Review of OTC Cough and Cold Medicines

Safety Data - Bromhexine, Topical nasal decongestants

Dr Ruth Savage
Topical Nasal Decongestants - Indicated for common cold in children
NZ MIMs - 1

- Imidazoline derivatives

  • Oxymetazoline
    - Drixine paediatric nasal drops (0.025%)
      » Precautions - children < 2 yrs, use > 3 days

  • Xylometazoline
    - Otrivine M-D nasal spray junior (0.05%)
    - Otrivine M-D nasal drops junior (0.05%)
      » Duration - max 5 days
Topical Nasal Decongestants - Paediatric or no doses
NZ MIMs - 2

• Anticholinergics
  - Ipratropium
    • Atrovent nasal aqueous
    • Apo-Ipravent nasal spray
      - Children 2 sprays each nostril bd for rhinitis
      - Only adult doses for common cold
Topical nasal decongestants
Safety data sources

• No RCTs or observational studies with safety endpoints

• No RCTs or observational studies large enough to provide adequate safety data
Topical nasal decongestants
Safety data sources

- Published Case Histories – CNS Depression
  - Dunn et al 1992 – single dose
    • Coma in a neonate following single intranasal dose of xylometazoline
  - Soderman P et al 1984 – rpt doses
    • CNS reactions to nose drops in small children
  - Thompson RE, 1970 – rpt doses
    • Nose drop intoxication in an infant
Topical nasal decongestants

Safety data sources

• Published Case Histories

• Musshoff et al 2003
    • Medical Error, pharmacy preparation x8 adequate childhood dose
Centre for Adverse Reactions Monitoring (CARM) data

- **Xylometazoline** (age not stated in all reports)
  - Total reports 33
  - Total < 19yrs 5
    - F 1/12, rhinitis medicamentosa, nasal obstruction, stertorous breathing, chest retraction (hospitalised)
  - F7, accidental administration adult spray, no adverse effect
  - M8, rebound congestion
  - F14, Aplastic anaemia 3-4/52 after Coldrex (A multi-ingredient preparation)
  - M18, angioedema
Centre for Adverse Reactions Monitoring (CARM) data

• Oxymetazoline
  - Total reports 1
  - Total < 18 yrs 0
NZ Poisons Centre

• Enquiries leading to medical attention

Topical nasal decongestants
None

Mucolytics
Robitussin ME - 1
Other Poisons Centres

Victoria, Australia
- 9/567 enquiries for cough and cold medicines were imidazoline-based nose drops or sprays

Maryland Poisons Centre, USA
- 18575 calls for children < 6 yrs
- Cough & cold medicines:
  - 11 potentially toxic exposures, but no outcome data
  - No others serious or fatal
  - 5 moderate, no topical nasals or mucolytics.
Novartis database
Xylometazoline nasal formulations

• Estimate - has been used by >2.5 mill population in UK

• ADRs reported to company to July 2007, UK
  28 AEs in 20 children, one duplicate

• Of 19 reports
  - Under 2 yrs  10
  - 2 - <6 yrs   7
  - 6 - <12 yrs  2
Novartis database
Xylometazoline nasal formulations

• ADRs 0 - 12 yr olds

• Most frequent System Organ Classes affected
  - Psychiatric
  - Skin and subcutaneous
  - General and admin site disorders

• Serious reports
  - apnoea (2), epilepsy, cyanosis, death (all < 2 yrs)
Novartis database
Xylometazoline nasal formulations

- Reports for 2 - <6 yr olds (8)
  - Probable ADR
    - New onset epistaxis with each of two doses

- Insufficient data to establish causality
  - Anxiety, hyperreflexia
  - Rash
  - Erythema (2)
  - Blisters
  - Hallucinations (2)
  - Drug abuse
Schering - Plough - Oxymetazoline

- Company database (CARES)

  - ICSRs for 2-12 yr olds
    - 62 events in 35 patients (single and multiple ingredient preparations)

    - Estimated incidence 0.56/100,000 pt yrs (cf 0.14 all age groups)
Schering - Plough - Oxymetazoline

- Company database (CARES)
  - ICSRs included
    - Accidental exposure, no adverse reaction  5
    - Epistaxis  4
    - Nasal discomfort  5
    - Cardiac arrest*  3
    - Cardiac failure*  1
    - Overdose  2
      - F10 hallucinations, personality change
      - M5, vomiting, sweating, somnolence

* 3/4 related to procedures, all recovered
Novartis - Number of Patients by Seriousness Following Pediatric Intranasal Exposure to Oxymetazoline and Xylometazoline

