

Cough and Cold Medicines in infants: inappropriate use and toxicity

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Concerns about the inappropriate use of cough and cold products being used in infants have led McNeil, Novartis and Wyeth to voluntarily withdraw certain of their infant formulations from the US market.¹

The deaths of three infants in 2005 that were attributed to ingredients found in cough and cold products led to investigations by several US agencies into the extent of the problem.² All three cases in 2005 were infants less than one year old, and post-mortem blood levels of pseudoephedrine were at least nine times higher than the therapeutic levels for two to twelve year olds, according to Food and Drug Administration (FDA) data. Doxylamine and dextromethorphan were also found, in one and two of the cases respectively. Two of the children had been given a prescription preparation and two had been given an OTC preparation.

Cough and cold preparations often contain mixtures of active pharmaceutical ingredients: analgesic and antipyretics, e.g. paracetamol and ibuprofen; first generation antihistamines, e.g. brompheniramine, diphenhydramine and triprolidine; antitussives, e.g. codeine, dextromethorphan and pholcodine; nasal decongestants, e.g. phenylephrine and pseudoephedrine; expectorants, e.g. guaiphenesin. In the US, products containing an analgesic/antipyretic, a nasal decongestant, an antihistamine, an expectorant or an antitussive in one or more combinations are labelled for use in infants (i.e. those under 2 years of age) with advice from a doctor.³

After these cases were reported, a survey by the US National Association of Medical Examiners showed that just over 1,500 children aged more than 2 years of age had been treated for adverse effects associated with the ingestion of cough and cold medications between 2004 to 2005.² The FDA records also showed that between 1969 and September 2006 there had been 54 deaths in infants attributed to this group of products.² However, guidelines drawn up by the US Physician's Associations did not advocate the use of these products in this age group. The American Academy of Pediatrics (AAP) advised against the use of codeine and dextromethorphan-containing preparations in children,⁴ and the American College of Chest Physicians advised against the use of all OTC cough medicines in cases of chronic cough, except in specific circumstances.⁵ The AAP also did not recommend the use of systemic decongestants and antihistamines in the management of chronic middle ear effusion⁶ or bacterial sinusitis.⁷

Since these drugs have a long history of apparently safe and effective use in older children, the reasons for these recommendations may not be obvious.

- Firstly, the aetiology, and therefore the responsiveness, of upper respiratory symptoms in infants differs to some extent from older children and adults⁸, so that matching a drug approved for use in older children with a symptom experienced by an infant may not be appropriate. Evaluation of symptoms has usually to be based upon the parent's or minder's perceptions and these may vary widely.

- Secondly, infants respond to, and handle, drugs differently to children and to adults, so that extrapolating the pharmacodynamic effects of a drug and/or its pharmacokinetic characteristics from data obtained in studies of children and adults is unsound.⁸ Hence, two years of age is widely used as a lower age limit in clinical studies and regulatory affairs.
- Thirdly, a systematic review of these classes of drugs for the treatment of acute cough in children concluded that there was no evidence of efficacy, and that the trials were of poor quality.⁹ Although seven of the eight clinical trials reviewed included children with a range of ages from infants up to around five years of age, all of them were small and none of them treated or analysed the infants as a sub-group, and so provide no additional information.⁹
- Fourthly, the small size of the clinical trials and the variability in the approaches taken to recording and reporting adverse effects meant that the information about adverse effects was unreliable.

In the absence of proven clinical benefit from the ingredients of cough medicines, it is unreasonable to expose these children to any risk at all from the ingredients.¹⁰ In contrast the other drugs frequently used for these conditions, paracetamol and ibuprofen, have been shown to be safe and effective analgesic and antipyretic drugs when used at the recommended doses in this age group, although few trials studied upper respiratory tract infection.¹¹ Doses are calculated on the basis of body weight, which is more accurate than age as a guide to the level of pharmacokinetic maturity. Nevertheless, patient education is continually needed. Recently, a national survey of a stratified sample of almost 1,000 over-fifteen year olds in Ireland found that only 15% knew the correct age limit for the use of aspirin in children.¹² Lack of awareness among consumers was evident in a substantial number of the US case reports. Parents and minders had administered OTC products intended for older children or for adults, or used prescription preparations that contained ingredients not found in infant formulations to the children in their care.

