The effect of a novel orally active selective PDE4 isoenzyme inhibitor (CDP840) on allergen-induced responses in asthmatic subjects


ABSTRACT: Recent studies have suggested that theophylline, a nonspecific phosphodiesterase inhibitor, has useful anti-inflammatory actions in asthma. Phosphodiesterase 4 (PDE4) represents the predominant PDE isoenzyme present in inflammatory cells. PDE4 inhibitors might, therefore, have beneficial effects in asthma. Side-effects, specifically nausea, have limited the use of existing agents. CDP840 is an orally active, potent and selective PDE4 inhibitor. We have examined the effect of CDP840 on the allergen-induced asthmatic response, its possible modes of action, and its tolerability at therapeutic doses.

A total of 54 patients were recruited to three double-blind, placebo-controlled studies. The first study examined the effect of CDP840 (15 mg b.i.d. for 9.5 days) on the allergen-induced asthmatic response in patients with known dual response to allergen. A second study examined the effect of CDP840 (15 mg b.i.d. for 9.5 days) on airway responsiveness to histamine. A third study examined whether single dose CDP840 (15 and 30 mg) had significant bronchodilatory effects.

In all studies, CDP840 was well-tolerated, with no patients reporting nausea. CDP840 did not lead to changes in baseline forced expiratory volume in one second (FEV1) as compared to placebo. The late asthmatic response (LAR) to allergen, expressed as area under the curve at 3–8 h (AUC 3–8h), was inhibited by 30% (p=0.016), an effect which persisted to the end of the observation period. The early asthmatic response (EAR) was unaffected, and there was no bronchodilatory effect (p=0.016), an effect which persisted to the end of the observation period. The early asthmatic response (EAR) was unaffected, and there was no bronchodilatory effect to allergen. A second study examined the effect of CDP840 (15 mg b.i.d. for 9.5 days) on airway responsiveness to histamine. A third study examined whether single dose CDP840 (15 and 30 mg) had significant bronchodilatory effects.

In conclusion, CDP840 significantly attenuated the late asthmatic response to allergen challenge in the absence of any bronchodilatory or histamine antagonist effect. This suggests that CDP840 may exert its effects via an anti-inflammatory mechanism.


Asthma is characterized by reversible airways obstruction, inflammation and airways hyperresponsiveness. The recognition that, even in mild asthma, a significant amount of airway inflammation is present [1], has led to recommendation of the early use of anti-inflammatory agents in its treatment [2]. The mainstay of such treatment remains the use of corticosteroid agents, but concern about side-effects of this class of drug remains, particularly in children [3].

The nonspecific phosphodiesterase (PDE) inhibitor, theophylline, is a long-established treatment in asthma. In recent years, it has become increasingly clear that, in addition to its action as a bronchodilator, theophylline has important immunomodulatory and anti-inflammatory actions [4]. In man, theophylline inhibits the allergen-induced late asthmatic response (LAR) and associated hyperresponsiveness [5, 6]. Six weeks of treatment with theophylline has been shown to reduce the number of activated eosinophils recruited to the airway following allergen challenge, and decrease the numbers of activated CD4+ cells in bronchoalveolar lavage (BAL) fluid postchallenge [7, 8]. In another study, withdrawal of theophylline treatment in asthmatic patients was accompanied by a fall in activated CD4+ cells in the peripheral blood and a concomitant increase in T-cells within the bronchial epithelium [9].

