Comparison of the effects of intravenous and oral montelukast on airway function: a double blind, placebo controlled, three period, crossover study in asthmatic patients

R J Dockhorn, R A Baumgartner, J A Leff, M Noonan, K Vandormael, W Stricker, D E Weinland, T F Reiss

Abstract

Background—Montelukast, a leukotriene receptor antagonist, improves parameters of asthma control including forced expiratory volume in one second (FEV1) when given orally to patients aged six years or older. This study was undertaken to compare the effect on FEV1 of intravenous and oral montelukast and placebo during the 24 hour period following administration.

Methods—Fifty one asthmatic patients (FEV1 40–80% predicted and >15% improvement after inhaled β agonist) were enrolled in a double blind, single dose, three period, crossover study to receive intravenous montelukast (7 mg), oral montelukast (10 mg), or placebo in a randomised fashion. The primary end point was area under the curve (AUC)0–24 h of the percentage change from baseline in FEV1. Additional end points were maximum percentage change in FEV1, and percentage change at different time points.

Results—Compared with placebo, intravenous and oral montelukast significantly increased the AUC0–24 h (means of 20.70%, 15.72%, and 7.75% for intravenous, oral and placebo, respectively; no statistical difference between intravenous and oral). The difference in least square means from placebo for intravenous montelukast was 13.27% (95% CI 7.07 to 19.46), p<0.001 and for oral montelukast was 7.44% (95% CI 4.47 to 10.41), p<0.001. The maximum percentage change in FEV1 with intravenous than with oral montelukast was 15.02% vs 4.67% at 15 min, p<0.001; 18.43% vs 12.90% at one hour, p<0.001 for intravenous and oral montelukast, respectively (placebo 3.05% at 15 minutes, 7.33% at one hour). Intravenous and oral montelukast were similar to placebo in the frequency of adverse events.

Conclusions—The onset of action for intravenous montelukast was faster than for oral montelukast and the improvement in airway function lasted over the 24 hour observation period for both treatments. Although not well understood, there was a trend toward a greater improvement in FEV1 with intravenous than with oral montelukast. These findings suggest that leukotriene receptor antagonists should be investigated as a treatment for acute severe asthma.

Keywords: asthma; leukotriene receptor antagonist; montelukast

The incidence of asthma has increased substantially in many countries during the last two decades in both children and adults. In addition, the number of patients presenting to emergency room departments with severe acute asthma exacerbations has also increased in some countries. The reasons for this increase remain speculative. Despite these changes in the epidemiology of acute asthma, drug treatment for acute severe asthma has changed little over the last two decades, consisting primarily of bronchodilators, corticosteroids, and oxygen.

Leukotrienes, products of inflammatory cells such as eosinophils and mast cells, are released during acute asthma attacks and have increasingly become recognised as inflammatory mediators that play a significant role in the pathophysiology of asthma. Recently, montelukast, an orally active, potent and specific cysteinyl leukotriene receptor antagonist, has been shown to improve asthma control in patients with chronic asthma aged six years or more. In addition, the improvement in forced expiratory volume in one second (FEV1) observed with oral montelukast appears to be additive to that of β agonists and to occur within a few hours after administration.
Comparison of the effects of intravenous and oral montelukast on airway function

The study was composed of a prestudy visit (where inclusion/exclusion criteria were determined) and three efficacy periods (periods I–III). Patients were allocated randomly to receive a single dose of intravenous montelukast (7 mg), oral montelukast (10 mg), or placebo during each of the three periods after withholding inhaled β agonist for six hours.

Study medication was administered the same time of morning (± one hour) on each treatment day; thereafter, patients were observed for 24 hours to document the effect on FEV₁. At least four (but no more than 14) days elapsed between treatment periods. Physical examinations, vital signs, local intravenous site evaluation, spirometric measurements, and laboratory safety tests were performed.

Spirometric measurements (Puritan-Bennett PB 100) were conducted 30 minutes and five minutes before administration of the study drug and 0.25, 0.5, 1, 2, 4, 8, 12, 16, and 24 hours afterwards in accordance with the reproducibility and acceptability criteria of the American Thoracic Society. If the FEV₁ was less than 40% predicted or more than 80% predicted prior to drug administration the patient was treated with inhaled salbutamol and rescheduled for administration of the study drug on another day. If after drug administration a patient’s FEV₁ fell by more than 25% of its initial value or fell below 40% of the predicted normal value, or if the investigator or patient felt it was indicated, the patient was treated with inhaled albuterol.

An intravenous catheter was inserted for collection of pretreatment blood for laboratory safety tests. After blood collection the intravenous site was converted to a heparin lock and used for administration of study drug with vehicle (dextrose 3.3%/sodium chloride 0.3%).

