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Montelukast

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Contents

Abstract

▲ Montelukast is a selective antagonist of the leukotriene D_4 (LTD_4) receptor. In patients with asthma, montelukast 5 to 250 mg/day attenuated LTD_4-induced bronchoconstriction and, at a dosage of 10mg, significantly reduced early and late airway response to allergen (dust mite extract) relative to placebo.

▲ In studies evaluating the effects of various dosages of montelukast on exercise-induced bronchoconstriction the optimal dose of the drug was found to be 10mg.

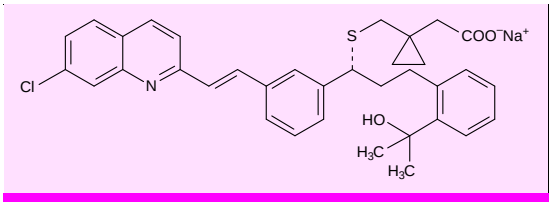
▲ Montelukast 10 mg/day controlled asthma significantly more effectively than placebo in a 3-month randomised double-blind study. In a 9-month open extension of this trial, during which patients were randomised to treatment with montelukast 10 mg/day or beclomethasone (≈400 μg/day), daytime symptom score and β-agonist use decreased to a similar extent in each group.

▲ In a further study, treatment with montelukast 10 mg/day permitted clinically significant tapering of corticosteroid dosage in patients with stable asthma.

▲ Montelukast (5 mg/day) has also demonstrated efficacy in childhood asthma.

▲ The tolerability profile of montelukast was similar to that of placebo in placebo-controlled clinical trials in adults and children; the most common adverse event was headache.

Features and properties of montelukast (MK-0476)	
Indications	
Adult and childhood asthma	
Mechanism of action	
Antiinflammatory	Leukotriene antagonist
Dosage and administration	
Usual dosage in clinical trials	10mg (adults) 5mg (children)
Route of administration	Oral
Frequency of administration	Once daily
Pharmacokinetic profile	
Peak plasma concentration	602.8 μg/L
Time to peak plasma concentration	2.7h
Area under the plasma concentration-time curve	3978 μg/L • h (3.98 mg/L • h)
Bioavailability	64%
Clearance	45.5 ml/min
Plasma elimination half-life	2.7-5.5h
Adverse events	
Most frequent	Headache



Montelukast

It has become clear that cysteinyl leukotrienes mediate allergen-induced airway obstruction, and leukotrienes C_4, D_4 and E_4 are now known to be responsible for the physicochemical and biological properties of the slow-reacting substance of anaphylaxis.

Montelukast is a potent selective antagonist of the leukotriene D_4 (LTD_4; $cysLT_1$) receptor that has been developed as a once daily oral treatment for adults and children with asthma.

1. Pharmacodynamic Profile

• In anaesthetised guinea-pigs intravenous (IV) montelukast inhibited the bronchoconstrictive response to IV LTD_4 but not arachidonic acid, histamine, serotonin or acetylcholine. Oral montelukast (0.01 mg/kg) blocked LTD_4 or ascaris-induced bronchoconstriction in conscious squirrel monkeys, and ovalbumin-induced bronchoconstriction in conscious sensitised rats. A continuous infusion of montelukast 8 μg/kg/min decreased peak early and late responses to ascaris aerosol challenge by 70 and 75%, respectively, in allergic conscious sheep.[1]

• In 12 patients with asthma [mean forced expiratory volume in 1 second (FEV_1) 79 to 109% of predicted (FEV_1-PP)], short term (3 10mg doses at 24-hour intervals) administration of montelukast protected against allergen (administered 12 hours before the last dose of montelukast)-induced airways response, but did not attenuate the associated increase in eosinophils and ECP in induced sputum.[2]

• In contrast, 4 weeks' treatment with montelukast 10 mg/day in 40 patients with asthma (FEV_1-PP 65 to 85) was associated with a significant reduction in sputum eosinophils relative to placebo in a randomised double-blind parallel study.[3]

