Review of OTC Cough and Cold Medicines

Safety Data

Dr Ruth Savage
Coughs and Sneezes ...
Health Canada Decision on OTC Cough & Cold Medicines

• When assessing risk Committee asked to consider -

"The severity of the adverse effects and the likelihood of harm."
Antihistamines - 1

- **Alkylamines**: *brompheniramine, chlorpheniramine, tripolidine* - highly potent H1 antagonists, significant sedative actions, paradoxical stimulation esp in children.

- **Monoethanolamines**: *clemastane, diphenhydramine, doxylamine* - pronounced sedative and muscarinic actions, low incidence GI ADRs.

- **Ethylenediamines**: *antazoline, mepyramine* - selective H1-antagonists, moderate sedation, gastric disturbances, skin sensitisation.
Antihistamines - 2

- Phenothiazines: promethazine - significant sedative, and antimuscarinic effects, photosensitivity reactions.

- Piperazines: cetirizine, cyclizine - moderate sedative actions.

- Piperidines: azatidine, loratadine - highly selective for H1 receptors, moderate or low sedation.

Martindale 2009
Antihistamines - 3

• Sedating:
  - CNS depression, drowsiness to deep sleep, incoordination.
  - Paradoxical stimulation
  - Headache, psychomotor impairment, antimuscarinic effects.
  - GI - nausea, vomiting, diarrhoea, or epigastric pain.
Antihistamines - 4

• Sedating cont’d - rare ADRs
  - palpitations and arrhythmias
  - rashes, hypersensitivity reactions, photosensitivity
  - blood disorders, including agranulocytosis, haemolytic anaemia
  - convulsions
Sympathomimetics
(decongestants - pseudoephedrine, phenylephrine, xylo- and oxymetazoline)

CVS - Hypertension, palpitations, tachycardia, arrhythmias

• CNS stimulation - insomnia, tremor, hallucinations (rare)

• Hypersensitivity
Antitussives

- **Dextromethorphan & Pholcodine**
  - CNS, - drowsiness, fatigue, dizziness, dystonia, psychosis, hallucinations, serotonin syndrome (dextromethorphan interaction), drug abuse, respiratory depression
  - Anaphylaxis, rashes
  - GI - constipation
Expectorants

• **Guaifenesin**
  - GI, discomfort, nausea, vomiting
  - Urolithiasis (abuse)
  - CI in porphyria

• **Ipecacuanha**
  - GI, vomiting, haemorrhagic erosions
  - Cardiotoxicitiy
  - Abuse
Mucolytic

- **Bromhexine**
  - Hypersensitivity - rashes, anaphylaxis
  - GI
    - Hepatic - transient increases in serum transaminases
    - Headache, dizziness, sweating.
Cough & Cold Medicines
Overdose effects

- Antihistamines
  - Children - CNS stimulation, ataxia, excitement, psychoses, hallucinations, convulsions, hyperpyrexia, tachycardia.

- Pholcodine, dextromethorphan
  - Children - excitation, confusion, extrapyramidal effects, respiratory depression.

- Sympathomimetics
  Excitement, nervousness, GI effects, nausea, ataxia, hallucinations, convulsions and tachycardia.
Safety of Cough and Cold Medicines

• Reasons for adverse effects:
  - Adverse reactions and interactions at therapeutic doses

  - Overdose
    • Accidental ingestion by child
    • Medication error, wrong dose etc
      - Parent, iatrogenic
    • Deliberate overdose
Safety of Cough and Cold Preparations
Information Sources - 1

- Placebo-controlled randomised trials
- Non-randomised trials
- Observational studies
- Meta-analyses and major reviews
- Case series, published
Safety of Cough and Cold Preparations
Information Sources - 2

• Pharmacovigilance Centres
  - National, international spontaneous adverse reactions reports (Individual Case Safety Reports, ICSRs)

• Poisons Centres
  - Regional, national - requests for advice

Pharmaceutical Companies
  - ICSRs
Randomised Placebo-controlled trials

None had safety end points

• Likely that only powered to detect difference between placebo and active medicines for very common adverse reactions

• Six trials included 2-6 year olds, one included ibuprofen

• Expected non-serious adverse effects, for most rate not significantly different from placebo.

