Oral montelukast in acute asthma exacerbations: a randomised, double-blind, placebo-controlled trial

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ABSTRACT
Background Although leukotriene receptor antagonists have an established role in the management of patients with chronic asthma, their efficacy in an acute asthma exacerbation is not fully known.

Methods 87 adults with acute asthma requiring hospitalisation were randomly assigned to receive either montelukast 10 mg or placebo on admission and every evening thereafter for 4 weeks (when they were reviewed as outpatients). All patients were admitted under the care of a consultant chest physician and received full care for acute asthma according to the British Thoracic Society guidelines. The primary end point was the difference in peak expiratory flow (PEF) between active and placebo treatment the morning following admission.

Results Primary end point data were analysed for 73 patients. At study entry, patients who received montelukast (n=37) had a mean (±SD) PEF of 227.6 (±56.9) l/min (47.6% predicted) and those who received placebo (n=36) had a PEF of 240.3 (±99.8) l/min (49.6% predicted). The morning after admission, patients who received montelukast achieved a PEF of 389.6 (±109.7) l/min (81.4% predicted) compared with 332.3 (±124.9) l/min (69.8% predicted) for placebo (p=0.046). The mean difference between treatment groups was 57.4 l/min (95% CI of 1.15 to 113.6 l/min or 1.95—21.2% predicted).

Conclusion In acute asthma exacerbations the additional administration of oral montelukast results in a significantly higher PEF the morning after admission than that achievable with current standard treatment.

Clinical trial number NCT01011452.

INTRODUCTION
The leukotriene receptor antagonists (LTRAs) have an established role in the management of chronic asthma.1–4 LTRAs may also provide benefit, additional to that achieved by current treatment, in acute asthma.5 Exacerbations of asthma are associated with increased cysteinyl leukotriene production, as evidenced by raised urinary LTE4 both at the time of admission6 and several weeks later.7–10 LTRAs have an acute bronchodilator effect additional to the bronchodilatation achieved by inhaled and nebulised β-agonists.11–14 which is seen within 20–60 min of administration of the intravenous drug12 15 and within 6 h of taking the LTRA orally.15 A small number of studies have shown benefits of LTRAs in acute asthma.15–19 The two largest studies using an LTRA in acute asthma are those of Camargo et al (201 patients) and Silverman et al (641 patients).15 16 Camargo et al15 demonstrated significant improvements in lung function from intravenous montelukast over the first 2 h while in the emergency room; their patients received β agonists but no anticholinergic medication. Silverman et al16 primarily assessed the effect of oral zaflurilukast on relapses in the 28 day follow-up period following an emergency room attendance. Ferreira et al18 studied 20 adults with acute asthma for their period in the emergency room and showed non-significant trends in favour of montelukast. Harmanci et al17 looked at 51 children (aged 2—5 years) also in the emergency department and evaluated montelukast’s role in avoiding steroids in asthma exacerbations. Cylly et al19 evaluated 70 patients over a 24 h period comparing montelukast alone with prednisolone alone and montelukast + prednisolone in a single-blind study where patients also received nebulised β-agonists (but not nebulised anticholinergics) and showed a non-significant trend in favour of montelukast.

This is the first study looking at patients with an acute asthma exacerbation of a severity that required hospitalisation and who received an LTRA in addition to maximal treatment as set out by the British Thoracic Society.1

METHODS
This was a randomised, double-blind, placebo-controlled, single-centre study. Patients presenting either to the accident and emergency department or the medical admissions unit at Norfolk & Norwich University Hospital NHS Trust with acute asthma requiring hospitalisation were enrolled. The study was performed without commercial input into or involvement with the design, execution, analysis or reporting. The study had ethical approval from Norfolk Research Ethics Committee and written informed consent was obtained from all participants prior to study entry.

Patients
The inclusion criteria comprised adults aged between 18 and 50, a primary diagnosis of acute asthma, no other acute pathology and a peak expiratory flow (PEF) at randomisation ≤75% of their known best (within the last 12 months) or, in the absence of this information, of their predicted PEF.

