

The Wheezing Infant

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Perhaps the most chronic complaint of childhood presenting to family practitioners is the infant with recurrent wheezing. Before one even gets to grip with the rational choice of medicines in this group, one has to make the difficult choice between asthma and viral-induced wheezing, coupled with the understanding that many children stop wheezing without any long-term medication. However, once a decision is made to treat, one then has to face two additional hurdles: the first is the difficulty in administering medication to this age group. The second, perhaps even more daunting, is that few medicines have been tested in clinical trials in infants. "Off-label" use is therefore often an unavoidable necessity.

This short article will review how the World Health Organisation's P-drug process might be of help in this difficult selection task. (*SA Fam Pract* 2003;45(1):66-68)

Therapeutic objectives have been well described in the latest GINA guidelines:

- Minimal or no chronic symptoms.
- Minimal episodes or attacks.
- No emergency visits.
- Minimal use of "as needed" β_2 agonists.
- No limitations on normal activities.
- Near-normal lung function.
- Minimal or no adverse effects from the medicines prescribed.¹

Not only can these be used to guide monitoring once an infant is put on such medication, but they can also be the basis for a search of the available literature for evidence of safety and efficacy. Of particular relevance are studies that directly compare two or more of the classes of medicines from which the initial choice must be made. In this case, an initial choice could be made from the following: inhaled or nebulised corticosteroids, inhaled cromoglycate, leukotriene receptor antagonists, ketotifen or theophylline. That regular β_2 agonists or anticholinergics (such as ipratropium) should not be considered was made clear in recent Cochrane reviews.^{2,3}

Space constraints preclude a comprehensive account of the literature available (a Medline search with the

term "wheezing infant" reveals 1680 papers), but the following examples show how evidence of the elements considered in the P-drug approach (efficacy, safety, suitability, cost) can be gathered.

A recent podium presentation at a European congress reported on a year-long, multi-centre, open-label, parallel group study comparing the safety and efficacy of inhaled fluticasone (100 μ g bd) and inhaled sodium cromoglycate (5mg qid) in 625 children aged 12-23 months.⁴ The proportion of symptom-free days and days with no rescue medication used – both of direct relevance to the therapeutic objectives – was significantly higher in the steroid group ($p < 0.001$ and $p = 0.023$ respectively). A similar study, in 335 children aged 2-6 years showed that those using nebulised budesonide (0.5mg daily) had fewer exacerbations (mean of 1.23 per year) than did those on nebulised sodium cromoglycate (20mg qid; mean of 22.41 per year).⁵ Other relevant efficacy measures were also significantly better with the steroid, such as the use of rescue medications and the need for emergency visits.

Similarly, evidence can be sought on comparative safety – a study of lower

leg length growth in 40 children aged 1-3 years on either inhaled fluticasone (200 μ g bd) or budesonide (200 μ g bd) or placebo showed a significant reduction after 4 weeks with the steroids, but no difference between the two agents.⁶ However, translating such data into clinically relevant safety assessments is not easy. Longer experience (and a richer literature) with older agents allows far easier conclusions to be reached: for example, that nebulised cromoglycate is very safe, that theophylline is associated with significant adverse effects (such as nausea and vomiting) and that ketotifen is safe, causing only transient drowsiness.

Suitability considerations are also easier – for example, nebulisation is tedious and requires access to expensive equipment. Inhalers, when used with appropriate spacer devices, are convenient and quick. Orally administered medications (such as theophylline, ketotifen and montelukast) are also easy to administer, especially when presented as oral sprinkles or solutions. However, multiple daily doses can be a significant barrier to use. Costs per month are also easily obtained, showing that nebulised solutions are considerably more expensive than any other options.

Combining each of the elements into

simple table can then be used to guide selection, with elements rated as either positive or negative:

Drug	Efficacy	Safety	Suitability	Cost
Nebulised corticosteroids (e.g. budesonide inhaler solution)	+	+	-	-
Inhaled corticosteroids (e.g. fluticasone or budesonide)	+	+	+	+
Inhaled cromoglycate	+	+	-	-
Leukotriene receptor antagonists (e.g. montelukast)	+	+	+	-
Ketotifen	-	+	+	+
Theophylline	+	-	-	+

From this it can be seen that the *inhaled corticosteroids* are the best first-line options (perhaps with choice between the two being guided by price). In those cases where there is resistance to the use of a steroid, inability to use a spacer and mask, or perhaps a lack of response, *montelukast* might offer a suitable alternative. However, as with so many other diseases of childhood, sufficient comparative trials of the available

therapeutic classes in children aged less than 5 years are still lacking. For example, while there is one large randomised

placebo-controlled trial showing that montelukast is better than placebo in children aged 2-5 years,⁷ comparative trials and systematic reviews will have to await the generation of far more data in this particular age group. The current consensus though would indicate that this might well be the convenient first choice of the future in children.⁸□

Please refer to CPD Questionnaire on pg 51.

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