

Viral-Induced Asthma: *Sorting through the Studies*



Malcolm R. Sears, MB, FRACP, FRCPC
Presented at the Respiriology Update Continuing Education Program, January 2005

Viral-associated wheezing is common and not highly responsive to treatment with beta-agonists or inhaled steroids.

As leukotrienes are elevated during viral infections, three recent studies have examined the usefulness of leukotriene receptor antagonists in children with viral-associated wheezing.

Viral infections in asthma

Clinical and epidemiologic studies have indicated that the majority of wheezing episodes in young children are related to viral infections.¹ There is a clear seasonal pattern to hospitalizations for asthma in children, with a major peak shortly after their return to school (Figure 1).² Rhinovirus has been identified as a frequent viral pathogen during epidemics of childhood asthma.^{3,4}

Leukotrienes in asthma

Cysteinyl leukotrienes are potent mediators of many of the features of asthma, including:

- mucus secretion,
- decreased mucus transport,
- epithelial cell damage,
- tachykinin release,
- eosinophil recruitment,
- blood vessel leakage,
- inflammatory cell recruitment and
- contraction of smooth muscle.

Daisy's Discomfort

Daisy, 4, has recurrent episodes of wheezing with mild respiratory distress that does not require emergency room (ER) management. These episodes generally start with an upper respiratory tract infection (a common cold) and last up to two weeks before finally resolving.



Daisy has been given salbutamol by a metered dose inhaler with a spacer.

What happens to Daisy? Go to page 96 to find out.

FAQ

Do inhaled steroids work to treat viral wheezing?

Inhaled steroids may improve baseline lung function and reduce persistent inflammation (especially in atopic asthmatics), but they have limited benefit in viral infections.

