absence of dosing recommendations for such age group, and the limited published evidence of the effectiveness for treating the symptoms of a common cold.[2] Furthermore, these medications have been blamed for adverse drug reactions (ADRs) and deaths in children less than 2 years old (<2yo).

In 2004-2005 alone, an estimated 1,519 children <2yo were treated in U.S. emergency departments for ADRs and overdoses. To date, there have been three reported deaths in infants less than six months related to the use of cough and cold products. Dextromethorphan has been associated with abnormal movements and hallucinations at standard doses, although these ADRs are not as severe as those experienced with pseudoephedrine and phenylephrine.[3] Pseudoephedrine has been associated with ADRs such as infant death, increased blood pressure, and arrhythmias.[4] Most of these reported ADRs occurred after the use of dextromethorphan or pseudoephedrine and from parents giving another medication with the same or similar ingredients.

The Consumer Healthcare Products Association (CHPA) is an association that represents most of the makers of OTC cough and cold medications used in children. Just recently, CHPA decided to voluntarily change the product labels of OTC cough and cold medicines to state ***"do not use"*** in children less than four years of age.[5] These changes are expected to take place during 2009.

OTC COUGH AND COLD MEDICATION OVERVIEW

Decongestants[6,14]

Although pseudoephedrine and phenylephrine are in the same therapeutic category, they differ in many aspects. Mechanistically, pseudoephedrine displaces norepinephrine from storage vesicles in prejunctional nerve terminals. On the other hand, phenylephrine functions by binding to alpha-adrenergic receptors. Pseudoephedrine when compared to phenylephrine has a slower onset of action, a longer duration of action, and is 100% intestinally absorbed. Therefore, pseudoephedrine doses will be lower and the frequency of dosing will be less than those of phenylephrine (only 38% absorbed). (See table 1)

Antihistamines[6, 7]

There are a variety of antihistamines available to patients. They can be divided into first generation (FGAs) and second generation antihistamines (SGAs), and are widely visible on pharmacy shelves and on direct to consumer advertisement. (See table 4)

FGAs can be further subdivided into the following classifications of ethanolamines (e.g., diphenhydramine) and alkylamine (e.g., chlorpheniramine). These antihistamines have a reported side effect profile of increased sedation and anti-cholinergic effects such as urinary retention, constipation, dry mouth, tachycardia, and dizziness. FGAs are used to relieve common allergies, allergic reactions, and motion sickness. The half-life of the FGAs is generally shorter than that of SGAs, therefore requiring more frequent dosing or a sustained release formulation.

Like FGAs, SGAs can be subdivided into several categories including piperidines (e.g. loratidine) and piperazines (e.g. cetirizine). SGAs do not cross the blood brain barrier as easily as the FGAs which make them less sedating. These antihistamines also have less anticholinergic side effects when compared to FGAs.

Cough Suppressants[8]

Cough is a natural reflex that should not be suppressed if it is productive and produces sputum upon coughing since retention of the sputum may interfere with the distribution of alveolar ventilation and the ability of the lung to resist infection. It should only be suppressed in the case that the cause is not known or specific treatment is not possible, the cough is nonproductive, and/or causes marked discomfort or sleep disturbance. It may be suppressed by the use of anti-tussives such as dextromethorphan (DM) and codeine which increases the threshold of the cough center. DM is available OTC and use in large amounts has been reported as a drug of abuse. Codeine-containing products may require a prescription in certain states. (See Table 2)

Expectorants[9-10]

The most widely known OTC expectorant is guaifenesin. Guaifenesin helps loosen phlegm and thins bronchial secretions to make coughs more productive. Its mechanism of action is believed to by irritating the gastric mucosa and stimulating respiratory tract secretions, thereby increasing respiratory fluid volumes and decreasing mucous viscosity. It has a limited to no side effect profile and can be safely used in children. Although widely used and prescribed, guaifenesin efficacy has been questioned.[11] Instead; it is recommended that patients drink plenty of water which will have a similar outcome as expectorants. (See Table 3)

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Why Are Cough and Cold OTC Medications Being Pulled of the Shelves? (Continued)

To clarify, these cough and cold products have not been pulled off the market completely, only labeling changes have been made specifically for children less than four years of age. Because providers may still be prescribing cough and cold products for children less than four years of age, it is important to review dosing. Some drug information textbooks do not provide dosing for younger children therefore older references may have been used. The tables provided in this article give some dosing recommendations, however; dosing should always be verified before prescribing, as changes may occur in recommendations.

COUNSELING POINTS FOR PARENTS[12]

- Do not give children medications that are indicated or dosed for adults only. Doses for children should be calculated based on age and weight if possible.
- Always use the medication dosage syringe, dropper, or cup that is included in the medication package to ensure exact dose is given. Avoid using kitchen spoons since they vary between 2 mL-10 mL.
- Medications should not be mixed in a bottle of milk or formula because if the child doesn't finish the bottle, he/she may not get the entire dose.
- Review the ingredients in cough and cold preparations to ensure the child is not getting a duplicate medication.
- Use caution with dosage forms since they may differ in concentrations.
  - Tylenol Infants' Drops- 80 mg/0.8 mL vs. Tylenol Children's Suspension 160 mg/5 mL
- Do not call medications "candy" since the child may consider it "candy" and ingest it without supervision.