The combinations of ingredients in different products can make it difficult to discern which one or ones contributed to the toxic effects. To evaluate their safety each one must be assessed both separately and in combination. Expectorants such as guaiphenesin are thought to promote the secretion of a less viscous mucous, and have been associated with poisonings only on rare occasions, and then in combination with another substance. There is little published information about mucolytics, which may lower the viscosity of secreted mucous, because they have not been as extensively marketed in OTC products, but their mechanism of action would suggest that they are unlikely to pose a significant risk in an acute setting. Cough suppressants such as pholcodine and dextromethorphan were introduced because they were more selective in their central actions at the doses used in OTC products than conventional opioids such as codeine. Pholcodine is not licensed in

the US and has not been extensively studied in children, while reports indicate that dextromethorphan may produce drowsiness, stupor, hyperactivity and coma in overdose, but that the principal risk is from abuse of the drug by older children and adolescents.¹³

By contrast, nasal decongestants and antihistamines have been associated with many cases of poisoning in children.¹⁴⁻¹⁷ Nasal decongestants are sympathomimetics that produce vasoconstriction of the mucosal vasculature. The compounds differ in both their structure and their pattern of activity. The most commonly used drug in this country is pseudoephedrine which causes tachycardia, hypertension and central nervous system stimulation in overdose. Decongestants that are administered topically appear to be much less likely to produce systemic adverse effects but this is neither a feasible nor an authorised route of delivery for infants. First generation antihistamines in cough and cold preparations are used primarily to dry up nasal mucous secretions because they also have anticholinergic properties, and, since they cross the blood-brain barrier, their antihistaminic action can lead to drowsiness and sedation. The adverse effects of these drugs are complex because of these multiple actions at peripheral and central sites (antihistaminic, anticholinergic, antiserotonin) and they can produce tachycardia, agitation, hyperactivity, blurred vision, dystonic reactions and seizures at higher than approved doses. Hyperactivity and agitation are paradoxical effects that are seen in some young children; other patients may become drowsy, lethargic and confused. Several published case studies suggest that both of these ingredients when used alone are capable of causing the death of a young child either through acute or chronic overdosing. In combination, these two types of ingredients can add to each other's effects on the heart. The majority of the aforementioned 54 deaths between 1969 and 2006, were children less than one year old who had been given decongestants, and the FDA has also concluded that antihistamines contributed to a further 69 deaths in young children in this period.² The incidence of cases also seemed to be increasing. But some of the cases that the FDA has on file involve children between two and six years of age.

Although the manufacturers responded quickly to these events, they were probably stimulated by the appearance, on a number of websites, of invitations to parents, whose children had taken the withdrawn products and may have experienced adverse effects, to bring their cases to one of a number of US law firms to seek compensation. In neighbouring Canada, similar action has been taken by manufacturers.¹⁸ In line with its policy of maximising access to medicines, US labelling meant that these medicines could be purchased by parents for use under the direction of a physician who, it was intended, would confirm that the product was suitable and recommend an appropriate dose.³ These events have shown that this approach of balancing open access to medicines with the risks of inappropriate use was unworkable. The FDA has established a review, much of which will be conducted in public, and it will consider proposals to

prohibit the inclusion of antihistamines, nasal decongestants, cough suppressants and expectorants from products for children under six years of age.¹⁹

In this country, the bulk of preparations approved for use in children less than two years of age are single ingredient analgesic-antipyretic products. However, there are some other cough products approved for use in infants, and a couple of products that contain diphenhydramine combined with an analgesic-antipyretic are available. Pharmacists in Ireland have long expressed concern that some parents and minders view some of these products as sleep aids for their children and discount pharmacists' advice to the contrary. They are uninterested when counselled about following the recommended dosage and are unconcerned when warned about the risk of adverse effects. In these situations, the products are being purchased and used for their side effects, and the benefit is sought as much for the adults as for the children.