• Two randomised double-blind placebo-controlled crossover studies have evaluated the ability of montelukast to inhibit LTD_4-induced bronchoconstriction in patients with asthma (median FEV_1-PP 82.3 for both studies). In the first trial (n = 8) LTD_4 challenge was started 4 hours after administration of montelukast 5, 20, 100 or 250mg, or placebo. In the second trial (n = 6) LTD_4 challenge was started 20 hours after administration of montelukast 40 or 200mg, or placebo. In both studies increasing (in 2-fold increments) doses of inhaled LTD_4 were administered until specific airways conductance (sGaw) decreased by ≥50% (PC_{50}) or the highest concentration of LTD_4 was reached. In the first trial all 4 doses of montelukast attenuated bronchoconstriction at the highest dose of LTD_4 (sGaw PC_{50} was not reached). In the second trial the 200mg, but not the 40mg dose attenuated LTD_4-induced bronchoconstriction.[4]

• Oral montelukast 10mg significantly reduced early (by 53.6%) and late (by 36.4%) airway response to inhaled antigen (dust mite extract) challenge, relative to placebo, in 12 atopic men with asthma (FEV_1-PP 79 to 109).[5]

• Two days' treatment with montelukast 100 mg/day significantly inhibited exercise-induced bronchoconstriction relative to placebo in patients (n = 19) with asthma (FEV_1-PP ≥65). Median FEV_1 fell 14 to 16.9% during exercise challenge in montelukast recipients compared with 25.3% in placebo recipients ($p \leq 0.05$). Montelukast was equally effective administered as 1 or 2 daily doses.[6]

• A dose-dependent effect was observed in 2 similar studies (n = 25 and 27) that evaluated the effects of montelukast over a range of dosages (0.4 to 50mg). Montelukast 10mg optimally inhibited exercise-induced bronchoconstriction in both studies.[7,8]

• In a further study, tolerance to the protective effect of montelukast 10 mg/day against exercise-

induced bronchoconstriction did not occur during 12 weeks of randomised double-blind treatment in 110 patients with asthma (FEV_1-PP ≥65). At the study end-point the maximum fall in FEV_1 after exercise was 22% in montelukast recipients versus 32% in the placebo group ($p = 0.003$).[9]

• The drug also inhibited exercise-induced bronchoconstriction in 27 children (6 to 14 years of age) with asthma (FEV_1-PP ≥70). Montelukast 5mg (chewable tablet formulation) or placebo were administered once daily for 2 days in a randomised double-blind crossover study. The maximum post-exercise test fall in FEV_1 was 18.3% in the montelukast group versus 26.1% in the placebo group ($p < 0.009$). The test was conducted at the end of the dosage interval, 20 to 24 hours after administration of the final dose of montelukast or placebo.[10]

2. Pharmacokinetic Profile

• The area under the plasma concentration-time curve $(AUC)_\infty$ of montelukast was dose related, increasing in proportion to increasing IV doses (3, 9 and 18mg) in male volunteers (n = 6). Plasma clearance [overall mean 45.5 ml/min (2.73 L/h)], steady-state volume of distribution (10.5L), plasma terminal elimination half-life ($t_{1/2}$) [5.1h] and mean residence time (3.9h) were essentially constant over the dosage range studied. Respective values of 47.6 ml/min (2.86 L/h), 9.6L, 4.5h and 3.6h were recorded in 6 female volunteers who received IV montelukast 9mg.[11]

• A 10mg oral dose of montelukast produced maximum plasma concentrations (C_{max}) of 385 and 350 μg/L 3.7 and 3.3 hours after administration (t_{max}) in men (n = 6) and women (n = 6), respectively. Respective values for AUC were 2441 and 2270 μg/L · h and for apparent $t_{1/2}$ 4.9 and 4.4h. The mean absorption time was 3.4 hours in men and 2.6 hours in women.[11] The mean oral bioavailability of the drug is 64% and plasma clearance averages 45 ml/min in healthy adults.[12]

• Montelukast AUC_{24h}, C_{max}, t_{max} and $t_{1/2}$ were 3978 μg/L · h, 602.8 μg/L, 2.7h and 5.6h after administration of 7 once-daily 10mg doses to 12 volunteers. AUC_{24h} was significantly ($p < 0.05$) higher at endpoint than on the first day of the study, but C_{max}, t_{max} and $t_{1/2}$ values were similar at both time points.[13] Analysis of several studies showed the mean plasma $t_{1/2}$ ranged between 2.7 and 5.5 hours in healthy young adults.[12]

• In volunteers (n = 6) 86.3% of a single oral 102mg dose of [^{14}C]montelukast was recovered in the faeces; less than 0.2% of radioactivity appeared in the urine. Radiochromatic analysis of bile in a subsequent study, in which a 58.4mg oral dose of [^{14}C]montelukast was given to 6 volunteers, identified 1 major and several minor metabolites, as well as small amounts of unchanged drug.[14]