Dose selection and administration
A preliminary study indicated that the plasma concentration–time profile of intravenous montelukast was proportional to the dose over the range of 3–18 mg. In an additional study (unpublished) an intravenous dose of 7 mg was identified as the dose resulting in a comparable area under the plasma concentration–time curve (AUC) as that obtained with 10 mg oral montelukast—demonstrating maximal clinical efficacy in patients with chronic asthma.

The intravenous dose of montelukast (7 mg, 0.23 mg/ml) or matching placebo was given as a manual bolus in a syringe (containing 30 ml of drug or placebo) over two minutes. The prepared solution of drug was light sensitive so the syringe was protected by wrapping in aluminium foil. At the end of the drug administration the catheter was flushed with 2–3 ml of vehicle. The study medication tablet (montelukast 10 mg or placebo) was administered with 150 ml water.

The patients were observed in the unit for 24 hours after administration of the study drug. Vital signs were measured frequently (patients sat or reclined for at least five minutes prior to measurements). All patients had laboratory safety tests (blood at prestudy visit, 30 minutes before and 24 hours after drug administration; urine at prestudy visit, 60 minutes before and 24 hours after administration of study drug). Adverse effects and vital signs were recorded at each visit.

Evaluations and statistical analysis
Data from all patients were included in the analysis of efficacy and safety (intention to treat approach).

The primary end point was AUC₀–24 h (area under the FEV₁ percentage change from baseline/time curve, standardised for time of follow up, see below). Secondary end points were maximum percentage change in FEV₁ from baseline and percentage change from baseline in FEV₁ at each measured time point following treatment. The baseline for all end points was the average of the two pretreatment values 30 and five minutes before each period. Post hoc analysis included evaluating the proportion of patients requiring rescue medi-

### Table 1 Baseline characteristics of patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean (SD)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients (n=51)</td>
<td>29.8 (11.2)</td>
<td>15.0–56.0</td>
</tr>
<tr>
<td>Men (n=29)</td>
<td>28.9 (12.0)</td>
<td>15.0–56.0</td>
</tr>
<tr>
<td>Women (n=22)</td>
<td>31.0 (10.5)</td>
<td>18.0–51.0</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>78.5 (15.5)</td>
<td>52.6–124.2</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>171.8 (8.4)</td>
<td>154.9–190.5</td>
</tr>
<tr>
<td>Duration of asthma (years)</td>
<td>19.2 (11.7)</td>
<td>2.3–50.4</td>
</tr>
<tr>
<td>FEV₁ (l)</td>
<td>2.5 (0.6)</td>
<td>1.3–3.8</td>
</tr>
<tr>
<td>FEV₁ (% of predicted)</td>
<td>63.8 (11.2)</td>
<td>42.8–80.2</td>
</tr>
</tbody>
</table>

*Measurements taken at prestudy visit.

In this study we have investigated the speed of onset, duration of action, and the magnitude of effect of intravenous versus oral montelukast on airway function in chronic asthmatic patients.

**Methods**

**Patients**

Fifty one patients (22 women) with at least a one year history of chronic asthma, an FEV₁ of 40–80% predicted, and with a ≥15% improvement in FEV₁ (absolute value) after inhaled β agonist were enrolled (table 1). Patients were eligible to participate if they were currently non-smokers (smoking history ≤ 7 pack years) and had not taken oral, intravenous, or intramuscular corticosteroids during the month prior to the start of the study (inhaled corticosteroids were allowed in up to 25% of patients as long as the dosing had been stable for two weeks prior to and during the study). Those taking long acting antihistamines within two weeks of the first prestudy visit, or theophylline, oral or long acting inhaled β agonists, cromolyn sodium or nedocromil, or inhaled anticholinergics within one week, or short acting antihistamines during the 48 hours before the visit were excluded. The study was approved by local ethics committees and the patients gave written informed consent.

**Study design**

This was a multicentre, double blind, randomised, placebo controlled, three period crossover study.

The study was composed of a prestudy visit (where inclusion/exclusion criteria were determined) and three efficacy periods (periods I–III). Patients were allocated randomly to receive a single dose of intravenous montelukast (7 mg), oral montelukast (10 mg), or placebo during each of the three periods after withholding inhaled β agonist for six hours.

### DOSE SELECTION AND ADMINISTRATION

A preliminary study indicated that the plasma concentration–time profile of intravenous montelukast was proportional to the dose over the range of 3–18 mg. In an additional study (unpublished) an intravenous dose of 7 mg was identified as the dose resulting in a comparable area under the plasma concentration–time curve (AUC) as that obtained with 10 mg oral montelukast—demonstrating maximal clinical efficacy in patients with chronic asthma.