• Hyperactivitiy with dextromethorphan noted in two trials, common and dose related in one. (Paul et al, 2004).
Post-marketing Surveillance Studies

- **Pseudoephedrine and hospitalisation:**
  
  - 0-19 yr - 81,965 scripts
  
  - 246 admissions, one seizure (F22) possibly drug related
Postmarketing Surveillance

- Pseudoephedrine, toxic dose (NB single substance)
- Wezorek et al. Prospective study to determine toxic dose through children who had ingested pseudoephedrine:
  - 140 children <6yrs.
    - 30-180 mg
      - drowsiness 21.7%
      - hyperactivity 6.9%
    - >180 mg
      - Drowsiness 15.4% (? Error)
      - Mild hyperactivity 15.4%
Published Case Reports & Case Series Overdosesss

• See Annex 3 in Review of the Safety and Efficacy of Cough & Cold Medicines for Use in Children, by Susan Kenyon

• Deaths,
  - < 2yrs 50
  - > 2yrs 6 (5 accidental, 1 undetermined)
    » (diphenhydramine 4, benadryl 1, cough mixture + verapamil 1)
ICSRs and Poisons Centre data

• No reliable denominator data

• Incomplete reporting
  - Number of reports
  - Quality of reports
American Association of Poison Control Centres

• National Poisoning Data System - 1 Jan 2000 to 30 June 2007

• Analysis of exposure data to gain info and identify root causes

• Number of “contacts, exposures or cases” over 6.5 years for OTC C&C meds in < 12yr olds - 774,960

• OTC meds most often involved - decongestants (48%), antihistamines (42%), antitussives (32%), expectorant (9%).
### AAPCC Reasons For Exposures to Cough and Cold Medications

- **In Children <12 years (y) of Age (2000-2007)**
- **Reasons for Medication Exposure**

**Inadequate Measures To Keep Medicines Out of the Reach of Children**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>N (%)</th>
<th>N (%)</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-&lt;2yrs</td>
<td>1422 (28.43%)</td>
<td>3465 (69.29%)</td>
<td>114 (2.28%)</td>
</tr>
<tr>
<td>Product stored inappropriately</td>
<td>1422 (28.43%)</td>
<td>3465 (69.29%)</td>
<td>114 (2.28%)</td>
</tr>
<tr>
<td>2-&lt;6yrs</td>
<td>628 (27.78%)</td>
<td>1594 (70.50%)</td>
<td>39 (1.72%)</td>
</tr>
<tr>
<td>Accessed medication in purse or suitcase</td>
<td>628 (27.78%)</td>
<td>1594 (70.50%)</td>
<td>39 (1.72%)</td>
</tr>
<tr>
<td>6-&lt;12yrs</td>
<td>1586 (29.31%)</td>
<td>3677 (67.95%)</td>
<td>148 (2.74%)</td>
</tr>
</tbody>
</table>
### American Association of Poison Control Centres – reasons for exposures - 2

- **Therapeutic/Medication Errors**
- **0-<2yrs**
  - 14447 (31.24%)
- **2-<6yrs**
  - 22736 (49.16%)
- **6-<12yrs**
  - 9065 (19.6%)
- **Other incorrect dose**
  - 4922 (32.03%)
  - 7486 (48.72%)
  - 2957 (19.25%)
- **Confused units of measure**
  - 2943 (23.52%)
  - 6057 (48.41%)
  - 3513 (28.07%)
- **More than one product containing same ingredient**
  - 610 (64.08%)
  - 249 (26.16%)
  - 93 (9.77%)
- **Health professional iatrogenic**
  - 633 (70.81%)
  - 195 (21.81%)
  - 66 (7.38%)
- **Ten-fold Dosing Error**
  - 3867 (30.39%)
  - 6337 (49.8%)
  - 2522 (19.82%)
- **Dispensing Cup Error**
  - 6325 (34.20%)
  - 8549 (46.22%)
  - 3621 (19.58%)
American Association of Poison Control Centres - reasons for fatalities

- AAPCC Reasons For Fatal Exposures to Cough and Cold Medications
- In Children <12 years (y) of Age (2000-2007)
- Reasons for Medication Exposure

<table>
<thead>
<tr>
<th>Reason</th>
<th>0-&lt;2</th>
<th>2-&lt;6</th>
<th>6-&lt;12</th>
<th>0-&lt;12y (N=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Reaction</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>4 (12%)</td>
</tr>
<tr>
<td>Intentional Misuse</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Malicious</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>6 (17%)</td>
</tr>
<tr>
<td>Therapeutic Error</td>
<td>3</td>
<td>4</td>
<td>0</td>
<td>7 (20%)</td>
</tr>
<tr>
<td>Unintentional General</td>
<td>4</td>
<td>6</td>
<td>0</td>
<td>10 (29%)</td>
</tr>
<tr>
<td>Unknown reason</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>7 (20%)</td>
</tr>
</tbody>
</table>
American Association of Poison Control Centres