• The bioavailability of a single oral 10mg dose of montelukast in elderly (mean age 69.4 years) volunteers was 61%, similar to that observed in younger volunteers. Mean AUC_∞, C_{max}, t_{max} and $t_{1/2}$ were also generally similar to those observed in younger volunteers, indicating that the dosage of montelukast does not require adjustment in older patients.[13]

3. Therapeutic Potential

• Initial studies evaluating the therapeutic efficacy of montelukast in patients with asthma used 100 to 600mg daily doses of the drug.[15-17]

• However, a subsequent 6-week double-blind study that compared the efficacy of montelukast at dosages ranging from 10 to 200 mg/day in patients (n = 361, ≈60 per treatment group) with asthma (FEV_1-PP 40 to 80) reported that the lowest dose (10mg) was significantly more effective than placebo.[18]

• In a similarly designed study, mean morning peak expiratory flow rate (PEFR) increased by 13.5% from baseline in patients with chronic asthma (FEV_1-PP 40 to 80) randomised to treatment with montelukast 10 mg/day (n = 68), compared with 14.7 and 13.1% in patients randomised to treatment with montelukast 2 (n = 72) and 50 (n = 72) mg/day, respectively, and 6.2% in placebo recipients (n = 69; $p < 0.05$ *vs* all active treatment

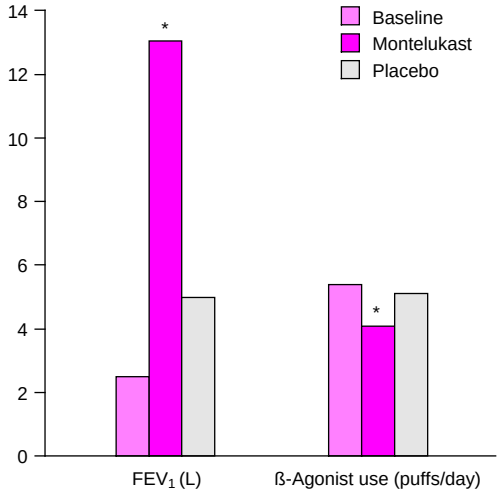


Fig. 1. Forced expiratory volume in 1 second (FEV_1) and β-agonist usage (puffs/day) during 3 months' randomised double-blind treatment with montelukast 10 mg/day or placebo in patients (n = 681) with asthma.[20] * $p < 0.001$ vs placebo.

groups). The percentage of patients with asthma exacerbations was significantly ($p < 0.05$) lower in the montelukast 10 and 50 mg/day groups (44.1 and 50.0% respectively) than in the placebo (69.6%) group. Patient-reported end-points including daytime symptom score, use of as-needed inhaled β-agonists and asthma-specific quality-of-life were also significantly improved in montelukast 10 and 50 mg/day recipients compared to placebo recipients.[19]

- A longer term (3-month) trial also reported montelukast 10 mg/day to be significantly more effective than placebo as treatment for patients with asthma (n = 681; FEV_1-PP 50 to 85) [fig. 1].[20]

- After completing the above trial, 373 patients entered a 9-month open extension phase and were randomised to treatment with montelukast 10mg once daily or beclomethasone (≈400 μg/day). FEV_1 increased 10.92% in the montelukast group compared with 16.31% in the beclomethasone group (respective baseline values were 2.4 and 2.5L) during this study. Total daily β-agonist use decreased by 35.6 and 37.3%, respectively, from baseline values of 5.6 and 5.7 puffs per day.[21]

- In 226 patients with stable asthma (FEV_1-PP ≥70), clinically significant tapering of inhaled corticosteroid therapy was possible during treatment with montelukast 10 mg/day. Inhaled corticosteroid doses were reduced at 2-week intervals during a 6-week single-blind run-in period; patients were then randomised to double-blind therapy with montelukast 10 mg/day or placebo for 12 weeks. During this double-blind treatment period, the mean corticosteroid dosage was able to be reduced from 976 to 526 μg/day in the montelukast group versus from 1079 to 727 μg/day in the placebo group ($p < 0.05$ *vs* montelukast) [fig. 2].[22]

- Montelukast also improved asthma control in aspirin-intolerant patients (n = 80) with asthma often incompletely controlled with oral or inhaled corticosteroids (mean FEV_1-PP 69). Patients who received double-blind treatment with montelukast 10 mg/day had fewer days with asthma exacerbations and more asthma-free days compared with

