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Tolerability of Montelukast

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Abstract

The tolerability of a medication, especially in children with asthma, is linked to a number of key factors. These include clinical effectiveness, adverse effects, frequency of drug regimen, ease and route of administration, and taste.

Montelukast is unusual in that, in most countries, a licence for children aged ≥6 years was granted at the same time as the adult licence. This is related to a variety of evidence, which includes pharmacological and adult studies suggesting the specificity and safety of the drug at many times the licensed dose, and a tolerability profile similar to that with placebo or inhaled corticosteroids in both adult and paediatric studies. The most common adverse effects in paediatric studies were headache, asthma and upper respiratory tract infection at rates not statistically significantly different from those with placebo.

Up to July 1999, more than 2 million patients worldwide have received montelukast, of whom nearly 220 000 have received the paediatric formulation. In the UK, one prescribing database suggests that, of children who commenced montelukast therapy, less than 25% discontinued the drug. This implies that montelukast is effective and well tolerated in most children.

Adverse effect monitoring by regulatory bodies has revealed little that would not be expected on the basis of the results of clinical trials. Montelukast has been associated with Churg-Strauss syndrome in a very small number of adults. In most, the syndrome was associated with corticosteroid withdrawal, which may have unmasked the condition. Churg-Strauss syndrome has not been reported in children.

Its clinical effectiveness, lack of major adverse effects, oral route of administration, palatability and the once-daily regimen combine to make montelukast a generally well tolerated medication in children.

Antileukotrienes are the first new class of drugs for asthma in more than 20 years. A large number of compounds were investigated, many of which were poorly tolerated or associated with liver toxicity, prior to the launch of the currently licensed products. Since montelukast was the first antileukotriene to be licensed for use in children aged ≥6 years, the tolerability of this compound is especially important.

Montelukast has been launched in many countries worldwide since October 1997 (Finland launch). In most countries, simultaneous licences were granted for the adult (a 10mg film-coated tablet) and children's formulations (a 5mg chewable tablet), which suggests that regulatory bodies were satisfied with the overall tolerability profile of the medication.

Antileukotrienes represent a new class of drugs; therefore, the number of patients treated and the duration of treatment with these agents are limited. Up to July 1999, more than 2 million patients worldwide have received montelukast, of whom

nearly 220 000 have received the paediatric formulation. In order to fully evaluate the tolerability of the antileukotrienes, it is important to examine every available strand of evidence. In this article, the tolerability of montelukast is examined by reviewing a variety of data, including preclinical pharmacology, randomised controlled trials, open label extension studies, prescribing databases and adverse drug reaction reports. The paper focuses on the tolerability of montelukast in children, but relevant issues raised in adult and animal studies are also addressed.

1. Pharmacology of Montelukast: Implications for Tolerability

1.1 Specificity and Selectivity

Montelukast is an orally active antagonist of leukotriene D_4 at the cysteinyl leukotriene type 1 receptor. The drug binds with high affinity and selectivity to this receptor, in preference to other important airway receptors, including cholinergic and β-adrenergic receptors.

1.2 Absorption

The mean oral bioavailability of montelukast 5mg in adults is 73% in the fasted state versus 63% when administered with a standard meal.[1] This difference is unlikely to be of clinical significance, as montelukast was administered in the evening in clinical trials without regard to the timing of meals, with no apparent resulting variation in efficacy.

1.3 Distribution

Montelukast is more than 99% bound to plasma proteins, and studies in rats with radiolabelled montelukast indicate minimal distribution across the blood-brain barrier. In addition, concentrations of radiolabelled material at 24 hours postdose were minimal in all other tissues.[1]

1.4 Metabolism

Montelukast is extensively metabolised by the liver. In studies with therapeutic dosages at steady state, the metabolites of montelukast were undetectable in the plasma of adults and paediatric patients.[2]

In vitro studies using human liver microsomes indicate that cytochrome P450 (CYP) 3A4 and 2C9 are involved in the metabolism of montelukast, with no significant differences between adults and children.[3] Further *in vitro* studies in human liver microsomes demonstrate that montelukast does not inhibit other important CYP isozymes.

