

The role of parent-initiated oral corticosteroids in preschool wheeze and school-aged asthma

Peter J. Vuillermin^a, Colin F. Robertson^b and Mike South^c

^aChild Health Research Unit, Barwon Health, Geelong,

^bDepartment of Respiratory Medicine and

^cDepartment of General Medicine, The Royal Children's Hospital, Parkville, Victoria, Australia

Correspondence to Dr Peter Vuillermin, Child Health Research Unit, Barwon Health, P.O. Box 281, Ryrie Street, Geelong, VIC 3220, Australia
Tel: +61 3 5260 3044; fax: +61 3 5226 7953;
e-mail: peterv@barwonhealth.org.au

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Purpose of review

To review the theoretical background and current evidence regarding parent-initiated oral corticosteroid (PIOCS) therapy in preschool wheeze and asthma in school-aged children.

Recent findings

In school-aged children with asthma PIOCS, given during acute episodes, has been associated with a modest reduction in asthma symptoms and health resource utilisation. In preschool wheeze, OCS (including PIOCS) therapy appears to be ineffective.

Summary

PIOCS is associated with modest benefits among school-aged children with acute asthma but is not effective among children with preschool wheeze. In older children with asthma, the potential benefits of PIOCS must be balanced against potential adverse effects associated with increased OCS administration.

Keywords

asthma, corticosteroids, respiratory, wheeze

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Introduction

The intermittent wheezing illnesses of childhood include preschool wheeze and asthma [1]. They are a leading cause of emergency department presentation and hospital admissions among children worldwide [2] and strategies are needed to reduce this burden. There is evidence that oral corticosteroids (OCSs) are effective in the treatment of acute wheeze in school-aged children when administered following physician review [3]. Many of the benefits of OCS have been shown to begin within 3 h of administration [4] and delayed administration may make it more difficult to effect resolution of the wheeze episode [5]. Parent-initiated oral corticosteroids (PIOCSs) for acute wheeze may expedite OCS initiation and consequently reduce the severity of wheeze episodes and the likelihood of health resource utilisation (HRU). However, it is important to recognise that OCSs appear to be ineffective among preschool children with wheeze [6^{••}], and that a strategy of PIOCS is likely to result in more frequent administration of OCSs, which may be associated with important adverse effects [7[•]]. Accordingly, a considered approach to PIOCS therapy is required.

During the first 12 months of life, respiratory syncytial virus (RSV) bronchiolitis is the predominant cause of intermittent wheeze. Current evidence suggests that corticosteroids do not have a role in the management of RSV bronchiolitis in the majority of cases [8], although

some argue that OCS may still have a role in very severe subgroups. Given that the role of OCS in bronchiolitis in the hospital setting is contentious, PIOCSs are clearly not appropriate for this group of patients. Beyond 12 months of age, two subgroups of intermittent childhood wheeze have been identified [1]. Younger children tend to suffer from discrete episodes of wheeze in association with viral respiratory tract infections [9,10], they generally do not have risk factors for atopic sensitisation and are often asymptomatic by 6 years of age [1]. This disease entity was initially described as wheezy bronchitis [9] and has subsequently been described by a variety of names including episodic (viral) wheeze [11] and preschool wheeze [12]. By comparison older (school-aged) children with intermittent wheeze often demonstrate atopic sensitisation and increased airway responsiveness to a range of stimuli [13,14]. These children can be described as having classical atopic asthma. This classification is cumbersome and imperfect but is nonetheless superior to describing all cases of intermittent childhood wheeze as 'asthma'. In this paper we discuss the role of PIOCS with reference to younger children with preschool wheeze and school-aged children with asthma.

There are two major strategies in the drug treatment of preschool wheeze and asthma. The first is the use of medications that cause relaxation of the airway musculature and decrease airway narrowing. These agents are the bronchodilators (β_2 -sympathomimetic agents,

anticholinergic agents and theophyllines). The second is the use of anti-inflammatory drugs, such as the corticosteroids, leukotriene antagonists, and the mast cell stabilisers. The anti-inflammatory properties of corticosteroids are complex and incompletely understood [15]. They include effects on inflammation, microvascular leakage, vascular proliferation, pulmonary vascular resistance, and β_2 -adrenoreceptor expression. The majority of the anti-inflammatory actions of corticosteroids are mediated by changes in gene transcription, which means that there is a latency of action – the initial cellular interaction is immediate, but the subsequent physiological and pharmacological effects lag behind because of the need to transcribe and secrete new proteins. However, corticosteroids also have rapid, nongenomic effects. These include the activation of nitric oxide synthetase [16], as well as increased β_2 -adrenoreceptor activity [17].

