# Efficacy and Safety of Montelukast as Monotherapy in Children with Mild Persistent Asthma

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***Objective:*** *To study the efficacy and tolerability of montelukast as monotherapy in the treatment of mild persistent bronchial asthma.* ***Design:*** *Open, non-comparative, prospective, 12-month study.* ***Setting:*** *Asthma clinic in urban multi-speciality trust hospital.* ***Methods:*** *Children (age 3-11 yrs) with mild persistent asthma, not on any prophylactic drugs were enrolled consecutively (from January to December 2003) and started on 4 mg (2-4 yrs) or 5mg (>4 yrs) montelukast for a period of 12 weeks. Efficacy was assessed by improvements in clinical score, peak expiratory flow rates (PEFR), spirometry measurements and reduction in reliever drug requirement after 4 and 12 weeks of therapy. Side effects were also judged after 12 weeks of therapy.* ***Results:*** *50 children (mean age 5.41 ± 2.11 years) completed the study. There was association with positive family history (92%), allergic rhinitis (64%), exercise induced asthma (40%), cough variant asthma (24%), seasonal asthma (80%) and high IgE (12%) levels. Clinical scores, viz, activity, wheeze and cough, improved effectively from (1.64 ± 0.5253) at baseline to (0.7 ± 0.7071) and (1.72 ± 0.701) to (0.92 ± 0.6952) and (1.5 ± 0.6145) to (0.88 ± 0.8241) respectively after 12 weeks of therapy. Significant clinical improvement (p <0.001) was also noted after 4 weeks of therapy. Peak expiratory flow rates (done in 19 cases) documented improvement from (120.21 ± 12.23) at baseline to (135.41 ± 23.34) after 12 weeks.* $FEV_1$ */ FVC (done in 11 cases) improved from (71.44 ± 1.35%) to (87.10 ± 8.34%) after 12 weeks. Mean improvement in all the parameters demonstrated P value less than <0.001. A total of 19 of 50 cases showed mild side-effects as anorexia (16%), elevated liver function tests (18%) and headache (10%).* ***Conclusion:*** *The clinical outcome showed significant improvement (p <0.01) after 4 and 12 weeks.*

**Key words:** *Mild persistent asthma, Montelukast, Monotherapy.*

**ASTHMA** is the most common chronic illness of childhood affecting approximately 10% of children(1). Persistent asthma is managed pharmacologically by the daily use of a preventer medication and a short acting beta-agonist for relief of exacerbations. Inhaled corticosteroids are often used as daily preventer therapy for patients with persistent asthma(2). However, long term inhaled corticosteroids (ICS) exhibit dose related systemic side-effects(3). Moderate to high doses have been associated with a transiently decreased rate of growth in children and decreased bone mineral density(4,5). Inhaled cromolyn or nedocromil have a better safety profile and may be considered in children, but these drugs require upto 6-8 hourly administration making compliance a big problem particularly so in children(6).

Leukotriene receptor antagonists (LTRAs) are the first new class of asthma therapy which block selectively the leukotriene pathways involved in the pathophysiology of asthma. Cysteinyl leukotrienes cause broncho-constriction, mucus secretion, increased vascular permeability and eosinophil

migration to the airways, as well as promote smooth muscle proliferation(7,8). Their synthesis and release appear not to be blocked by corticosteroid therapy(9). Montelukast is a potent, specific LTRA. Administered once daily in tablet form, Montelukast reduces the signs and symptoms of persistent asthma in children as young as 2 years of age, with a tolerability profile similar to that of placebo(10,11). Additionally, Montelukast has been shown to attenuate exercise-induced bronchoconstriction in these children. Western studies have shown the beneficial effects of LTRAs in children with persistent asthma(12,13).

GINA guidelines clearly recommend the use of LTRAs (montelukast) as a single drug prophylaxis in mild persistent asthma(14). Considering the inhibition among parents about inhaled therapy in their children and side-effects of long-term use of inhaled steroids in children, this trial was conducted to evaluate the efficacy and safety of montelukast in children with mild persistent asthma.

## Subjects and Methods

It was a prospective, open, non-comparative study in an urban childhood asthma clinic in a multi-speciality hospital in Howrah, West Bengal. Prior ethical approval of the Institutional Review Board of the Hospital and written informed consent of the legal guardians of all participating parents was obtained.