1.5 Elimination

After an oral dose of radiolabelled montelukast, 86% of the radioactivity was recovered in 5-day faecal collections and <0.2% was recovered in urine. This indicates that montelukast and its metabolites are excreted almost exclusively in bile.[4]

1.6 Special Conditions

1.6.1 Hepatic Insufficiency

In patients with mild-to-moderate hepatic insufficiency and clinical evidence of cirrhosis, the elimination of montelukast was decreased compared with healthy individuals (mean half-life 7.4 hours compared with 2.7 to 5.5 hours in healthy individuals). However, no dosage adjustment is recommended in patients with mild-to-moderate hepatic insufficiency. The pharmacokinetics of montelukast in patients with more severe hepatic impairment or with hepatitis have not been evaluated.[2]

1.6.2 Renal Insufficiency

Since montelukast and its metabolites are not excreted in the urine, no dosage adjustment is recommended in patients with renal dysfunction.

1.6.3 Phenylketonuria

Patients with phenylketonuria should not receive the 5mg chewable tablets, as that dosage form contains phenylalanine.[2,5]

1.7 Drug Interactions

Several drugs of relevance to paediatric practice have been evaluated in drug interaction studies with montelukast in adults. Montelukast 10mg did

not affect the plasma concentration of terfenadine or its metabolite fexofenadine, and did not prolong the QTc interval after coadministration with terfenadine 60mg twice daily.[2] Montelukast 100 mg/day at steady state did not significantly change the plasma profile of prednisolone.[2] The drug had no clinically significant effect on the anticoagulant effect of warfarin.[6]

At the recommended dosage of montelukast, there were no clinically important changes in the pharmacokinetics of theophylline, although 20- to 60-fold higher dosages of montelukast had some impact in reducing theophylline blood concentrations.[7]

Phenobarbital, a well-known inducer of hepatic metabolism, decreased the area under the curve of a single 10mg dose of montelukast by approximately 40%. No dosage adjustment for montelukast is recommended; however, it is reasonable to carefully monitor the clinical response in patients when potent inducers of CYP, such as phenobarbital or rifampicin (rifampin), are coadministered with montelukast.[2]

2. Summary of Tolerability Data from Controlled Clinical Trials

The tolerability of montelukast 5 mg/day was evaluated in approximately 320 children aged 6 to 14 years in controlled clinical trials. Montelukast was generally well tolerated in these patients, and adverse effects, which were usually mild, did not generally require discontinuation of therapy. The largest study had a withdrawal rate of 4% in the montelukast group and 2% in the placebo group.[8] The overall incidence of adverse effects in montelukast recipients was comparable to that in patients treated with placebo or inhaled corticosteroids.[2]

In the largest paediatric trial, 201 patients received montelukast 5 mg/day and 135 patients received placebo for 8 weeks.[8] There were no significant differences between the montelukast and placebo treatment groups in the frequency of any adverse effect, with the exception of allergic rhinitis, which occurred more frequently in placebo than montelukast recipients ($p = 0.01$). The most common adverse effects were headache, asthma, and upper respiratory tract infection in both treatment groups (table I). The following events occurred in ≥2% of patients and were more frequent in those receiving montelukast than placebo, regardless of causality assessment: diarrhoea, laryngitis, pharyngitis, nausea, otitis, sinusitis, and viral infection. 11 patients withdrew from the study because of an adverse effect: 8 (4%) in the montelukast group and 3 (2%) in the placebo group. 11 patients (5.5%) in the montelukast group and 2 (1.5%) in the placebo group had abnormal laboratory values, the majority of which were transient and self-limiting. Importantly, there were no significant differences between groups in the frequency of serum transaminase elevations.

Table I. Incidence of the most common adverse effects occurring in more than 6% of patients in either treatment group in an 8-week placebo-controlled study with montelukast 5 mg/day in children aged 6 to 14 years with chronic asthma

	Placebo (%) [n = 20]	Montelukast (%) [n = 135]
Upper respiratory tract infection	29.6	23.9
Headache	21.5	18.9
Asthma	22.2	16.4
Pharyngitis	12.6	13.9
Influenza	4.4	8.5
Cough	7.4	6
Fever	3.7	7.5

Cumulatively, 245 children have been enrolled into long term open label extensions of clinical trials.[9] Among the 207 montelukast recipients, the average duration of treatment was 1.1 years with a maximum of 1.4 years. Clinical and laboratory adverse effect profiles were generally similar in patients treated with montelukast or inhaled corticosteroids (n = 38). There were no clinically important changes in serum transaminase levels in either group.