Study patients had to have a lifetime smoking history of <10 pack-years. Patients well enough to be discharged after initial treatment were not eligible. Females who were pregnant or breastfeeding or unable to take adequate contraceptive precautions were excluded. Patients already taking an LTRA or phenytoin, phenobarbitone or rifampicin (montelukast affects the levels of these three drugs) were excluded.
Study design
Enrolment occurred at the time of the decision to admit or first consultant assessment. Patients were seen by, and admitted under the care of, a consultant chest physician on one of their two-daily ward rounds. Subjects were randomised to receive either montelukast 10 mg or placebo, in a 1:1 ratio. A study capsule was given at enrolment and then at 22.00 h daily for a period of 4 weeks when they were reviewed in the outpatient clinic. Patients enrolled before 22.00 h would therefore receive two study capsules on the day of admission. All subjects received oral prednisolone 40 mg at presentation and daily thereafter, and initial treatment with nebulised salbutamol (5 mg at least every 6 h) and nebulised ipratropium (500 μg every 6 h). Additional oxygen, intravenous magnesium and/or aminophylline and further nebulised salbutamol were prescribed if indicated. At the 4-week outpatient visit, full pulmonary function tests were performed along with a clinical review, and the study participation ended.

Efficacy measurements
The protocol-defined primary efficacy measure was the difference between active and placebo treatment in post-bronchodilator PEF measured the morning following admission. This end point was chosen as it was felt that in hospitalised patients with asthma the peak flow the morning after admission was the earliest clinically relevant objective asthma measurement that is consistently recorded.

On admission patients had a measurement of PEF made using a new mini-Wright’s PEF meter (Clement Clarke International, Harlow, Essex, UK). Patients kept the same PEF meter throughout the study. Inpatients’ spirometry was performed between 08:00 h and 10:00 h each morning on the same handheld spirometer (Vitalograph) by either SM or one of the consultant chest physicians at Norfolk & Norwich University Hospital NHS Trust.

Statistical analyses
It was calculated that 200 patients would need to be enrolled, to allow for withdrawals, in order to have a 80% chance of detecting a difference of 25 l/min in PEF at a 5% level of significance, assuming an SD of 60 l/min from previous work in our department. Data collection and entry was performed by DP and SM, and data analysis was performed by AMW. Data are presented as group mean±SD unless otherwise indicated. Statistical testing was performed, as defined in the protocol, on the absolute values of the PEF (not the per cent predicted). Normally distributed data, which included the primary end point data, were analysed using an unpaired t test and categorical data using a χ² test. Time to discharge data were non-parametric, and are presented as median and interquartile ranges and analysed using Kaplan–Meier survival analysis. Analysis was performed using Microsoft Excel Version 2003 and SPSS 14.0 for windows.

RESULTS
Recruitment to the study was slow partly due to the moderately stringent entry criteria, and the study was terminated early. Of the 87 enrolled patients 45 were randomised to receive montelukast. Fourteen patients were withdrawn (six from the montelukast limb) from the study, the details of which are in the Consort diagram. Therefore, the data of 73 patients (37 on montelukast) were analysed for the primary end point.

Patient characteristics
These are summarised in table 1 for the patients on whom the primary end point data were derived. Baseline demographic characteristics were well matched between the treatment groups with no statistically significant differences for any parameters. In particular, the mean PEF at study entry and the known best
or predicted PEF were almost identical in each group. With the exception of two patients, in whom the admission was their first diagnosis of asthma, all patients were taking a short-acting β-agonist (SABA) at presentation. Only 59 (53%) patients were being prescribed and were concordant with regular inhaled corticosteroids (ICS) prior to admission. A total of 85% of subjects had a smoking history of less than five pack-years and 40% of subjects were never smokers. In 60 patients (>80%) the severity of the attack was severe, life-threatening or near fatal as classified in the British Thoracic Society (BTS) guidelines, although in only 13 (18%) was either intravenous magnesium or/and aminophylline prescribed.