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The patients were observed in the unit for 24 hours after administration of the study drug. Vital signs were measured frequently (patients sat or reclined for at least five minutes prior to measurements). All patients had laboratory safety tests (blood at prestudy visit, 30 minutes before and 24 hours after drug administration; urine at prestudy visit, 60 minutes before and 24 hours after administration of study drug). Adverse effects and vital signs were recorded at each visit.

### Evaluations and Statistical Analysis

Data from all patients were included in the analysis of efficacy and safety (intention to treat approach).

The primary end point was AUC₀–24 h (area under the FEV₁ percentage change from baseline/time curve, standardised for time of follow up, see below). Secondary end points were maximum percentage change in FEV₁ from baseline and percentage change from baseline in FEV₁ at each measured time point following treatment. The baseline for all end points was the average of the two pretreatment values 30 and five minutes before each period. Post hoc analysis included evaluating the proportion of patients requiring rescue medi-
who needed rescue medication the last recorded FEV₁ value before administration of rescue medication was carried forward through all subsequent time points in that treatment period.

The study was analysed using an ANOVA model including factors for study centre, patient (within centre), period, and treatment. The difference between treatments was estimated by the difference in least square means and the associated 95% confidence interval (CI).

The effect of first order carryover was tested at a significance level of α = 0.10 and was found to be not significant and was therefore subsequently removed from the model. The “treatment by centre” interaction was assessed at the level of α = 0.10 and was found to be not qualitatively significant.

The normality assumption of the ANOVA model was assessed by the Shapiro–Wilk statistic. Plots of residuals versus predicted values were also used to examine the assumption of variance homogeneity and no evidence of non-normal distribution was found.

There are two main comparisons of interest in this study. The first is the placebo comparison—that is, between intravenous montelukast and placebo—and the second is the active treatment comparison—that is, between intravenous and oral montelukast. These two comparisons were prespecified as separate hypotheses of equal interest so no adjustment for multiplicity was necessary.

With 48 completing patients there was a 90% power to detect a 6.5% point difference in FEV₁ (AUC₀–二十四 h in percentage change from baseline) between the active treatment groups assuming a significance level of 0.05 and within-patient variability of 9.7% as observed in a previous study.¹²

Results

Fifty one patients were randomised and 50 patients completed the study. One patient withdrew after treatment in period I. This patient developed a poison ivy rash and declined to continue in the study (the patient had been randomised to receive oral montelukast). Tables 1 and 2 list baseline characteristics. Four (8%) patients used concomitant inhaled corticosteroids throughout the trial. Predosing baseline FEV₁ values did not differ among the treatments or periods (table 2).

AUC₀–二十四 h

The mean AUC₀–二十四 h values following treatment are shown in table 3. The between group differences for least square (LS) means AUC₀–二十四 h were significant for intravenous (p<0.001) and oral montelukast (p = 0.020) compared with placebo. The difference between intravenous and oral montelukast favoured the intravenous form but did not reach statistical significance (p = 0.067). The percentage change from baseline in FEV₁ over the 24 hours following treatment is shown in fig 1.

### Table 2 Baseline FEV₁ by period and treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No.</th>
<th>Mean (SD)</th>
<th>95% CI for mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>50</td>
<td>50.92 (11.47)</td>
<td>(44.42 to 57.43)</td>
</tr>
<tr>
<td>Oral montelukast</td>
<td>51</td>
<td>52.16 (11.16)</td>
<td>(46.36 to 57.97)</td>
</tr>
<tr>
<td>IV montelukast</td>
<td>50</td>
<td>51.58 (11.33)</td>
<td>(45.58 to 57.59)</td>
</tr>
</tbody>
</table>

The mean AUC₀–二十四 h values following treatment

The mean AUC₀–二十四 h values following treatment are shown in table 3. The between

### Table 3 Area under the curve of percentage change from baseline in FEV₁, standardised for time of follow up (AUC₀–二十四 h)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean (% change)</th>
<th>95% CI for mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>50</td>
<td>64.40 (11.41)</td>
</tr>
<tr>
<td>Oral montelukast</td>
<td>51</td>
<td>63.66 (12.82)</td>
</tr>
<tr>
<td>IV montelukast</td>
<td>50</td>
<td>62.88 (11.55)</td>
</tr>
</tbody>
</table>

*One patient withdrew after period I (see Results section).

The normality assumption of the ANOVA model was assessed by the Shapiro–Wilk statistic. Plots of residuals versus predicted values were also used to examine the assumption of variance homogeneity and no evidence of non-normal distribution was found.

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With 48 completing patients there was a 90% power to detect a 6.5% point difference in

### Figure 1 Percentage change from baseline in FEV₁ over the 24 hours following treatment.

The study was analysed using an ANOVA model including factors for study centre, patient (within centre), period, and treatment. The difference between treatments was estimated by the difference in least square means and the associated 95% confidence interval (CI).