In addition to the results in children, tolerability data are available for approximately 2600 adolescent and adult patients aged ≥15 years who received montelukast 10 mg/day in placebo-controlled clinical trials. Adverse effects reported by ≥1% of

Table II. Adverse effects occurring in ≥1% of patients aged 15 years and over treated with montelukast 10 mg/day or placebo, for which the incidence was greater in montelukast than placebo recipients, regardless of causality assessment

	Montelukast (%) [n = 1955]	Placebo (%) [n = 1180]
Body as a whole		
Asthenia/fatigue	1.8	1.2
Fever	1.5	0.9
Pain, abdominal	2.9	2.5
Trauma	1.0	0.8
Digestive system disorders		
Dyspepsia	2.1	1.1
Gastroenteritis, infectious	1.5	0.5
Pain, dental	1.7	1.0
Nervous system/psychiatric		
Dizziness	1.9	1.4
Headache	18.4	18.1
Respiratory system disorders		
Congestion, nasal	1.6	1.3
Cough	2.7	2.4
Influenza	4.2	3.9
Skin/skin appendages disorder		
Rash	1.6	1.2
Laboratory adverse experiences[a]		
ALT increased	2.1	2.0
AST increased	1.6	1.2
Pyuria	1.0	0.9

a Number of patients tested (montelukast and placebo, respectively): ALT and AST, 1935, 1170; pyuria, 1924, 1159.

patients and for which the incidence was greater in montelukast than placebo-treated patients are shown in table II.[2] These results were not assessed for causality.

3. Tolerability Compared with Other Treatments for Asthma in Children

Prescribing decisions are often based on a combination of factors, which include efficacy, tolerability, ease of administration and patient preference. Parents and caregivers play a critical role in the management of childhood asthma. In many instances, they are responsible for administering asthma therapy and monitoring the child's condition. Thus, it is important to consider both parental and child preferences in asthma therapy. How then is montelukast tolerated compared with currently recommended treatments for childhood asthma?

3.1 Versus Inhaled Corticosteroids

The adverse effects of inhaled corticosteroids are well recognised. Potential adverse effects include local effects such as oral thrush and dysphonia,[10] and systemic effects such as suppression of the hypothalamic-pituitary-adrenal (HPA) axis and decreased linear growth.[11,12] Most data indicate that, for patients with moderate asthma receiving 400 μg/day or more of inhaled beclomethasone dipropionate, a mild (1 cm/year) decrease in growth velocity may occur in studies of 1 to 2 years' duration;[11,13,14] however, according to 2 studies,[15,16] adult height appears unaltered by prolonged exposure to inhaled corticosteroids in childhood. Studies with low dosages of inhaled fluticasone propionate (<200 μg/day) have not shown significant growth suppression in children.[17] At present, most regulatory bodies advise that growth should be monitored in all children

receiving inhaled corticosteroids and that the benefits of these agents, especially at higher doses, need to be weighed against their potential hazards.

Even if it is not entirely rational, there is significant fear of the adverse effects of inhaled corticosteroids on the part of patients and parents. This fear may have a major negative impact on compliance.[18]

The only comparative tolerability data regarding montelukast and inhaled corticosteroids in children are from the extension study described above (section 2). The efficacy and tolerability of montelukast versus inhaled corticosteroids have been studied in adults.[19]

Montelukast 10 mg/day, inhaled beclomethasone dipropionate 200μg twice daily, given via a spacer device, or placebo were administered to 895 patients with chronic asthma in a randomised, double-blind, double-dummy, parallel-group study. Both montelukast and inhaled beclomethasone dipropionate had tolerability profiles similar to that of placebo during the 12-week study.[19]