Many of the actions of theophylline in asthma may well be due to its action as a nonspecific inhibitor of the PDE enzyme. The cyclic nucleotides, cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), play a key role in cellular regulation, and are inactivated within the cell by the action of PDE. Increases in cellular cAMP are associated with a generalized downregulation of inflammatory cell activity [10, 11]. It has been postulated, therefore, that PDE inhibitors might have a role in the treatment of asthma.
EFFECT OF PDE4 INHIBITOR, CDP840, ON LAR

A total of 54 asthmatic subjects with atopic asthma were recruited to the three parallel studies, at three independent centres. All were male nonsmokers maintained on inhaled short-acting beta-agonist alone. All subjects gave written informed consent. The studies received ethics approval from King’s College Ethics Committee (Study 1), the Joint Southampton University Hospital Ethics Committee (Study 2), and Guy’s Hospital Ethics Committee (Study 3). CDP840, (supplied by Celltech Therapeutics Ltd, UK), was administered throughout, at doses which had previously been shown to be well-tolerated in healthy volunteers (data on file). The dosing period for the allergen response and bronchial hyperresponsiveness (BHR) studies was the maximum permitted under licensing regulations at the time of the study.

Methods

At present, seven distinct PDE gene families are recognized (PDE 1–7), each with different tissue specificity [14]. PDE4 represents the predominant PDE isoenzyme present in the majority of inflammatory cells. Inhibition of the PDE4 isoenzyme suppresses activation of a wide range of inflammatory cells, including eosinophils [15–17], neutrophils [18], mononuclear cells [19, 20], macrophages [21] and basophils [22].

Selective PDE4 isoenzyme inhibitors have been demonstrated to inhibit the eosinophil infiltration induced by allergen in allergic animals [17, 23, 24], including primates [25]. PDE4 inhibitors are effective in inhibiting microvascular leakage induced by a variety of proinflammatory mediators [26]. There is also evidence that, as well as enhancing nonadrenergic noncholinergic (NANC) relaxation [27], PDE4 inhibitors may have direct bronchodilatory effects [28, 29]. No selective PDE4 inhibitor has yet been evaluated for its anti-inflammatory effects in man. The mixed PDE3/4 inhibitor, zardaverine, has been shown to elicit mild bronchodilatation in man, albeit at doses that elicit nausea and vomiting [30]. Rolipram, a PDE4 inhibitor, has been known to treat the symptoms of depression, but has been limited by side-effects, specifically nausea [31].

CDP840 is a novel, potent, selective inhibitor of PDE4 (median inhibitory concentration (IC50) 4 nM against recombinant PDE4A4), with over a 10,000 fold selectivity for PDE4 compared to other known classes of PDE [32]. In rats, CDP840 was effective in inhibiting interleukin-5 (IL-5)-induced pleural eosinophila. When administered to sensitized guinea-pigs, CDP840 inhibited antigen-induced bronchospasm, and pulmonary eosinophil accumulation, and was effective in maintaining eosinophil peroxidase (EPO) levels [32]. In an allergic rabbit model, CDP840 was as effective as the corticosteroid agent, budesonide, in inhibiting antigen-induced pulmonary eosinophilia and airway hyperresponsiveness to histamine [33].

In the present study, we have investigated the effect of CDP840 on allergen-induced responses in subjects with mild allergic asthma. Furthermore, we have examined the ability of CDP840 to affect basal bronchial tone and to inhibit nonspecific bronchial hyperresponsiveness, as manifested by the response to histamine challenge.

Study population

Allergen response study. Fourteen volunteers, aged 19–34 yrs (mean±SD age 26±4 yrs), were recruited. At screening, all had baseline forced expiratory volume in one second (FEV1) >70% of predicted (Cotes formula) (mean ±SD 89±12%). All exhibited a positive skin response (≥5 mm wheal) to Dermatophagoides pteronyssinus (Der p1), and a dual asthmatic response to inhaled Der p1, defined as a >20% fall in mean FEV1 within 30 min of antigen challenge (early asthmatic response (EAR)) and, subsequently, a >20% fall in mean FEV1 in the period 3–8 h postchallenge (late asthmatic response (LAR)).

Bronchial hyperreactivity study. Twenty seven volunteers, aged 18–35 yrs (mean±SD 24±6 yrs), were recruited. All had baseline FEV1 >85% pred and a provocative concentration causing a 20% fall in FEV1 (PC20) to histamine of <8 mg·mL⁻¹.