The most compelling clinical evidence regarding OCS in childhood wheezing illnesses comes from a Cochrane systematic review that included a total of 315 children attending an emergency department with acute wheeze [18]. The pooled analysis demonstrated that early treatment with a systemic corticosteroid was associated with a reduced rate of hospital admission, and that the benefit was apparent was first apparent 4 h post-treatment and peaked at the 6-h mark [18]. Important limitations to the generalisability of these findings were that the participants had relatively severe acute asthma (the admission rate in the placebo arm was greater than 40% in most of the included studies). In addition, very few preschool-aged children were included in the review. In a subsequent well conducted, large ($n=700$) emergency department based trial [19] of OCS therapy among children aged 10–60 months with acute wheeze, a 5-day course of oral prednisolone was associated with no benefit in terms of hospitalisation or other outcome measures.

There are important theoretical considerations when extrapolating from hospital-based studies such as these into a community-based strategy of PIOCS. Population-derived data indicate that only a minority of episodes of acute wheeze result in a medical review [20]. It follows that many episodes of acute asthma that occur in the community improve before they become severe enough to result in a hospital visit. Thus the episodes for which parents would be initiating an OCS in the community are likely to be (in general) less severe than the episodes included in the Cochrane review cited above [3]. Second, a strategy of PIOCS in asthma relies on the ability of the parent to make an accurate assessment of their child's clinical status, and studies have shown that parents have difficulty in making this assessment [21].

It is also important to recognise that a strategy of PIOCS may result in more frequent administration of OCS.

Key points

- Oral corticosteroids (include parent-initiated oral corticosteroids, PIOCSs) are ineffective among children with preschool wheeze.
- PIOCS therapy among school-aged children with asthma is associated with a modest reduction in symptoms and health resource utilisation.
- A strategy of PIOCS is likely to result in more frequent administration of oral corticosteroids which may have adverse effects.

There are two reasons for this: first, parents may simply have a lower threshold for commencing OCS than their doctor; second, PIOCS is likely to be associated with earlier initiation of OCS, and some episodes destined to spontaneously improve before resulting in a medical review would still result in OCS therapy. This raises justifiable concerns about safety and side effects. The potential adverse effects may be short term, such as behavioural changes, or longer term, such as changes in bone metabolism, adrenal metabolism and growth. The majority of controlled trials of systemic corticosteroid therapy in acute asthma have failed to adequately document potential short-term adverse effects. Until recently, existing (cross-sectional) data regarding the risks of recurrent short courses of OCS in children with asthma had been reassuring [22]. However, a more recent prospective longitudinal assessment of the effect of corticosteroid use on bone mineral density among children involved in the Childhood Asthma Management Program (CAMP) study was concerning [7^{*}]. In this study, 877 children with intermittent wheeze were followed for a median of 7 years. Repeated short courses of OCS produced a dosage-dependent reduction in bone mineral accretion and increased risk for osteopenia in boys but not girls. The clinical significance of this reduction in bone mineral accrual is not clear; however, the study clearly demonstrates that the frequent OCS short courses are associated with systemic side effects. OCS must be used judiciously, and it is important to evaluate the efficacy of PIOCS, rather than simply assuming that the benefits will justify the risks.

There have been three published trials that have directly evaluated the efficacy of PIOCS in children (Table 1) [19,23,24^{**}]. Grant *et al.* [23] conducted a randomised placebo-controlled crossover trial involving 86 children 2–14 years of age with a diagnosis of 'asthma' who were identified from clinic records. The intervention consisted of a single 2 mg/kg dose of prednisolone. The patients were observed for a predetermined 12-month period. During one 6-month period the study medication that parents kept at home was prednisolone. During the other 6-month period it was placebo. The order of these time periods (prednisolone or placebo) was randomly assigned. The primary outcome measure was the number of

Table 1 The characteristics of the current studies regarding parent-initiated oral corticosteroids in preschool wheeze and school-aged asthma