Children (age 3-11 yrs) with mild persistent asthma and not on any prophylactic drugs were enrolled consecutively (January to December 2003). Exclusion criteria were active upper respiratory infection within three weeks, acute sinus disease requiring antibiotic treatment within one week, emergency treatment of asthma within one month or hospitalization for asthma within three months before enrolment. Children with a history of hypersensitivity to montelukast were excluded, only by asking the parents whether this drug was used previously and the child had any side-effects.

Children fulfilling the inclusion criteria were given 4 mg (3 to 4 yrs) / 5 mg (>4 yrs) tablets of montelukast in the evening regularly for 12 weeks. Children were considered to be compliant with the study medication if at least 80% of the study medications were taken according to the prescribed regimen. Short acting beta-agonists, either oral or inhaled (salbutamol or terbutaline) were used "as needed" during the study. The frequency and duration of their use were also noted. The use of oral theophylline, ICS, nasal steroid and inhaled or nasal cromolyn were not permitted. However, oral antihistamines, cough suppressants or expectorants, nasal decongestants (but not nasal steroids or nasal steroids or nasal cromolyn) were allowed. Appropriate treatment of acute asthma attacks were done according to hospital protocol and were documented.

Children were called for a pre-study screening just for enrollment in the study. After inclusion, a detailed history and clinical examination were completed for each child. For assessment, the physician examined the patient, recorded the adherence therapy, and any adverse effect and the clinical response on the following visits:

*Visit I*: Start of therapy;
*Visit II:* Four weeks after; and
*Visit III:* Twelve weeks after therapy.

Patients were advised to report at any time if there was exacerbation of asthma symptoms.

### Efficacy assessment

1. *Clinical assessment score* (*Table I*): was evaluated at entry (baseline), at 4 weeks

and at 12 weeks respectively as per NHLBI guidelines(1).

2. The frequency of use of beta agonists, intensity of acute attacks, need for oral steroids, nebulization or hospitalization during the study period was recorded.

3. *Pulmonary function testing* (*wherever possible*)*:* Peak expiratory flow rates (PEFR) at 8 am and 8 pm and spirometry (by any one author) were done regularly in some patients. FEV1 / FVC percentage was chiefly evaluated.

Children were closely monitored for any clinical adverse effects in each visit. Laboratory examinations (serum SGPT in selected subjects) were done at 12 weeks only.

## Results

A total of 65 children were enrolled in the study, but 50 children finally completed the study (6 excluded for non-compliance of the treatment and 9 excluded as they were in moderate persistent group on re-analysis). There were 28 boys and 22 girls with a mean age of 5.41 ± 2.11 yr (range 3-11 yrs). Demographic profile of these patients is presented in *Table II*.

Short acting bronchodilators were required for symptomatic relief for 3.84 ± 0.92 days, 2.52 ± 0.56 days, and 1.64 ± 0.23 days a week (on average) at baseline, after 4 weeks of therapy and after 12 weeks of therapy, respectively. No patient required hospitalization during therapy. Short course of oral steroids and nebulization was needed in 5 cases only (within 4 weeks).

Of total 40 cases with seasonal asthma, 22 cases started therapy one month before the season. Fourteen (63.67%) out of these 22 cases responded with improvement of symptoms (upgrading in all the scores with reduced use of beta-agonists) than the previous season. 18 cases started therapy during the season and only 6 (33.33%) of them responded favorably after 12 weeks. Fourteen (43.7%) out of 32 cases with allergic rhinitis showed clinical response for rhinitis symptoms within 4 weeks, while 18 (56.25%) cases did so after 12 weeks.

Improvement of clinical scores were significant in all the three parameters (*Table III*) *e.g.*, activity, wheeze and cough after 4 weeks and 12 weeks of therapy ($P < 0.001$). PEFR (done in 19/50 cases) and $FEV_1$ (done in 11/50 cases) documented mild improvement ($P < 0.05$) after 4 weeks while significant improvement ($P < 0.001$) occurred after 12 weeks of therapy.