Bronchodilator study. Thirteen volunteers, aged 21–31 yrs (mean±SD 25±3 yrs), were recruited. Baseline FEV1 ranged 47–86% (mean±SD 75±8%). Reversibility to inhaled salbutamol, 200 µg, ranged 16–44%.

Procedures

Allergen response study. Initial screening was performed to demonstrate the presence of a dual asthmatic response. Der p1 (Alk, Horsholm, Denmark) was administered by tidal breathing via a Wright nebulizer, calibrated to deliver 0.13 mL·min⁻¹, in increasing concentrations until such time as an EAR occurred or a concentration of 100,000 Standardized Quality (SQ) (Aquagen® SQ, Alk)-mL⁻¹ had been reached. In the presence of an EAR, monitoring was continued and a LAR was judged to have occurred if there was a secondary fall in mean FEV1 of 20% or more over the subsequent 8 h.

Using a double-blind, placebo-controlled, cross-over design and following a 3 week wash-out period after the screening allergen challenge, patients were randomized to receive either 15 mg b.i.d. CDP840 or placebo capsules for 9 days. The first dose was taken under supervision and was followed by blood pressure, pulse and FEV1 readings over a period of 2 h to assess safety. The final dose, again supervised, was taken on the 10th day and was followed immediately by allergen challenge. After a 4 week wash-out period, subjects entered the second treatment phase. Allergen challenge on each of the two study days was performed by administration of the final concentration of Der p1, which had produced a satisfactory dual response on the screening day. The mean of three FEV1 readings was recorded over 20 min at 5 min intervals, and then at 10 min intervals until 1 h after allergen exposure. FEV1 readings continued, thereafter, at 30 min intervals for a further 7 h.

Bronchial hyperreactivity study. Using a parallel group design, patients were allocated either 15 mg b.i.d. CDP840 or placebo for a period of 9.5 days. The primary variable was bronchial responsiveness to histamine, defined as the provocative concentration of histamine (histamine
acid phosphate in 0.9% NaCl) producing a 20% fall in FEV1 (PC20) at 2 h after the final dose compared to baseline level. Histamine challenge was performed using the cumulative dose method, modified from the method described by Chiu [34]. Baseline FEV1 was calculated following inhalation of 0.9% saline via a System 22 Disposable Sidestream Nebulizer (Medic-Aid, Pagham, UK) for 2 min (mass median diameter 3 µm at 6 L-min⁻¹, resolvable output 80%). FEV1 was measured three times at 1 min and three times at 3 min postinhalation. The maximal FEV1 values at 1 min and at 3 min were compared and the lower of the two measurements used as the baseline. Histamine was then delivered in doubling concentrations, the initial dose being 0.03 mg·mL⁻¹ rising to a maximum concentration of 8 mg·mL⁻¹. The challenge was terminated when a fall in FEV1 of at least 20% from the baseline value was achieved, or the maximum concentration of agonist (8 mg·mL⁻¹) was reached.

Patients who achieved a 20% fall in FEV1 following inhalation of 8 mg·mL⁻¹ histamine or less and who fulfilled the other entry criteria commenced dosing with CDP840 or placebo. The first dose was supervised and was followed by blood pressure, pulse and FEV1 readings over a period of 2 h to assess safety. After 9.5 days of dosing with drug or placebo, histamine challenge was repeated 2 and 6 h after the final treatment dose, patients being allowed a rescue dose of inhaled salbutamol 200 µg from a metered-dose inhaler (MDI) after each challenge.

Bronchodilator study. Baseline FEV1 and reversibility following dosing with 200 µg of salbutamol from a MDI was assessed. Subjects who had a baseline FEV1 of ≤86% pred and showed ≥15% reversibility to salbutamol entered the study. Subjects received single oral doses of 15 and 30 mg of CDP840 and placebo in a double-blind, three-arm, cross-over design, with a minimum of 2 weeks between each dose. FEV1 was measured over a period of 6 h after dosing.