For more information, visit the OTC Safety Website at www.otcsafety.org

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Table 1. Oral Decongestants

Medications	Peak time (hrs)	Half life (hrs)	**Adverse Effects**	Dosing	
				Adults	Children
MOA: Directly stimulates a-adrenergic receptors of respiratory mucosa causing vasoconstriction					
Pseudoephedrine, plain	1.4-2	4.3-8	Palpitations, ↑ HR, dizziness, excitability, HA, insomnia, nervousness, tremor, diaphoresis	60 mg Q 4–6 h Max: 240mg/day	6–12 y: 30 mg Q 4–6 h prn, Max: 120mg/day 2–5 y-15 mg Q 4–6 h prn, Max 60mg/day 4mg/kg/day in 4 divided doses[5]
Pseudoephedrine, SR	3.8-6.1	4.3-8		10–20 mg Q 4 h, Max:120mg/d*	6–12 y: 10 mg Q 4 h prn, Max: 60mg/day* 2–6 y: 5mg Q 4 h prn, Max: 30mg/day* 1-2 y: 1.5-3mg Q 6 h prn, Max 4 doses/day** 6mo-1yr: 0.9-1.5mg Q 6 h prn, Max 4 doses/day** 3-6 mo: 0.5-0.9 mg Q 6 h prn, Max 4 doses/day**
Phenylephrine*	0.75-2	2.62			

*Max Dose calculated by daily dose X frequency of dose
**Dose calculated from recommended combination product dosing in children <2yo[3]

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Table 2. Cough Products

Medications	Peak time (hrs)	Half life (hrs)	**Adverse Effects**	Dosing	
				Adults	Children
MOA: Depresses the medullary cough center, exerts drying effects on the respiratory tract mucosa, and increase viscosity of bronchial secretions					
Dextromethorphan	2-2.5	3.4- 29.5	Abdominal discomfort, constipation, dizziness, drowsiness, GI upset	10-20mg Q4h or 30mg Q6-8h prn Max: 120mg/day	6-12yo: 5-10mg Q 4 h or 15mg Q 6-8 h prn; Max: 60mg/24hrs 2-6yo: 2.5-5mg Q 4 h or 7.5mg Q 6-8 h prn; Max: 30mg/24hrs

Table 3. Expectorants

Medications	Peak time (hrs)	Half life (hrs)	**Adverse Effects**	Dosing	
				Adults	Children
MOA: Increases respiratory tract fluid leading to reduced viscosity of tenacious secretions					
Guaifenesin	Unknown	1	Dizziness, drowsiness, HA, rash, uric acid levels ↓, N/V, stomach pain	200-400mg Q 4 h prn Max: 2.4g/ day ER: 600mg-1.2g Q12h prn Max: 2.4g/day	6-12yrs: 100-200mg Q 4 h prn; Max: 1.2g/day ER: 600mg Q 12 h prn; Max: 1.2g/day 2-6 yrs: 50-100 mg Q 4 h prn; Max: 600mg/day ER: 300mg Q 4 h prn; Max: 600mg/day <2yrs: 12mg/kg/day in 6 divided doses prn[5]

Table 4. Antihistamines

	Medications	**Peak time (hrs)**	**Half life (hrs)**	**Children Dosing**
FGAs	Brompheniramine	2-5	11.8-34.7	6-12yo: 2-4mg q6-8 h prn Max: 12-16mg/day <6yr: 0.5mg/kg Q 6-8 h prn
	Chlorpheniramine maleate, plain	2-6	20-24 ↓children	6–12 y: 2 mg Q 4-6 h prn Max: 12mg/day 2–5 y: 1 mg Q 4-6 h prn Max: 6mg/day 0.35mg/kg/24hr prn[5]
	Clemastine fumarate[b]	2-5	Not established	6–12 y: 0.67 mg Q 12 h prn Max: 4.02mg/day
	Diphenhydramine HCl	1-4	2.4-9.3 ↓children	5 mg/kg/d divided in 4 doses prn Max: 300mg/day
	Doxylamine Succinate	2-3	10	6-12 yrs: 6.25-12.5mg Q4-6h Max: 75mg/day 2-6 yrs: 1.9-3.125mg Q 4-6 h Max: 18.75mg/day
SGAs	Cetirizine	1 hr	8	2-5yrs: 2.5 mg daily-BID Max: 5mg/day <2yrs: 2.5mg daily
	Loratadine	1-3	8-15	6–11 y: 10 mg once daily 2–5 y: 5 mg once daily

Adverse Reactions*: Sedation, ↑HR, ↑ or ↓BP, palpitations, dizziness, disturbed coordination, muscular weakness, paradoxical excitement, N/V, constipation, diarrhea, xerostomia, dysuria, blurred vision, thickening of bronchial secretions *Less common in Second Generation Antihistamines

Table 5. Antihistamine Profile

Antihistamine	**Sedative Effects**	**Antihistaminic Activity**	**Anticholinergic Activity**
First Generation Antihistamines			
Brompheniramine	+	+++	++
Chlorpheniramine	+	++	++
Clemastine	++	+ to ++	+++
Diphenhydramine	+++	+ to ++	+++
Second Generation Antihistamines			
Cetirizine	+	+	+
Loratadine	+	+	+

*++++ = very high, +++ = high, ++ = moderate, + = low, ± = low to none

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