- Sources FDA ADR databases, US National Poisons Service Database, literature

<table>
<thead>
<tr>
<th></th>
<th>Oxymetazoline total</th>
<th>Xylometazoline total</th>
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<tbody>
<tr>
<td><strong>serious/fatal</strong></td>
<td>0</td>
<td>1 (1.3%)</td>
</tr>
<tr>
<td><strong>Serious/non-fatal</strong></td>
<td>17 (1.2%)</td>
<td>17 (15.3%)</td>
</tr>
<tr>
<td><strong>Seriousness unknown</strong></td>
<td>543 (41%)</td>
<td>19 (24.7%)</td>
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Oxymetazoline - Safety Summary
Martindale, 2008

• Oxymetazoline is a direct-acting sympathomimetic with marked alpha-adrenergic activity

• Rebound congestion may occur after frequent or prolonged use.

• Systemic effects may occasionally follow the topical use of sympathomimetic decongestants; these include nausea, headache, and dizziness.

• Overdosage or accidental dosage by mouth may cause CNS depression with marked reduction of body temperature and bradycardia, sweating, drowsiness, and coma, particularly in children,

• *sympathomimetic decongestants should be used with great caution, if at all, in infants and young children* (Martindale, 2008).
Actions of other Regulators

• Italy has prohibited use of sympathomimetic nasal decongestants under 12 yrs.

• MHRA, under 6 yrs

• Not included in Health Canada’s decision
Mucolytics
Preparations in NZ MIMs

Bisolvon (Bromhexine)
- bronchitis, emphysema, asthma and other conditions with tenacious or excessive mucoid secretions

Benadryl Chest Forte (guaifenesin, bromhexine)
- relief of heavy chest cough

Duro-Tuss exp (pholcodine, bromhexine)
- relief of productive and persistent cough

Robitussin ME, (guaifenesin, bromhexine)
- relief of congested chest and cough due to common cold
Mucolytics

• Bromhexine - ADRs
  - Hypersensitivity - rashes, anaphylaxis
  - GI, caution if previous gastroduodenal ulceration
  - Hepatic - transient increases in serum transaminases
  - Headache, dizziness, sweating.
**Mucolytics - Ambroxol study**  
(Schulz et al, 2006)

- **Observational uncontrolled study**
  - Participant self assessments
  - 266 pharmacies, 2664 evaluable questionnaires
  - **Adverse Events** - 81 in 67 participants
    - Gastrointestinal 53
    - Skin and subcutaneous 9
    - “No serious or unknown adverse events”
Mucolytics

- Published case reports
- Rimsza & Newberry 2008
  - Ambroxol/atropine*
    - M 2/12 - death
  - Ambroxol*
    - F 5/12 - death
- * Causes of death notified as viral respiratory infection and SIDS. Ambroxol and atropine in blood
NZ Data - Mucolytics

• CARM
  - Mucolytics*
    • Total reports 4
    • Total < 18yrs 0
  *Age unknown in some reports.

• NZ Poisons Centre
  - Mucolytics**
    • Robitussin ME 1

**Enquiries leading to medical attention
Boehringer-Ingelheim Adverse Reaction Information System global (ARISg)

All ICSR reports received, literature, clinical studies, disease registries etc.
B-I ARISg database

- Children 2 - <6 years
  - 82 reports
    - Fatal 0
    - Serious 3
    - Non-serious 70
    - Unknown 9

- One fatality in 6-12 yr
Company ICSRs - Bisolvon (bromhexine) - mucolytic

- ? 164 million exposures in < 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
Conclusion

• Appear to be fewer serious and fatal reactions to topical nasal decongestants and, even more so, mucolytics than other cough and cold preps

• But relative sales unknown
CDC and NAME Survey

CDC and NAME survey,

- three deaths, no topical nasal decongestants or mucolytics
Expectorants

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

• Ipecacuanha
  - GI, vomiting, haemorrhagic erosions
  - Cardiotoxicity
  - Abuse
Paracetamol and Ibuprofen

- NZ National Poisons Centre
  - Paracetamol
    - Children, 2003 - 2008, Increase from 562 to 806 enquiries
  
  - Ibuprofen
    - Children, 2003 - 2008, increase from 119 to 296 enquiries
Sympathomimetics
(decongestants - pseudoephedrine, phenylephrine, xylo- and oxymetazoline)

ADRs

CVS - Hypertension, palpitations, tachycardia, arrhythmias

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

• Hypersensitivity
Sympathomimetics
(decongestants - pseudoephedrine, phenylephrine, xylo- and oxymetazoline)

Overdose Effects

- Gastrointestinal

- Tachycardia, arrhythmias

- CNS stimulation - excitement, nervousness, ataxia, hallucinations, convulsions

- CNS depression