• Serious (<3%)
  - Moderate effect 0.86%
  - Major effect 0.04%
  - Death 0.0045% (N=35)
  - Unable to follow
    • potentially toxic 1.7%
National Poisons Information Centre UK

- 100,000 calls over 4 yrs for OTC C&C preps
- 230 children admitted over 1 year period
NZ Poisons Centre Data
Cases requiring medical referral

Number of Calls

Year

2002 2003 2004 2005 2006 2007 2008

<2 years 2-<6 years 6 years and above
NZ Poisons Centre Data

- Greatest proportion of childhood reports (0-16 yrs) was in 2-6 yr group

- Medicines implicated Phenergan (81), Histafen (50), Polaramine and polaramine repetabs (37), Sudomyyl (15) and isolated cases of exposure to other medicines

  - *ie most reports to single ingredient antihistamine preps primarily indicated for allergy.*
ADR reports to regulatory authorities/pharmacovigilance centres

- **US, Canada, UK, Australia**
  - Fatalities mostly in < 2 yr olds
  - Serious reactions at therapeutic doses in children > 2 yrs.
- **UK, serious in under 12s.**
  - Nasal decongestants (138, 64% 6 yrs and under)
  - Antihistamine containing preps (127, 72% < 6 yrs)
  - Expectorants (78, 70% < 6 yrs)
  - Antitusives (54)
  - For all except expectorants main suspected ADRs are CNS related
  - Expectorants, hypersensitivity
ADR reports to regulatory authorities/pharmacovigilance centres

- **Canada**
  - 111/145 reports (76%) for children < 6 yrs.
  - Fatalities in under 2s only
ADR reports to regulatory authorities/pharmacovigilance centres

- **US AERS database**
  - Decongestants: Fatal reports 9/54 for children 2-6 years.
  - Antihistamines Fatal 28/69 for 2-6s
  - ODs, 48% contributed to serious adverse events - antihistamines, antitussive, decongestant
  - Deaths and serious events - CNS, cardiac, respiratory in therapeutic doses and overdoses.
  - Convulsions more common in > 2yrs and more common after therapeutic dose.
  - Serious cardiac and respiratory events more often after overdose.
CARM data

Reported age

- under 2
- 2 to under 6
- 6 to under 12
- 12 to 18

Number of cases

- Antihistamines
- Expectorants
- Nasal decongestants
- Antitussives
CARM (NZ) Data

44/306 reports for ages 18 yrs or below.

- Majority allergic or CNS adverse effects
- Less than a quarter are OD but CARM does not usually record ODs as ADRs.
- Seven patients hospitalised
- One life-threatening reaction (M6, phenylephrine OD /pulmonary oedema)
- No childhood deaths have been reported
- Only 2/8 serious reactions in > 2 yr olds.
Company ICSRs - Polaramine (dextrochlorpheniramine), Demazin (chlorpheniramine/phenylephrine)

• Probability assessed by RS.
• Polaramine. Nine identified as “probable”.
  - Antimuscarinic and CNS effects inc hallucinations and decreased consciousness
  - Allergic reactions including laryngeal oedema
• Demazin  Two “probable” -
  - ODs with tachycardia
  - Death, most likely cause pneumonia
Company ICSRs - Bisolvon (bromhexine) - mucolytic

- 164 million exposures < 12 year olds based on sales of age appropriate products & 2 week courses. NB coughs and colds not main indication.

- Most ADR reports are of allergy, including anaphylaxis and skin reactions, and GI reactions. Most are listed as having "insufficient data".

- Similar number of ICSRs in 0-2 and >2-6 year olds (81, 82) and three serious reports in each group. Fewer reports for >6-12 yr olds.

- Serious reports >2-6 yrs. Accidental O/D - diarrhoea; skin reaction/weight loss/tonsillitis; SJS.

- Overdose has caused skin and GI reactions, no significant toxicity or death.

- One report of SJS in >2-6 yr olds and one of TEN in >6 to 12 yr olds. Alternative explanations. Not supported by WHO data.
Health Canada Decision on OTC Cough & Cold Medicines

• When assessing risk Committee asked to consider -

"The severity of the adverse effects and the likelihood of harm. "

Issues

- Fatal reports of ADRs or overdose very rare in > 2 yr olds

- Serious reports rare or very rare in > 2 yr olds
  - BUT widespread use!

- Anaphylaxis common to all the ingredients, cardiovascular and CNS reactions less likely with bromhexine and possibly guaifenesin

- Reasons for overdose of concern but accidental childhood ingestion may often involve preparations purchased for adults especially in NZ

- Will contraindication for < 6 yr olds lead to more dose errors if parents do give these medicines?