Plasma CDP840 concentrations were measured at various time-points during all three studies. Both in the allergen and histamine challenge studies, the second to penultimate dose was unsupervised. Therefore, CDP840 was measured just prior to the final dose to confirm exposure to the drug. In the allergen challenge study, a further assessment of drug concentration was made 24 h after the final dose.

Statistical analysis

In the allergen challenge study, area under the curve (AUC) was calculated using the trapezium rule. A two-treatment, two-period, cross-over analysis of variance (ANOVA) was performed on the AUCs for the LAR (AUC3–8h), EAR (AUC0–3h) and on the AUC7–8h, allowing for the effects due to patient, period, carry-over and treatment. In each analysis, the presence of carry-over effect was investigated. The assumptions of normality and constant variance were checked to assess the validity of the analyses.

In the bronchial hyperresponsiveness study, absolute values of PC20 were log-transformed prior to analysis to improve the assumptions of normality of distribution required by the statistical methods. An analysis of covariance was performed on the PC20 values at 2 and 6 h, using the screening value as a covariate. Assumptions of normality of distribution, homogeneity of variance and homogeneity of regression slopes were investigated in the analysis.

In the bronchodilator study, a three-period, cross-over ANOVA was performed on the change from baseline of maximal FEV1 measured between 15 min and 6 h postinhalation, allowing for the effects due to patient, period, carry-over and treatment. The presence of a treatment by period interaction and carry-over effect were investigated initially in each analysis. The assumptions of normality and constant variance were checked to assess the validity of the analyses. A p-value of less than 0.05 was considered significant.

Results

In each study, CDP840 was well-tolerated and no serious adverse events were reported. In particular none of the subjects in any of the three studies experienced nausea or vomiting. Of a total of 23 nonserious adverse events, six occurred during placebo periods and 17 during treatment with CDP840. Whilst the pattern of events seemed sporadic, there did appear to be a nonsignificant slight excess of headache in the CDP840-treated group. One patient in the allergen challenge study had mildly raised hepatic transaminases at his screening visit. These rose slightly during the placebo period but actually fell during the CDP840 treatment period. Subsequent assessment by a hepatologist revealed no significant abnormality in liver function, and because of the time scale of these transient abnormalities they were not felt to be drug-related.

With the exception of one subject, who took part in the allergen challenge study, plasma drug concentrations confirmed exposure to study drug. This patient had no drug detected in blood taken prior to his final dose on the morning of his allergen challenge. However, 24 h after this final, supervised dose, CDP840 was present at a level comparable with the other subjects in the study, suggesting that its absence in the previous sample was not due to rapid clearance of drug in this patient. It was concluded, therefore, that he had been noncompliant and data from this patient were excluded from the analysis.

In the allergen challenge study, 9.5 days of treatment with CDP840 did not significantly affect baseline values of FEV1 (mean FEV1 3.52 and 3.46 L), on Day 1 and Day 10, respectively, and there was no significant difference between baseline FEV1 on either of the allergen challenge days (mean FEV1 3.53 and 3.46 L, in placebo and active period, respectively). The percentage changes in FEV1 following allergen challenge are shown in figure 1. There was no statistically significant effect on the EAR, defined as the AUC0–3h, (13% inhibition; p = 0.64). The LAR, defined as AUC3–8h, was significantly reduced (30% inhibition; p = 0.016) in the treatment arm as compared to placebo (table 1). The AUC7–8h remained significantly reduced in the treatment group (34% inhibition; p = 0.018), i.e. the effect of drug treatment was persistent at the end of the observation period.