Pharmacists have not found that any of the other health service or medicines bodies have acknowledged that there could be a problem, and no support for the pharmacist's position has been forthcoming. This type of misuse is hard to substantiate and, as the US experience shows, may only come to light after a tragic event is publicised and other cases are then investigated. Poisonings with medicines in young children continue to occur in this country and requests for information about poisoning in this age group, almost two thirds of which concern drugs, make up over 40% of the total enquiries to the National Poisons Information Service in Dublin.²⁰

Evaluation of the existing regulatory requirements in this country for cough and cold products in under-six year olds, including the extension of the use of child-resistant containers to other types of OTC medicines, should be considered. The fact that different products, with identical ingredients, are approved for different age groups of children, is confusing to patients and professionals alike. A public education campaign about the use of non-prescription cough and cold medicines in young children is needed; not least because the appropriate use of cough and cold medicines in older children and the use of antihistamines in allergic conditions in children can be beneficial. The use of products that are authorised for the child's age, following the recommended dosing guidelines and safe storage of medicines must also be emphasised. While useful public information has been provided by IPHA in this country, most recently in conjunction with the IPU²¹, more is needed. This is the responsibility of the Health Service. Advice and information from such a source would be especially well regarded by the public. It would also be an opportunity for the part of the HSE concerned with patient care, to work with front line healthcare professionals – public health personnel, community pharmacists, GPs and others in primary care in a multi-disciplinary campaign, and to be seen to support their efforts in encouraging the responsible use of these medicines. Non-prescription medicines provide a great deal to our health service, but neither the HSE nor the Department of Health and Children has a policy, let alone a comprehensive one, to maximise the benefits that could flow from their appropriate use and minimise the potential risks.

In the meantime pharmacists can provide useful advice to those who wish to hear it:

- Check the lowest age limit for the use of the medicine, irrespective of the name of the medicine. Most products are not approved for use in children under 2 years of age
- Administer only the recommended dose and check that you know the recommended maximum daily dose
- Use single-ingredient products whenever possible. Check the pack to confirm the ingredients

- Do not use more than one medicine to treat the symptoms of coughs and colds unless advised by your doctor or pharmacist
- Never give a child a medicine that was prescribed for another member of the family
- If you intend to use herbal or other complementary preparations with a medicine for coughs or colds, check with your doctor or pharmacist that they can be safely used together
- For liquid medicines, use an oral syringe or a calibrated dropper or a measuring cup - sometimes these come with the product. Do not use household spoons such as teaspoons or tablespoons to measure out liquid medicines
- Sit the baby in your lap and support the baby's head while administering the medicine
- Give the medicines in small amounts to prevent choking
- Use a suppository if an oral product is not suitable
- If you are not going to administer the medicine yourself, instruct the person who is, and confirm that they understand your instructions
- A decongestant chest rub of the sort that contains menthol, which is an effective decongestant, and other volatile oils may be helpful, but ensure that this is not applied to the face or around the nose because high concentrations can interfere with the baby's breathing and the oils can be irritant to the eyes
- Humidifying the air in a child's room may help to reduce coughing
- Plenty of fluids (water-based) helps keep the mucous flowing easily
- Saline nose drops can be used to liquefy nasal mucous and reduce congestion
- A suction bulb can be used to remove nasal mucous
- Provide reassurance and comfort while administering medicines
- Pleasant distractions can take everyone's mind off the symptoms and help re-establish a normal routine of daily activities
- Children under five years of age may suffer anything from three to eight colds in a year. This is normal and shows that their immune system is recognising and responding to the 200 or so types of viruses that can cause these symptoms.
- The usual duration of cough caused by upper respiratory tract infection in children less than five years of age is from one to three weeks. In approximately 90% of cases it will resolve spontaneously
- If a child's condition continues to deteriorate bring them for a medical examination
- Smoking in the home increases the incidence of cough in infants and children and it increases the occurrence of respiratory infections and the development of asthma in children
- Keep all medicines out of reach of children all of the time

Referral should be considered if:

- There is evidence of infection – yellow-green sputum and/or fever
- The child is still having difficulty in feeding despite regular removal of nasal mucous by one means or another
- There is wheeze
- Persistent fever – more than two days, in line with analgesic/antipyretic pack-labelling statements
- Fever unresponsive to paracetamol or ibuprofen
- Any blood appears in the sputum
- The cough and/or other symptoms have progressively increase in severity despite reasonable

attempts to make the child comfortable

- There has been daily cough lasting 4 weeks or more
- Persistent night-time cough despite reasonable attempts to ensure that the room in which the child sleeps is neither too warm nor the air too dry

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