**Primary outcome measures**

Patients who received montelukast had a significantly (p=0.046) higher PEF than those who received placebo the morning after admission. The mean difference between treatment groups was 57.4 l/min (95% CI of 1.15 to 113.6 l/min). The data and graphics for the PEF profile during the study are presented in figure 1 and table 2.

**Secondary outcome measures**

By the time of discharge the PEF difference between the treatment groups had fallen to 41.6 l/min (95% CI of 1.15 to 113.6 l/min). The data and graphics for the PEF profile during the study are presented in figure 1 and table 2.

**DISCUSSION**

The magnitude of benefit from montelukast in this study is comparable with previous publications on the use of LTRAs in acute15–18 and chronic12–14 asthma and compares favourably with other drugs used in addition to steroids and nebulised β-agonists in acute asthma.21–30

Acute asthma studies differ in how they present and analyse PEF data, some comparing PEF data by numerical value (as we have done) some comparing the PEF as percentage best/predicted and others comparing relative changes in PEF. It could be argued that comparing the percentage best/predicted is more cliniclly relevant and in this study the difference between montelukast (81.4%) and placebo (69.8%) the morning after admission was significant at p=0.019.

Camargo showed a 14.8% improvement at 2 h from baseline forced expiratory volume in 1 s (FEV1) for intravenous montelukast compared with 3.6% for placebo (p=0.007) in patients with acute asthma with a presentation FEV1 of just under 50% predicted.15 While Silverman et al were primarily assessing outpatient relapses, prior to their discharge from the emergency department, there was a small benefit in FEV1 (2.12 litres vs 2.03 litres) in favour of oral Zafirlukast (p=0.04) at 3.5 h.16

In subjects with stable asthma, not given any other acute treatments, with a baseline FEV1 of 68%, oral montelukast produced a 15.72% improvement in FEV1, compared with 7.75% for placebo and 20.7% for the intravenous form (area under the curve of percentage change from baseline).13 Similarly Gaddy et al showed that intravenous LTRA could produce a 22% improvement in FEV1 from baseline in those with stable asthma with a baseline FEV1 of 50–80% predicted.15

Improvements in PEF expressed as a percentage of the baseline PEF value will invariably be larger than if expressed as a percentage of the predicted PEF. In this study, the montelukast group had a mean PEF improvement of 162.1 l/min compared with the placebo group’s 92.0 l/min which is a 33.8% and 20.2% improvement, respectively, of their predicted/best PEF. However, expressing the change as a percentage from baseline would show a 72% improvement for the montelukast group and 38% for placebo.

The benefit from montelukast of 57.4 l/min the morning following admission had fallen to a non-significant 41.6 l/min by the time of discharge. However, one of the criteria by which patients are judged to be fit for discharge is a PEF of ≥80% of their best/predicted. Fulfilling this PEF criterion reduces the likelihood of there being a difference between treatment groups.

**Figure 1** Study peak expiratory flow (PEF) profile.

**Table 2** Study peak expiratory flow (PEF) data profile group

<table>
<thead>
<tr>
<th></th>
<th>Admission</th>
<th>Following morning*</th>
<th>Discharge</th>
<th>4 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Montelukast</strong></td>
<td>227.5 (±56.9)</td>
<td>389.6 (±109.7)*</td>
<td>450.1 (±80.6)</td>
<td>424.1 (±103.6)</td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td>240.3 (±99.8)</td>
<td>332.3 (±124.9)*</td>
<td>408.5 (±105.8)</td>
<td>436.7 (±125.5)</td>
</tr>
<tr>
<td><strong>Difference 95% CI</strong></td>
<td>−50.9 to 25.5</td>
<td>1.15 to 113.6*</td>
<td>−2.5 to 85.6</td>
<td>−77.6 to 52.3</td>
</tr>
<tr>
<td><strong>p Value</strong></td>
<td>0.508</td>
<td>0.046*</td>
<td>0.064</td>
<td>0.698</td>
</tr>
<tr>
<td><strong>PEF expressed as a percentage of patients best/predicted</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Montelukast</strong></td>
<td>47.7 (±11.6)</td>
<td>81.4 (±19.5)</td>
<td>94.1 (±14.5)</td>
<td>89.2 (±19.1)</td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td>49.6 (±15.3)</td>
<td>69.8 (±20.7)</td>
<td>86.1 (±21.2)</td>
<td>91.5 (±25.4)</td>
</tr>
<tr>
<td><strong>Difference 95% CI</strong></td>
<td>−8.3 to 4.4</td>
<td>2.0 to 21.2</td>
<td>−0.6 to 18.5</td>
<td>−15.1 to 10.4</td>
</tr>
<tr>
<td><strong>p Value</strong></td>
<td>0.543</td>
<td>0.019</td>
<td>0.067</td>
<td>0.715</td>
</tr>
</tbody>
</table>