A total of 19 out of 50 cases showed mild side-effects as anorexia (16%), elevated liver

**TABLE I**–*Clinical Assessment Score*

| Parameter | 0 | 1 | 2 | 3 |
|---|---|---|---|---|
| Wheeze | None | Some | Medium | Severe |
| Cough | None | Occasional | Frequent | Continous |
| Activity | None | Can run short distance or climb 3 flights of stairs | Can walk only | Missed school/work or stayed indoors |
| Sleep | Fine | Slept well, slight wheeze or cough | Awake 2-3 times, wheeze and/or cough | Bad night, awake all the time |

**TABLE II–***Demographic Profile*

| Parameter | Segments | Distribution |
|---|---|---|
| Population | Rural | 10 (20%) |
| | Urban | 40 (80%) |
| History of allergic rhinitis | Negative | 18 (36 %) |
| | Positive | 32 (64 %) |
| Family history of asthma | Negative | 04 (8 %) |
| | Positive | 46 (92 %) |
| History of exercise induced asthma | Negative | 30(60 %) |
| | Positive | 20 (40%) |
| Cough variant asthma | Negative | 12(24 %) |
| | Positive | 38(76 %) |
| Seasonal asthma | Negative | 10 (20 %) |
| | Positive | 40 (80 %) |
| Serum total IgE level | Negative (normal) | 44 (88 %) |
| | Positive (high) | 6 (12 %) |

**TABLE III**–*Overall Clinical Response*

| Scores | Bameline Mean (SD) | After 4 weeks Mean (SD) | P value | After 12 weeks Mean (SD) | P value |
|---|---|---|---|---|---|
| Activity | 1.64 ± (0.52) | 1.18 ± (0.69) | <0.001 | 0.7 ± (0.70) | <0.001 |
| Wheeze | 1.72 ± (0.70) | 1.28 (0.64) | <0.001 | 0.92 ± (0.69) | <0.001 |
| Cough | 1.50 ± (0.61) | 1.06 ± (0.71) | <0.001 | 0.88 ± (0.82) | <0.001 |
| PEFR | 120.21 ± (12.23) | 130.21 ± (16.34) | <0.05 | 135.41 ± (23.34) | <0.001 |
| $FEV_1$ | 71.44 ± (1.35) | 78.52 ± (3.45) | <0.05 | 87.1 ± (8.34) | <0.001 |

function tests (18%) and headache (10%). However, they were not excluded from the study.

## Discussion

In the present study, it was observed that once daily treatment with montelukast (as a single preventer agent) in mild persistent asthma in children showed significant efficacy. Montelukast showed significant (P <0.001) improvement in activity, cough and wheeze scores while PEFR and $FEV_1$ also improved (P <0.001) in the selected cases where it could be done. The response was evident within 4 weeks and continued till 12 weeks. This study results matches that of the National Montelukast survey 2005 conducted in 56 centers in United Kingdom which also confirmed that a significant proportion of children have their symptoms dramatically improved (41.3%) as compared to adults (33.5%)(15). Moreover, the use of short-acting bronchodilators as rescue therapy was significantly reduced following montelukast therapy as evidenced in other studies too(13).

**Key Messages**

- Oral, montelukast improves multiple clinical efficacy end-points when administered as a single prophylactic drug once daily in children with mild persistent asthma.
- Montelukast is well tolerated and its compliance is satisfactory.

Important issues to consider in treatment of children with asthma are drug administration and long-term adherence. ICS, the mainstay of preventer therapy so far are often difficult to administer, have variable drug delivery, more so in small children, and compliance may become questionable, especially if parents are not co-operative(16,17). In the present study the compliance with the orally used, once daily administered montelukast was satisfactory, with only 6 dropouts out of the initial 65 children enrolled (9.2%) as evidenced in other studies too(11). Moreover, the symptoms of seasonal asthma responded significantly in those who started the drug one month in advance *i.e.,* 14 (63.67%) out of 22 cases. The allergic rhinitis symptoms also improved in 14 (43.75%) out of 32 cases within 4 weeks, and in 18 (56.25%) cases after 12 weeks as evidenced in other studies too(15). In adults too, montelukast has shown its beneficial effects with improvements in multiple parameters of asthma control(11,12). The present study definitely suggests that these benefits of montelukast do extend to children as well.

Montelukast has been used in many trials as an add-on therapy with ICS in mild and moderate persistent asthma in children. This study has been targeted to see its effect as a single drug as a starter, preventer therapy in mild persistent asthma and has shown significant benefits as in other studies(8). During this 12 week therapy montelukast was well tolerated and had little side effects. This is similar to the studies in adults and children published before(18).

The present study was limited by being a non-randomized controlled one, the placebo effect was not accounted for, and the study of total eosinophil count was not included as it was difficult to have a single laboratory as reference. However, it is a short study report and is being continued for further evaluation later.

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