In the bronchial hyperresponsiveness study, 9.5 days of treatment with CDP840 had no effect on airways hyperresponsiveness to histamine either at 2 or 6 h after
Table 1. – The effect of 9.5 days of treatment with CDP840 15 mg twice daily on the allergen-induced late asthmatic response expressed as maximal change in FEV1 and as area under the curve (AUC)

<table>
<thead>
<tr>
<th>Patients</th>
<th>FEV1 Maximal change %</th>
<th>Adjusted mean*</th>
<th>SEM</th>
<th>Mean difference 95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-28.8 ± 1.94</td>
<td>13</td>
<td></td>
<td>-23.2 ± 1.94</td>
<td>0.064</td>
</tr>
<tr>
<td>CDP840</td>
<td>-23.2 ± 1.94</td>
<td>13</td>
<td></td>
<td>-5.64 ± 0.064</td>
<td></td>
</tr>
<tr>
<td>AUC3–8 h</td>
<td>79.1 ± 5.82</td>
<td>55.6</td>
<td></td>
<td>23.50 ± 0.016</td>
<td>0.016</td>
</tr>
<tr>
<td>Placebo</td>
<td>55.6 ± 5.82</td>
<td>24.6 ± 2.11</td>
<td></td>
<td>8.25 ± 0.016</td>
<td>0.018</td>
</tr>
<tr>
<td>CDP840</td>
<td>23.50 ± 0.016</td>
<td>24.6 ± 2.11</td>
<td></td>
<td>8.25 ± 0.016</td>
<td></td>
</tr>
</tbody>
</table>

*: adjusted for period and carry-over effects. FEV1: forced expiratory volume in one second; 95% CI: 95% confidence interval; CDP840: phosphodiesterase 4 inhibitor.

Table 2. – Provocative concentration (mg·mL⁻¹) of histamine producing a 20% fall in FEV1 (PC20) at histamine challenge 2 and 6 h after oral dosing with CDP840 or placebo

<table>
<thead>
<tr>
<th>Time after final dose</th>
<th>Placebo</th>
<th>CDP840 15 mg b.i.d.</th>
<th>Ratio of CDP840 to placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geometric mean at screening</td>
<td>1.35 (0.54–3.38)</td>
<td>0.75 (0.30–1.88)</td>
<td>0.51 (0.20–1.32)</td>
</tr>
<tr>
<td>Geometric mean 2 h after final dose</td>
<td>1.85 (0.82–4.17)</td>
<td>0.71 (0.31–1.60)</td>
<td>0.51 (0.20–1.32)</td>
</tr>
<tr>
<td>Geometric mean ratio to screening p-value</td>
<td>1.37 (0.60–3.13)</td>
<td>0.95 (0.42–2.16)</td>
<td>0.154</td>
</tr>
<tr>
<td>Geometric mean 6 h after final dose</td>
<td>2.86 (0.94–8.74)</td>
<td>1.27 (0.39–4.14)</td>
<td>0.55 (0.18–1.63)</td>
</tr>
<tr>
<td>Geometric mean ratio to screening p-value</td>
<td>2.95 (1.33–6.55)</td>
<td>1.70 (0.73–3.94)</td>
<td>0.262</td>
</tr>
</tbody>
</table>

Values in parentheses are 95% confidence intervals. FEV1: forced expiratory volume in one second; CDP840: phosphodiesterase 4 inhibitor.
Following single doses of CDP840, treatment with theophylline, as well as attenuating the LAR and the accompanying BHR [6, 39–41]. Leukotriene antagonists are all successful in attenuating the increase in BHR, it is considered to be a useful model of airway inflammation [39]. Corticosteroids, sodium cromoglycate, nedocromil sodium, theophylline and leukotriene antagonists are all successful in attenuating the increase in the numbers of eosinophils in BAL fluid 24 h after allergen exposure [8]. Corticosteroids and low-dose theophylline have little effect on the EAR.