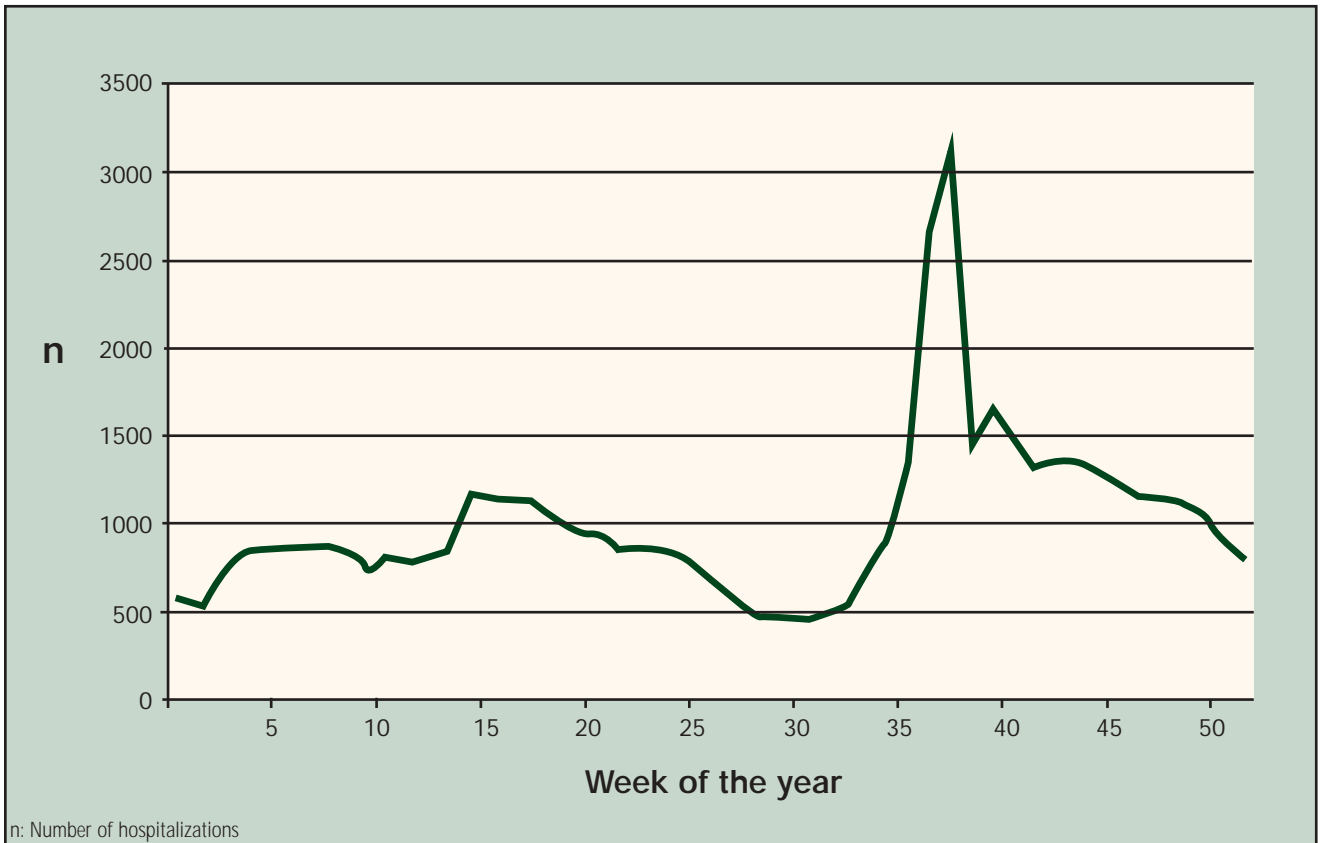


Figure 1. Number of hospitalizations of children 2-15 years for asthma in Canada (excluding Quebec) by week of the year, composite April 1995-March 2000. Courtesy of Neil Johnston, Firestone Institute for Respiratory Health.

They are released in response to allergic sensitization and exercise, in acetylsalicylic acid-induced asthma and also during viral infections.⁵

Studies of leukotriene receptor agonists in viral-associated wheezing

1. International study

The largest randomized, controlled trial of a leukotriene receptor antagonist in apparent viral-induced asthma was conducted in children aged two to five years.⁶ After a run-in period, 549 children with a history of viral-induced wheezing were randomized to receive either placebo or montelukast, 4 mg daily (or 5 mg if they turned six years old during the study) for 48 weeks (Figure 2).

FAQ

Should montelukast be given every day or only when viral infections occur?

Current studies suggest either continuous or short courses of montelukast provide a 30% to 40% reduction in wheezing and related outcomes.



Dr. Sears is a Professor of Medicine, McMaster University, and Research Director, Firestone Institute for Respiratory Health, St. Joseph's Healthcare, Hamilton, Ontario.

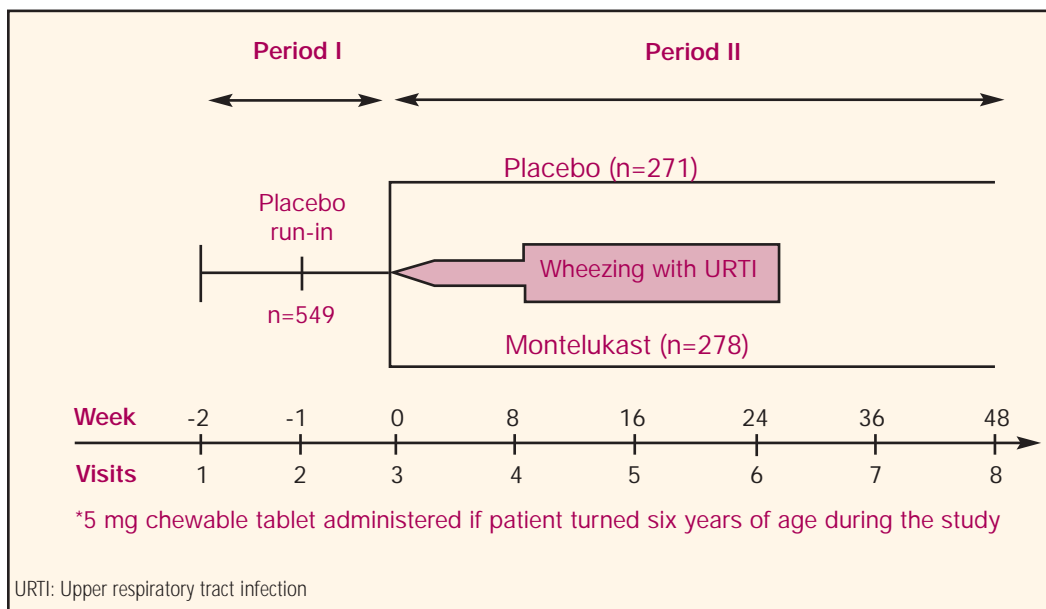


Figure 2. Study design, montelukast versus placebo over one year.⁶

The primary outcome study was the occurrence of an asthma exacerbation defined as three consecutive days with:

- daytime symptoms and more than two beta-2-antagonist treatments each day,
- inhaled corticosteroid treatment on more than three consecutive days or oral corticosteroids for more than one day or
- hospitalization for asthma.

