

Review of OTC Cough and Cold Medicines

Safety Data - Bromhexine,
Topical nasal decongestants

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
 - M7. Intranasal naphazoline - CNS depression, bradycardia.
 - 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
 - Total < 18 yrs

1

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

* $\frac{3}{4}$ 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

- Oxymetazoline total	1323
• serious/fatal	0
• Serious/non-fatal	17 (1.2%)
• Seriousness unknown	543 (41%)
- Xylometazoline total	77
• Serious/fatal	1 (1.3%)
• Serious/nonfatal	17 (15.3%)
• Seriousness unknown	19 (24.7%)

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

- **Guaifenesin**
 - 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