The effect of first order carryover was tested at a significance level of α = 0.10 and was found to be not significant and was therefore subsequently removed from the model. The “treatment by centre” interaction was assessed at the level of α = 0.10 and was found to be not qualitatively significant.

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MAXIMUM PERCENTAGE CHANGE IN FEV1 FROM BASELINE

The mean maximum percentage increases in FEV1 from baseline over the 24 hour period were 33.57% (95% CI 25.92 to 41.21), 27.19% (95% CI 19.32 to 35.06), and 20.33% (95% CI 14.24 to 26.42) for intravenous montelukast, oral montelukast, and placebo, respectively. The between group difference for LS means maximum percentage change from baseline in FEV1 was significant for intravenous montelukast (13.56%, p<0.001) compared with placebo but did not reach statistical significance for oral montelukast compared with placebo or for intravenous versus oral montelukast (6.78%, p = 0.071 for both).

PERCENTAGE CHANGE IN FEV1 FROM BASELINE AT DIFFERENT TIME POINTS AFTER TREATMENT

Those receiving intravenous montelukast had a significantly better response (increase in FEV1) than the placebo group beginning 15 minutes after treatment (p<0.001; figs 1 and 2). The increase in airway function was sustained over the entire 24 hour period (p=0.004). The mean percentage change from baseline in FEV1 was significantly higher at the earlier time points (15 minutes to one hour) for intravenous than for oral montelukast. The difference between the two treatments decreased over time and was not significant at 2, 4, 8, 12, 16, and 24 hours after drug administration (p>0.05). A plot of the mean percentage changes from baseline in FEV1 over two hours is shown in fig 2.

RESCUE MEDICATION WITH β AGONIST FOLLOWING TREATMENT

Nine, 12, and 15 patients required inhaled short acting β agonists for intravenous montelukast, oral montelukast, and placebo, respectively. The difference in proportion approached statistical significance (p = 0.053).

SAFETY RESULTS

Adverse experiences were similar in frequency in the three treatment groups. The most frequently reported adverse events included headaches, which occurred in three patients (6%) on placebo, four (7.8%) on oral montelukast, and one (2%) on intravenous montelukast, and influenza which occurred in two patients (4%) while taking placebo. Specifically, there were no locally reported adverse events relating to the intravenous administration of montelukast.

Discussion

This study was designed to compare the effect of a single dose of intravenous montelukast (7 mg), oral montelukast (10 mg), and placebo on FEV1 in patients with chronic asthma. To our knowledge this study is the only direct comparison of intravenous and oral formulations of a cysteinyl leukotriene receptor antagonist.

When administered as a two minute bolus intravenous montelukast produced a significant improvement in FEV1, compared with placebo. This improvement was evident when considered as AUC0–24 h, for FEV1, after treatment, maximal increase in FEV1, after treatment, or comparisons at each individual time point.

The improvement in FEV1, with intravenous montelukast was noted at the earliest time point measured (15 minutes), indicating a rapid onset of action. Moreover, it was long lasting, occurring at least up to 24 hours after dosing, and clinically important as there were fewer β agonist rescues required during the 24 hour period following treatment with intravenous montelukast (n = 9) than with placebo (n = 15). Like intravenous montelukast, oral montelukast also caused significant improvement in pulmonary function compared with placebo (as measured by AUC0–24 h in percentage change from baseline FEV1). The onset of action for intravenous montelukast was faster than for the oral formulation.

Not surprisingly, intravenous administration also caused maximal airway relaxation (over an observation period of 24 hours or less) to occur more rapidly than with oral formulations. While there was no statistically significant difference in the AUC0–24 h and mean maximal improvement in FEV1, the mean effect of the intravenous drug was numerically larger than the oral drug, despite the fact that both formulation doses caused the same single dose AUC (time-concentration profile). While it is true that peak plasma concentrations are greater with intravenous than with oral montelukast, a dose related response in FEV1, has not been seen with doses of oral montelukast above 10 mg. A comparison of between study effects with other antileukotriene agents has suggested similar findings. It is possible that the administration of montelukast intravenously might have more favourable interaction kinetics with the cysteinyl leukotriene receptor. Further pharmacokinetic and pharmaco dynamic studies should address these issues.

Previous clinical studies with intravenously administered cysteinyl leukotriene receptor antagonists have been consistent in demon-
stratizing a rapid improvement in airway obstruction, usually within minutes of administration. For example, MK-0679 produced improved airflow within 15 minutes (trend toward greater efficacy even though the plasma AUC levels were similar to oral montelukast. Since intravenous leukotriene receptor antagonists have a rapid and sustained effect on the airways, they might be particularly useful in the treatment of acute asthma.

The authors wish to thank S Schon for her editorial assistance.

Source of funding: Merck Research Laboratories.

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Thorax 2000 55: 260-265
doi: 10.1136/thorax.55.4.260

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