Montelukast treatment was associated with a > 30% decrease in the number of exacerbations per year and reduced usage of inhaled corticosteroid (0.66 courses versus 1.10 in the placebo group, $p=0.027$) (Figure 3). The mean time to a first exacerbation was 206 days, versus 147 days with placebo, $p=0.024$.

2. Australian study

A further study of a leukotriene antagonist given in a different regime was recently reported from Australia.⁷ The objective was to see whether a short course of montelukast, introduced at the onset of an acute wheezing episode, would modify severity and reduce health-care utilization.

More on Daisy

Daisy had several further episodes of wheezing with mild respiratory distress, including one last September that required an ER visit.

Children aged two to 14 years with intermittent asthma received montelukast, 4 mg or 5 mg, depending on their ages, or received matching placebo ($n=201$). Treatment was initiated at the first sign of a viral upper-respiratory tract infection or asthma symptoms and continued for seven days or until symptoms resolved for 48 hours. The same blinded treatment was given for each subse-

FAQ

Is montelukast safe for use in young children?

Montelukast is approved for use in children two years and older. The adverse effect profile is not different from that of placebo.

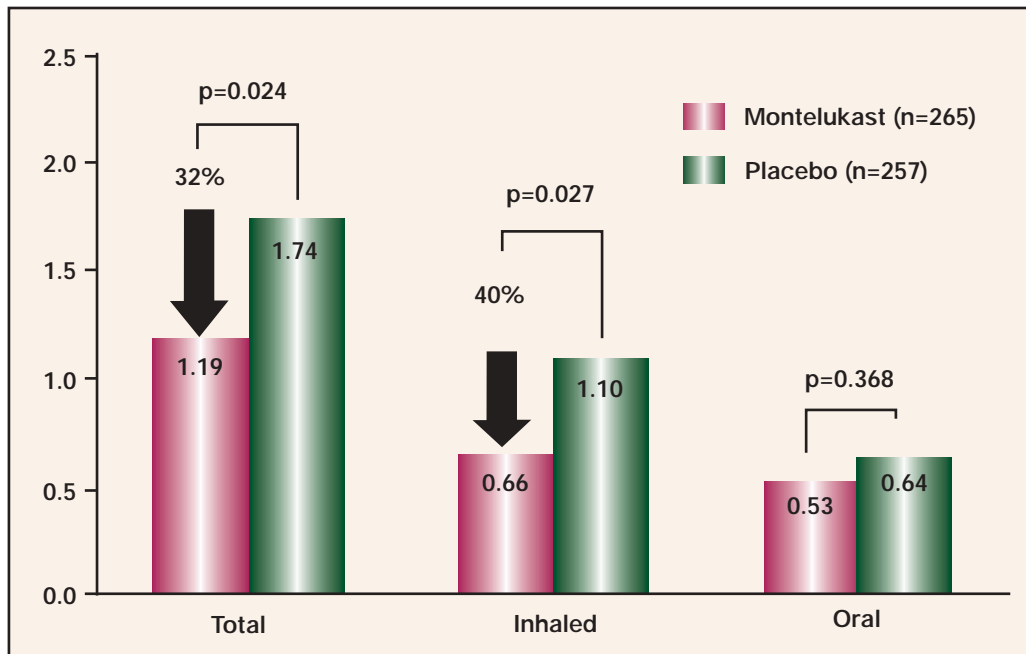


Figure 3. Course of corticosteroids, per year, montelukast versus placebo.⁶

quent episode during the next 12 months.

There was no difference in the frequency of viral episodes between the treatment groups with active montelukast compared to placebo. There were (Figure 4):

- significant reductions in emergency department utilization (45.6% reduction, $p < 0.01$),
- reductions in time off school (36.6% reduction, $p < 0.01$),
- reductions in parental time off work (33.5% reduction, $p < 0.01$),
- overall health-care utilization (23.6% reduction, $p < 0.01$) and
- a smaller, but significant, reduction in the number of nights awake per episode (9.4% reduction, $p < 0.05$).

asthma emergency room visits and admissions, with a sharp peak in these events in September after children return to school (Figure 1).⁴

An emergency room study in 2001 found a substantial prevalence of rhinovirus infection in asthmatic children visiting the ER compared with community controls with asthma of equal severity, but not requiring emergency room

3. Canadian study

Epidemiologic studies in Canada have revealed a very striking seasonal pattern to childhood

use.⁴ Even in the controls, there was a significant prevalence of rhinovirus infections. However, maintenance anti-inflammatory therapy was used twice as frequently in the community controls as in the children visiting emergency rooms.