CDP840 had no effect on the allergen-induced EAR. It is, therefore, unlikely that, at the doses used, CDP840 is influencing the mast cell mediator release responsible for the EAR; an observation consistent with previous studies in this clinical model with the nonselective PDE inhibitor theophylline. At doses clearly influencing the LAR induced by allergen, CDP840 failed to modify basal lung function. CDP840, at both doses, did not significantly affect basal airway calibre in patients with demonstrable β₂-agonist sensitive bronchoconstriction. Moreover, CDP840 did not significantly modify histamine-induced bronchoconstriction, confirming that at these doses CDP840 is not acting as a bronchodilator. The inability of CDP840 to influence histamine-induced bronchoconstriction also suggests that the ability of this drug to influence the LAR is not via functional antagonism of released constrictor mediators.

It seems likely, therefore, that the inhibition of the LAR by CDP840 is via an anti-inflammatory action, since it is well-recognized that other agents which modify the LAR, such as glucocorticosteroids and theophylline, inhibit inflammatory cell infiltration into the airway mucosa [8, 42–44]. This is consistent with evidence from experimental models of airways inflammation, in which it is well-documented that CDP840, like other classes of selective PDE4 inhibitor, can have marked anti-inflammatory actions, often at doses not causing bronchodilatation [23, 32, 33].

In conclusion, therefore, CDP840 is an orally active, selective PDE4 isoenzyme inhibitor, CDP840 has a statistically significant effect on the allergen-induced LAR. This effect was achieved using a dose regimen that did not elicit nausea or any other noteworthy side-effects, a problem that has hampered earlier clinical development of PDE4 inhibitors. The significant inhibitory effect of CDP840 against the allergen-induced LAR was not accompanied by any significant inhibition of the acute bronchoconstrictor response to allergen.

The dual asthmatic response is seen in a significant proportion of atopic asthmatics following exposure to allergen. The EAR begins almost immediately following exposure to allergen, reaches its peak at 15–20 min and is followed by resolution over the next 1–2 h. This process, involving the actions of histamine, prostaglandin D₂ and cysteinyl leukotrienes (LTC₄, LTD₄, LTE₄) is felt to be largely mast cell-dependent [35]. The LAR occurs 3–8 h after exposure to allergen and is associated with a marked influx of inflammatory cells (mast cells, eosinophils, neutrophils and lymphocytes) into the submucosa and epithelium [36]. At this time, there is a significant increase in the numbers of eosinophils in BAL fluid [37], a finding that persists for up to 96 h following exposure to allergen [38]. As the LAR is accompanied by inflammatory cell recruitment and often by an associated increase in BHR, it is considered to be a useful model of airway inflammation [39]. Corticosteroids, sodium cromoglycate, nedocromil sodium, theophylline and leukotriene antagonists are all successful in attenuating the LAR and the accompanying BHR [6, 39–41]. Treatment with theophylline, as well as attenuating the final dose, nor was there any difference between the active and placebo treatment groups at either time-point (table 2). Whilst the geometric mean PC₂₀ in the placebo group was almost double that for the CDP840 group, it is unlikely that this influenced the outcome of the study, since the treatment groups were compared after adjusting for the screening values.

There was no significant difference in change in FEV₁ following dosing with 15 or 30 mg CDP840 compared with placebo (table 3). In addition, no bronchodilatory effect was observed following the first dose of CDP840 either in the allergen challenge or bronchial hyperresponsiveness study.

Discussion

Our results show that the novel, orally active, selective PDE4 isoenzyme inhibitor, CDP840 has a statistically significant effect on the allergen-induced LAR. This effect was achieved using a dose regimen that did not elicit nausea or any other noteworthy side-effects, a problem that has hampered earlier clinical development of PDE4 inhibitors. The significant inhibitory effect of CDP840 against the allergen-induced LAR was not accompanied by any significant inhibition of the acute bronchoconstrictor response to allergen.