Values are given as the mean (±SD).

*Primary end point.
at discharge, although it might be anticipated that the time to achieve the 80% PEF threshold would be shorter in the montelukast group. There was no difference in time to discharge, but a study would require far more patients than we had in order to be able to detect such a difference in these data (which are invariably non-parametric).

Lung function at the outpatient visit also showed no differences between montelukast and placebo. In both treatment limbs patients had on average completed a 9-day course of oral prednisolone at 40 mg/day <5 weeks earlier and were receiving high doses of ICS daily. There was no demonstrable benefit of an LTRA in what were now well-controlled patients with asthma, following a course of prednisolone, with near normal lung function.

The main weakness of this study is its size (with only 75 patient's data available for the primary end point it had 80% power to detect a 40 l/min difference) and, although the baseline characteristics of both groups were well matched, the numbers of patients who received intravenous magnesium and/or aminophylline differed. In total 9 (24%) patients on montelukast received aminophylline and/or magnesium compared with only 4 (11%) on placebo.

We performed two posthoc subgroup analyses and present the PEF data the morning after admission by treatment subgroups.

In the first analysis we looked at the prescription of additional intravenous aminophylline/magnesium (n=13).

In patients who received intravenous aminophylline/magnesium, the PEF results were: montelukast 351.8 l/min (±88.6), placebo 184.0 l/min (±92.1), 95% CI for difference between treatment groups +10.8 to +254.7 l/min. For patients who did not receive either intravenous aminophylline/magnesium the results were: montelukast 406.2 l/min (±110.8), placebo 352.0 l/min (±115.9), 95% CI for difference between treatment groups –5.5 to +113.8 l/min.

We also performed a posthoc analysis by usage of ICS prior to admission (n=59).

In patients on ICS prior to admission the PEF results were: montelukast 375.5 l/min (±101.5), placebo 313.1 l/min (±115.0), 95% CI for difference between treatment groups –10.2 to +151.5 l/min. For patients not on ICS the results were: montelukast 405.4 l/min (±119.3), placebo 353.9 l/min (±135.5), 95% CI for difference between treatment groups –39.5 to +142.5 l/min. While it is of interest to split the data into these subgroups this was not the per-protocol analysis and the smaller numbers in the subgroups preclude any reliable inferences to be drawn.

In conclusion, in adults presenting with an acute asthma exacerbation requiring hospitalisation, the addition of oral montelukast led to a significantly greater PEF by the morning after admission than that which was achievable with maximal current standard treatment alone. Given the good safety profile of oral montelukast and the ease of administration it would seem reasonable to consider its routine use in asthma exacerbations.

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Competing interests CFR has received educational grants towards attending international conferences and speakers fees from Merck Sharp & Dohme and has previously participated in their advisory boards. He has also previously received educational grants towards attending international conferences and speakers fees from GSK. Whilst a research registrar, part of the funding for his posts came indirectly from SmithKline Beecham and MSD. AMW is currently the principal investigator of a clinical study funded by Merck. He is also currently undertaking studies for Bayer, Schering Plough, Pharmaxis and Boehringer Ingelheim. He has given talks for GSK, Merck and Astra-Zenica in the last 3 years. He undertook some consultancy work for GSK in April 2007. DP and SM have no competing interests.

Ethics approval This study was conducted with the approval of the Norfolk Research Ethics Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

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