3.2 Sodium Cromoglycate and Nedocromil

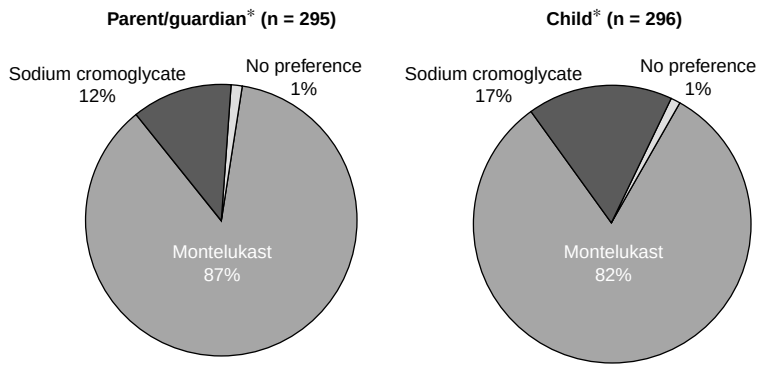
Sodium cromoglycate and nedocromil have been used for decades as treatments for asthma with no serious adverse effects, although their efficacy is inferior to that of inhaled corticosteroids.

A recently presented study examined how montelukast 5 mg/day was viewed in comparison with inhaled sodium cromoglycate 2600μg 4 times daily.[20] The primary objective of the 12-week, open label, crossover study was to evaluate the preferences of the parents or guardians of 333 children (aged 6 to 11 years) with asthma for oral therapy with montelukast or inhaled therapy with sodium cromoglycate. The childrens' preferences (including taste preferences), compliance and the overall satisfaction of both parents and children were also assessed.

The majority of parents or guardians (87%) preferred montelukast to inhaled sodium cromoglycate (fig. 1). Preferences among children paralleled the findings in parents or guardians; 82% of children preferred montelukast.[20]

The findings with respect to preference for both parents/caregivers and children were reflected in greater overall satisfaction with montelukast than sodium cromoglycate, as measured by a questionnaire ($p < 0.001$). While these findings could be related to oral administration and the once-daily dosage frequency, most children (72%) preferred the taste of the chewable montelukast formulation.[20]

The percentage of children who maintained a high rate of compliance (i.e. took the medication as prescribed on >95% of days during the study)



* $p < 0.001$ montelukast *vs* sodium cromoglycate

Fig. 1. Preferences of parents/guardians and children for oral therapy with montelukast (5 mg/day) or for inhaled inhaled sodium cromoglycate (2600μg 4 times daily) in a 12-week, open label crossover study.

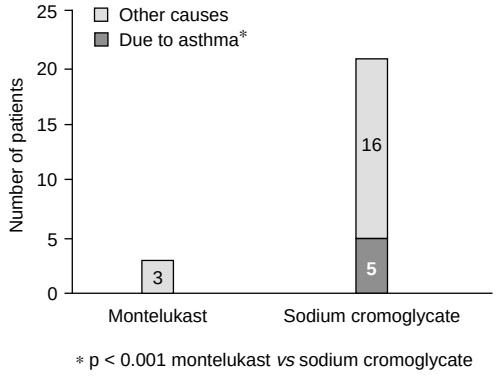


Fig. 2. Discontinuation rates in children receiving oral therapy with montelukast (5 mg/day) or inhaled sodium cromoglycate (2600μg 4 times daily) in a 12-week, open label crossover study.

with the montelukast regimen was nearly twice that observed with inhaled sodium cromoglycate (78 *vs* 42%, respectively; $p < 0.001$).[20]

Overall, both montelukast and inhaled sodium cromoglycate were generally well tolerated; however, asthma exacerbations were reported in significantly more patients receiving sodium cromoglycate than montelukast (7 *vs* 4%; $p < 0.05$). Moreover, significantly ($p < 0.001$) more patients discontinued inhaled sodium cromoglycate than montelukast because of asthma exacerbations (fig. 2).[20]

4. Prescribing Databases

Tolerability data for montelukast are available from a small number of prescribing databases.

The Mediplus database, which includes prescription records for approximately 888 000 patients in the UK, suggests that less than 25% of 123 children who were prescribed montelukast discontinued the drug. Reasons for cessation are not available but may include lack of effectiveness and/or adverse effects, patient preference or condition resolved (personal communication).