The dual asthmatic response is seen in a significant proportion of atopic asthmatics following exposure to allergen. The EAR begins almost immediately following exposure to allergen, reaches its peak at 15–20 min and is followed by resolution over the next 1–2 h. This process, involving the actions of histamine, prosta
glandin D₂ and cysteinyl leukotrienes (LTC₄, LTD₄, LTE₄) is felt to be largely mast cell-dependent [35]. The LAR occurs 3–8 h after exposure to allergen and is associated with a marked influx of inflammatory cells (mast cells, eosinophils, neutrophils and lymphocytes) into the submucosa and epithelium [36]. At this time, there is a significant increase in the numbers of eosinophils in BAL fluid [37], a finding that persists for up to 96 h following exposure to allergen [38]. As the LAR is accompanied by inflammatory cell recruitment and often by an associated increase in BHR, it is considered to be a useful model of airway inflammation [39]. Corticosteroids, sodium cromoglycate, nedocromil sodium, theophylline and leukotriene antagonists are all successful in attenuating the LAR and the accompanying BHR [6, 39–41]. Treatment with theophylline, as well as attenuating the LAR, is associated with a decrease in activated eosinophils in bronchial biopsies 24 h after allergen exposure [8]. Corticosteroids and low-dose theophylline have little effect on the EAR.

CDP840 had no effect on the allergen-induced EAR. It is, therefore, unlikely that, at the doses used, CDP840 is influencing the mast cell mediator release responsible for the EAR; an observation consistent with previous studies in this clinical model with the nonselective PDE inhibitor theophylline. At doses clearly influencing the LAR induced by allergen, CDP840 failed to modify basal lung function. CDP840, at both doses, did not significantly affect basal airway calibre in patients with demonstrable β₂-agonist sensitive bronchoconstriction. Moreover, CDP840 did not significantly modify histamine-induced bronchoconstriction, confirming that at these doses CDP840 is not acting as a bronchodilator. The inability of CDP840 to influence histamine-induced bronchoconstriction also suggests that the ability of this drug to influence the LAR is not via functional antagonism of released constrictor mediators.

It seems likely, therefore, that the inhibition of the LAR by CDP840 is via an anti-inflammatory action, since it is well-recognized that other agents which modify the LAR, such as glucocorticosteroids and theophylline, inhibit inflammatory cell infiltration into the airway mucosa [8, 42–44]. This is consistent with evidence from experimental models of airways inflammation, in which it is well-documented that CDP840, like other classes of selective PDE4 inhibitor, can have marked anti-inflammatory actions, often at doses not causing bronchodilatation [23, 32, 33].

In this study, we observed no effect of CDP840 on BHR. A similar marginal effect on BHR but substantial effect on the allergen response has been described following short-term treatment with steroids [45]. Whilst established anti-inflammatory agents, such as steroids, reduce BHR, most studies have examined this effect after two or more weeks of treatment. Moreover, the maximal effects of treatment may not be seen for several weeks or more [46]. It is possible, therefore, that the treatment period used in this study was insufficient to clearly establish whether or not CDP840 has an effect on BHR. In addition, some studies have suggested that route of administration may be important. In a study comparing 3 weeks of treatment with oral prednisolone, 12.5 mg daily, to inhaled beclomethasone, 1.200 µg daily, both had similar beneficial effects on recorded peak expiratory flow rate. Prednisolone, as opposed to beclomethasone, however, failed to affect BHR [47]. It is clear, therefore, that further studies would be necessary to adequately assess the effects of CDP840 on BHR and relate this to our observed effect on the LAR to allergen.

In conclusion, therefore, CDP840 is an orally active agent, which proved effective in attenuating the late asthmatic response to allergen, and was well-tolerated. Our results are consistent with this effect being mediated via an anti-inflammatory mechanism. This is the first demonstration that this class of drug may be effective in a clinical model of asthma. In the future, it is anticipated that selective phosphodiesterase 4 (PDE4) inhibitors may emerge as a new anti-inflammatory therapy in the treatment of allergic diseases, such as asthma.
Acknowledgements: The authors would like to thank C. Novak for her invaluable assistance in the statistical analysis, and A. Farnsworth and N. Cox for their assistance with the study.

References