Study	Patients	Design	Intervention	Control	Primary outcome
Grant <i>et al.</i> [23]	86 children aged 2–14 years identified as having asthma from clinic records	Crossover study: participants observed for two consecutive 6-month periods	A single 2 mg/kg dose of prednisolone	Placebo	Unscheduled medical review
Oommen <i>et al.</i> [19]	217 children aged 1–5 years old who had been admitted to hospital with an episode of viral wheeze	Parallel	20 mg prednisolone once daily for 5 days	Placebo	7-day mean daytime and nighttime respiratory symptom scores
Vuillermin <i>et al.</i> [24**]	230 children aged 5–12 years with a diagnosis of asthma confirmed by the study's paediatric clinician	Cross-over study: randomised episodes of acute wheeze rather than participants	1 mg/kg/day of prednisolone for 3–5 days (at the parent's discretion)	Placebo	7-day daytime symptom score

unscheduled medical reviews for acute asthma. The analysis was paired; that is, each of the 78 participants who completed the study was compared with his or herself. All participants who completed the study were included in the analysis, regardless of whether they suffered from zero, a single or multiple episodes of acute wheezing. Surprisingly, they found that a significantly greater number of unscheduled medical reviews occurred during the period that the participants' study medication was prednisolone as compared with placebo (Table 2). In a secondary analysis restricted to participants treated with the study medication they found a nonsignificant trend towards an increase in the number of unscheduled medical reviews during the 6 months that the study medication was prednisolone, as compared with placebo ($P=0.08$). However, the proportion of episodes that resulted in an unscheduled medical review was not different ($P=0.30$). They conducted subgroup analysis of children 5 years of age and younger and those 6 years of age and older. The younger children were more likely to require an unscheduled medical review during the 6-month period that their study medication was prednisolone. Amongst the older children there was no difference detected between treatment groups. The proportion of children within these two age brackets could not be extracted from the paper, nor obtained following correspondence with the authors. However, there are two reasons to suspect that there were relatively few participants in the older age group: first, intermittent wheeze is substantially more common in preschool-aged children than school-aged children; second, the results for all participants (2–12 years old) were similar to the results obtained for those 5 years of age and younger, but differed from those obtained from the children 6 years of age and older. Thus, it is likely that the analysis of data from children 6 years of age and older was underpowered.

Oommen *et al.* [19] conducted a second randomised placebo-controlled trial that involved 217 children 1–5 years old who had been admitted to hospital with a diagnosis of 'viral wheeze' (Table 1). The intervention consisted of 20 mg of prednisolone administered once

daily for 5 days. The period of observation following enrolment was not predetermined and ranged from several months to more than 3 years. Data were captured on 111 episodes of treatment with the study medication. The primary outcome measures were the mean 7-day daytime and 7-day nighttime symptom scores. The analysis comprised a parallel comparison restricted to only those participants who suffered an episode of wheeze resulting in parent-initiated treatment with the study medication and successfully completed the symptom diary. They found no difference between treatment groups in the daytime or nighttime symptom score, salbutamol use, substitution of the study medication with a known OCS or hospital admission rates (Table 2). The authors stratified participants by the presence or absence of an elevated serum eosinophil cationic protein or eosinophil protein X. The results from related subgroup analyses did not differ from those of the primary analysis. Although this was a robust and well conducted study, there are several reasons why they may have failed to identify a clinically important benefit associated with PIOCS. In particular, it was a relatively small study and a clinically useful difference between treatment groups may have been obscured by variation in episode severity as well as the parent's interpretation of symptom severity. In addition, less than 2% of the episodes treated with placebo resulted in a hospital admission, suggesting that the majority of episodes were relatively minor. A benefit to PIOCS among more severe episodes of preschool wheeze cannot be excluded.

Finally, we conducted a randomised controlled crossover trial [24**] of parent-initiated prednisolone among a population-derived sample of 230 children aged 5–12 years with a diagnosis of asthma confirmed by a single paediatrician. The intervention was a short course of prednisolone: 1 mg/kg/day for 3–5 days (initiated at the parent's discretion). The primary outcome measure was a 7-day daytime symptom score. The secondary outcomes were a nighttime symptom score, HRU and school absenteeism. Episodes of acute wheeze rather than participants were randomised. Over a 3-year period, 131 participants

Table 2 The outcome of the current studies regarding parent-initiated oral corticosteroids in preschool wheeze and school-aged asthma