Prescription records for montelukast in the Thorpewood Medical Group database, which includes 1340 patients with asthma, have also been analysed. 40 patients, of whom 19 were aged 6 to 14 years, met the study's inclusion criteria. These were as follows: (i) patients treated for persistent asthma of mild to moderate severity for 1 year prior to starting montelukast; (ii) full clinical records of prescribing and healthcare utilisation for at least that 1-year period. The study was carried out prospectively from the time montelukast was started.

Of the 40 patients, 6 (including 2 children) ceased treatment within the 6 months – because of lack of efficacy (4), adverse effects (headache in 1 patient) or dislike of taste (1). Among the 34 remaining patients, the following personal targets were achieved in at least 75% of those setting the target: an increased ability to do certain activities or exercise (59% of patients), fewer exacerbations (38% of patients), fewer daytime symptoms (35% of patients), reduction in potential adverse effects of inhaled corticosteroids (by reducing the dosage of inhaled corticosteroid; 18% of patients), improvement in rhinitis (15% of patients), and improvement in eczema (18% of patients). The mean patient-reported benefit for all these targets was a 75% or greater improvement. The objective changes found are shown in table III.[21]

5. Postmarketing Surveillance

5.1 Churg-Strauss Syndrome

The greatest concern raised during postmarketing surveillance with montelukast is Churg-Strauss syndrome. Reports of Churg-Strauss vasculitis, systemic eosinophilia or eosinophilic vasculitis in adults during treatment with zafirlukast or montelukast are considered by most authors to reflect the emergence of an underlying disease because of the withdrawal of corticosteroids, rather than a cause and effect relationship with the antileukotriene.[22] Most of these patients had a history of severe asthma and were receiving multiple medications, often including systemic corticosteroids, and some had features consistent with Churg-Strauss syndrome prior to starting therapy with montelukast or zafirlukast. In most but not all patients, the clinical features of Churg-Strauss syndrome occurred or worsened during reductions

Table III. Prospective evaluation of 40 patients who were begun on montelukast, using their clinical records to compare the 6 months before with the 6 months after starting montelukast

Parameter	Outcome after 6 months' montelukast treatment
Change in clinic recorded mean peak flow	+14.7%*
Mean change in daily β-agonist use	–43.1%*
Mean change in number of general practice consultations	–38.6%*
Mean change in inhaled corticosteroid	–57%*
Mean change in number of antibiotic courses	–92%*
Mean change in number of oral prednisolone courses	–92%
Average change in drug costs per patient per annum	+£37.24
Average change in total healthcare costs	–£2.26

*$p < 0.05$ *vs* baseline.

in the corticosteroid dosage. A causal association between montelukast and Churg-Strauss syndrome has not been established, although there has been some debate regarding this (Paul O'Mahony, personal communication: Committee on Safety of Medicines, London, UK).[2] It is noteworthy that this condition has been reported with other asthma therapies, including inhaled corticosteroids.[23]

No eosinophilic conditions have been reported in children receiving montelukast.

5.2 Other Events

Between February 1998, when montelukast was launched in the UK, and July 1998, the British Committee on Safety of Medicines received 173 case reports of 317 suspected adverse effects for montelukast. Suspected adverse effects not identified during clinical trials include the following: oedema (50), psychiatric reactions including agitation/restlessness (15), allergy including anaphylaxis, angioedema and urticaria (10), chest pain (7), tremor (5), dry mouth (5), vertigo (4) and arthralgia (3).[24]

Up to May 1999, the Committee received 54 reports of adverse effects in children aged 6 to 14 years during treatment with montelukast. This represents approximately 8% of adverse effects reported in children during that period. It is estimated that 5000 children aged 6 to 14 years received prescriptions for the drug in that period. The reported adverse effects were similar to those described above (Paul O'Mahony, personal communication: Committee on Safety of Medicines, London, UK).

Although the short term safety profile of montelukast has thus far been excellent, further postmarketing surveillance may reveal rare but significant adverse effects. So, vigilance, as with all new compounds, remains essential.

6. Conclusions

Dosage frequency and the complexity of administration can be important compliance considerations with respect to asthma therapy. In children, compliance can be further confounded by the level of support and supervision that parents and caregivers are able to provide. Simplicity of the treatment regimen, as well as efficacy and the frequency of adverse effects contribute to the tolerability of a drug. In general, montelukast is well tolerated in paediatric patients, although it remains important to continue to monitor patients for adverse effects.

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