A study in September 2004 examined the potential role of a leukotriene antagonist during this high-risk period.⁸ Children aged two to 14 years with asthma and needing a beta-agonist reliever inhaler three or more times per week were recruited prior to September 1 and given montelukast, 4 mg or 5 mg, (depending on age) or a matching placebo, for 30 days during September in addition to their usual asthma therapy. The study showed a 33.7% reduction in the number of days with asthma symptoms with montelukast.

Drawing conclusions...

There are now three studies suggesting the benefit of leukotriene receptor antagonist therapy, compared with placebo, in apparent viral-induced asthma. While further studies are required, these studies suggest there is likely to be a useful role of leukotriene antagonist therapy in children with viral-induced wheezing, whether given continuously as monotherapy, given in short courses during viral infections or added to baseline control therapy during periods of high-risk viral infections.

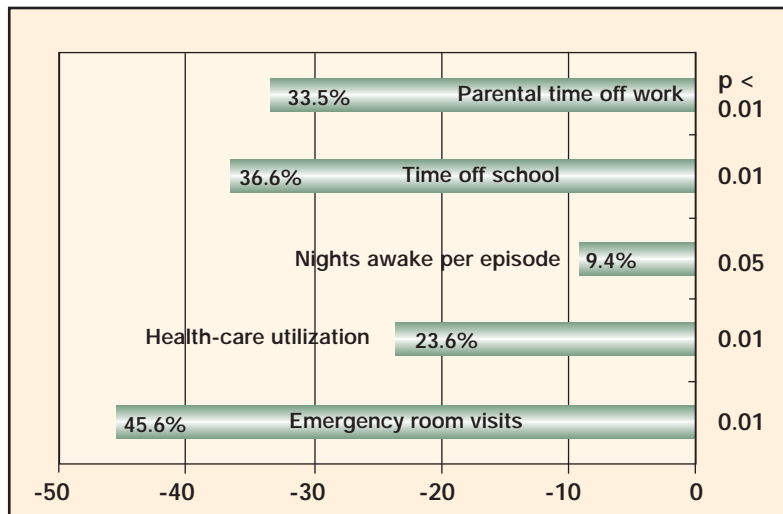


Figure 4. The benefit of montelukast over placebo (per cent reduction) in the Australian Study.⁷

References

1. Johnston SL, Pattemore PK, Sanderson G, et al: Community study of role of viral infections in exacerbations of asthma in 9-11 year old children. *Br Med J* 1995; 310(6989):1225-8.
2. Johnston SL, Pattemore PK, Sanderson G, et al: The relationship between upper respiratory infections and hospital admissions for asthma: A time-trend analysis. *Am J Respir Crit Care Med* 1996; 154(3 Pt 1):654-60.
3. Message SD, Johnston SL: Viruses in asthma. *Br Med Bulletin* 2002; 61:29-43.
4. Johnston NW, Johnston SL, Duncan JM, et al: The September epidemic of asthma exacerbations in children: A search for etiology. *J Allergy Clin Immunol* 2005; 115(1):132-8.
5. Gentile DA, Fireman P, Skoner DP: Elevations of local Leukotriene C4 levels during viral upper respiratory tract infections. *Ann Allergy Asthma Immunol* 2003; 91(3):270-4.
6. Bisgaard H, Zielen S, Garcia-Garcia ML, et al: Montelukast reduces asthma exacerbations in 2- to 5-year-old children with intermittent asthma. *Am J Respir Crit Care Med* 2005; 171(4):315-22.
7. Robertson CF, Henry RL, Mellis C, et al: Short course montelukast for intermittent asthma in children: The Pre-empt study. *Am J Respir Crit Care Med* 2004; 169: A149 (Abstract).
8. Mandhane PJ, Lambert KE, Duncan JM, et al: Effect of montelukast on asthma symptoms associated with lower respiratory tract infections during the September epidemic: A randomized placebo-controlled trial. *Proc Am Thorac Soc* 2005; 2: A688 (Abstract).