	Grant <i>et al.</i> [23]			Oommen <i>et al.</i> [19]			Vuillemin <i>et al.</i> [24**]		
	Observation period			Treatment groups			Treatment groups		
	Intervention (n = 78)	Control (n = 78)		Intervention (n = 52)	Control (n = 69)		Intervention (n = 155)	Placebo (n = 153)	
Unscheduled medical reviews	1.2 (1.8)	0.68 (1.1)	$P = 0.004$	NA	NA		48 (31%)	69 (45%)	OR = 0.54 (0.34–0.86) ^a
Number of hospital admissions	9	7	$P = 0.73$	6	2		6 (4%)	12 (8%)	OR = 0.41 (0.16–1.05) ^a
Substitution of trial medication	NA	NA		9	8		30 (19%) ^b	54 (35%) ^b	OR = 0.44 (0.26–0.73) ^a
with an OCS									
Mean daytime symptom score	NA	NA	NA	0.95	0.96	MD = –0.01 (–0.22 to 0.20) ^a	1.19 ^b	1.35 ^b	OR = 0.85 (0.74–0.98) ^a
Mean nighttime symptom score	NA	NA	NA	0.92	0.82	MD = 0.10 (–0.12 to 0.32) ^a	–0.77	–0.54	OR = 0.84 (0.7–1.00) ^a
Mean salbutamol actuations ^b	NA	NA	NA	1.59	1.66	MD = 0.93 (0.65–1.32) ^a	NA	NA	
Mean duration of hospital stay (days)	0.31	0.35	$P = 0.82$	NA	NA		NA	NA	

The values are given as mean (SD) or *N* (%). MD, Mean difference; OR, odds ratio.

^a 95% confidence interval.

^b Mean and SD for DTSS and NTSS are of (natural) log values, whereas comparison is back-transformed to give geometric mean ratio comparing prednisolone with placebo.

contributed 155 episodes of acute wheeze randomised to parent-initiated treatment with prednisolone and 153 episodes randomised to treatment with placebo. The mean daytime symptoms score was 15% [95% confidence interval (CI) 2–26; $P = 0.022$] lower among episodes treated with prednisolone. Consistent with this, treatment with prednisolone was associated with a 16% (95% CI 0–30; $P = 0.050$) reduction in nighttime symptom score, a reduced risk of HRU (number of episodes needed to treat = 7.1, 95% CI 4.0–30.3; $P = 0.010$), and reduced school absenteeism. We defined subgroups on the basis of subjective impression of parental competence, interval symptoms, regular inhaled steroid use and atopic sensitisation. There was no evidence that the magnitude of treatment effect was greater in particular subgroups (data not shown).

There are several reasons why we may have observed a benefit from PIOCS in contrast to the previous PIOCS trials that had not [19,23]. Most notably, the children involved in our study were school-aged, whereas, most of the participants in the previous PIOCS trials were pre-school-aged [19,23]. It may also be relevant that we emphasised co-administration of high-dose β -agonist. The early effects of oral corticosteroids are partly due to upregulation of β receptors on the surface of airway smooth muscle, rather than anti-inflammatory effects [17]. In the previous PIOCS trials the recommended dose of β -agonist was either lower (up to 400 μ g of salbutamol) [19], or not specified [23]. Finally, our study had greater statistical power as we collected data on a greater number of episodes, and the data were paired.

Conclusion

What then is the role of PIOCS in the management of preschool wheeze and childhood asthma? At present there is little evidence of OCSs that are effective among children with preschool wheeze. In 2008, the European Respiratory Society recommended that OCS should be reserved for episodes of preschool wheeze severe enough to require hospitalisation [11]. There has been no evidence since to alter this position, and PIOCS remains an inappropriate strategy among children with preschool wheeze. Among school-aged children current evidence suggests that PIOCS is associated with a modest reduction in symptoms and HRU. From a health resource viewpoint, PIOCS is cheap whereas HRU is costly. However, from the patient's viewpoint, the symptom benefit is modest, and a relatively large number of episodes may need to be treated to prevent the need for a medical review (NENT = 7) or hospital admission (NENT = 25). In addition, the detrimental effects of recurrent short courses of OCS may be significant [7*]. We recommend that, if a school-aged child has suffered repeated episodes of acute asthma resulting in HRU, the

parent should be advised to keep an OCS available to be commenced in the event of a relatively severe episode of acute asthma. However, it is important that the clinician regularly review the frequency and appropriateness of PIOCS administration and HRU in order to minimize the risk of OCS-related adverse events. In particular, the clinician must ensure that the parents are maintaining safe criteria for seeking a medical review despite commencing their child on an OCS, and also that the parents are maintaining an adequate threshold for commencing an OCS, in order to avoid excessive OCS administration.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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This large and robust trial found no evidence of benefit associated with oral prednisolone therapy in preschool children with acute virus-induced wheeze. This study demonstrated that as few as four short courses of oral corticosteroids per year in children with recurrent wheeze were associated with diminished bone mineral accrual.

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In this relatively large, population-based, crossover trial we demonstrated that parent-initiated prednisolone for acute asthma in school-aged children was associated with a modest reduction in symptoms and health resource utilisation.