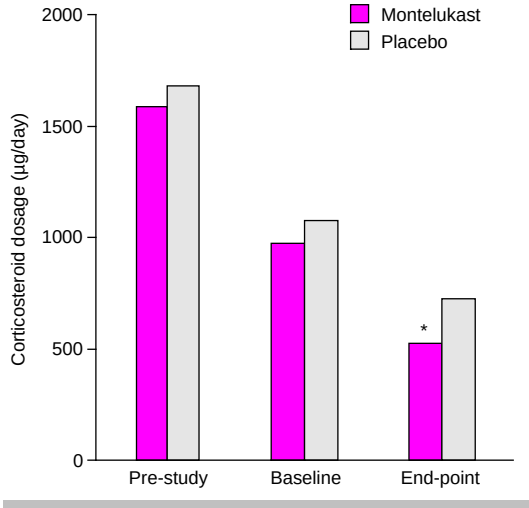


Fig. 2. Results of corticosteroid dosage tapering during treatment with montelukast 10 mg/day or placebo. 226 patients entered a 12-week single-blind run-in phase during which their inhaled corticosteroid dosage was tapered at 2-week intervals. Then, after a 7- to 10-day baseline period, stable patients were randomised to 6 weeks' double-blind treatment with montelukast or placebo during which corticosteroid dosage was adjusted downward, provided asthma control remained within defined limits.[22] * $p < 0.05$ *vs* placebo.

placebo recipients. FEV_1 increased 8.55% from baseline in the montelukast group compared with a 1.74% decrease in the placebo group. In addition, montelukast recipients were able to reduce their β-agonist usage by 1.04 puffs per day compared with a reduction of 0.08 puffs per day in the placebo group.[23]

- The therapeutic efficacy of montelukast has also been demonstrated in children (aged 6 to 14 years) with chronic asthma (mean FEV_1-PP 72). 336 children were randomised to 2 months' double-blind treatment with montelukast 5mg once daily or placebo. FEV_1, the primary endpoint, increased 8.23% (least squares mean) during montelukast therapy compared with 3.58% during placebo therapy ($p < 0.001$). Certain secondary outcomes, including total daily as-needed β-agonist usage and quality-of-life measures, were also more favourable in montelukast versus placebo recipients ($p < 0.05$). Other secondary outcomes, including daytime asthma symptoms, patient reported morning and evening PEFR, physician's and patient's global evaluation, nocturnal awakenings, discontinuations resulting from worsening asthma, rescue oral corticosteroid use, asthma control days and percentage of school days lost, did not differ significantly between the 2 treatment groups. It was noted, however, that the study lacked sufficient power to detect between treatment differences in secondary outcomes.[24]

- 246 children who participated in the above study subsequently entered a 4-month open extension and were randomised to continued treatment with montelukast 5mg once daily or inhaled corticosteroid therapy (≈252 μg/day). FEV_1 increased 12.42% in montelukast recipients and 14.32% in inhaled corticosteroid recipients during this extension phase.[25]

4. Tolerability

Single 20 to 800mg doses of montelukast were well tolerated by male volunteers in a double-blind, crossover placebo-controlled study. 11 of 18 participants experienced adverse events considered by the investigator to be possibly related to treatment. These included headache (6 episodes during active treatment *vs* 4 with placebo), diarrhoea (1 *vs* 1), facial flushes (1 episode during active treatment) and tenderness in the right hypochondrium, abdominal cramps and abdominal discomfort (1 episode of each during placebo treatment). All adverse events were considered mild and self-limiting; none required treatment.[26]

- Tolerability data are available from 1955 adult patients who participated in placebo-controlled clinical trials evaluating montelukast at a dosage of 10 mg/day. The most common adverse event (regardless of drug relationship) was headache which occurred in 18.4% of montelukast versus 18.1% of placebo recipients, other adverse events that occurred in >2.5% of montelukast recipients included cough (2.7% in montelukast *vs* 2.4% in placebo recipients), influenza (4.2 *vs* 3.9%) and abdominal pain (2.9 *vs* 2.5%). The adverse event profile of montelukast in patients aged 6 to 14 years ($n \approx 320$) was generally similar to that seen in adults and in placebo recipients.[12]

5. Montelukast: Current Status

Montelukast is a selective leukotriene D_4 receptor antagonist that has demonstrated clinical efficacy in, and is approved for, the once daily treatment of asthma in adults and children.

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