Methods. After a run in period of 2–4 weeks during which treatment consisted of only on-demand β-agonists, patients were randomized to receive (in double blind fashion) either albuterol, 0.2 mg, with budesonide, 0.2 mg, three times daily, or albuterol with placebo three times daily. No other medications were allowed, however, fenoterol was also given as a “rescue” medication. Spirometry (FEV₁) and airway responsiveness (histamine PC₂₀) were monitored alternately every 2 months.

Results. In light of interim results, all patients receiving placebo were transferred to budesonide after 10 to 28 months of the planned 36 months of treatment. At the time of termination, 29 patients had been withdrawn from the study, 26 of which were randomized to receive β-agonists plus placebo. Pulmonary function parameters (FEV₁, peak flows, peak flow variability), symptoms, school absences, β-agonist use, exacerbations requiring prednisone, and hospitalizations all favored the group receiving corticosteroid. Airway responsiveness (histamine PD₂₀) was improved in the budesonide group, whereas no change was observed in the placebo group. No major adverse effects were reported, including effects on growth (height).

Conclusions. Inhaled corticosteroids are important in the long-term treatment of childhood asthma.

Reviewer’s Comments. The authors point out that “regular” β-agonist therapy, which has been implicated as being detrimental to the control of asthma, was studied and imply that differing results might have been obtained if inhaled corticosteroid alone and/or on demand β-agonist alone were studied. Nevertheless, this investigation clearly demonstrates the importance of inhaled corticosteroids in the treatment of asthma, even in relatively mild cases. It remains unknown to what extent discontinuation of therapy would have on the disease.

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TIMING OF PREDNISONE AND ALTERATIONS OF AIRWAYS INFLAMMATION IN NOCTURNAL ASTHMA


Purpose of the Study. To study the influence of dose timing on the ability of corticosteroids to block circadian recruitment of inflammatory cells into asthmatic airways and attenuate nocturnal exacerbations.

Study Population. Seven male adult asthmatics aged 21 to 48 years with nocturnal worsening defined as a mean fall of peak flows from bedtime to awakening of >20% on three consecutive nights were examined. Patients were otherwise stable and had not received treatment with cromolyn, had not inhaled or taken oral corticosteroids within 6 weeks, and had not experienced acute respiratory illness within 6 weeks, immunotherapy within 3 months, any nonasthmatic pulmonary disease, and other significant medical illnesses.

Methods. In a randomized, double blind, placebo-controlled, crossover fashion patients received a single dose of prednisone, 50 mg, or placebo at 0800, 1500, or 2000. On study nights blood eosinophils were obtained at 2000 and 0400, baseline spirometry was performed at 2300 and 0345, and bronchoscopy with lavage was performed at 0400.

Results. Overnight fall in FEV₁ was significantly reduced and 0400 FEV₁ was significantly improved with 1500 prednisone dosing (versus placebo). No differences were observed with the 0800 and 2000 dosing regimens. Blood eosinophils were reduced (versus placebo) at 2000 and 0400 with 1500 prednisone dosing, whereas 0800 dosing resulted in a significant reduction at 2000 only, and 2000 dosing result in reductions at 0400 only. The 1500 dosing scheme resulted in a significant pancellular reduction in lavage cytology which was not observed with the other regimens.

Conclusions. This study supports the importance of timing prednisone doses in altering inflammatory cells associated with nocturnal worsening of asthma. Dosing at 1500 provided a lesser fall in overnight FEV₁, improved 0400 FEV₁, and a greater reduction in 0400 lavage cellularity than 0800 and 2000 dosing.

Reviewer’s Comments. Significant changes which support 1500 prednisone dosing in asthmatics with nocturnal symptoms were observed in this study. It is important to note that this study was a single-dose study only, and that further clinical investigation is necessary, especially with regards to the relative safety (ie, effects on adrenal function) of 1500 dosing.

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BIOCHEMICAL ACTIVITY, PHARMACOKINETICS, AND TOLERABILITY OF MK-886, A LEUKOTRIENE BIOSYNTHESIS INHIBITOR, IN HUMANS


Purpose of the Study. This study evaluated the tolerability, pharmacokinetics, and biochemical activity of single doses of MK-886, a leukotriene synthesis inhibitor, in whole blood.

Study Population. Thirty-six healthy nonsmoking males participated in this investigation.

Methods. Two studies were performed. The first was a randomized, double-blind, placebo-controlled crossover study utilizing single doses of placebo, 250, 500, and 750 mg of MK-886. Blood samples were obtained predose through 24 hours postdose for plasma drug concentrations and LTB₄ synthesis following stimulation with a calcium ionophore (AS-23187). LTB₄ synthesis was measured using a competitive binding assay. The second study was similar to the first, except that treatment consisted of placebo, 100 or 250 mg of MK-886 three times daily (TID) for 11 days. Blood samples were obtained predose through 24 hours postdose on day 11. Clinical measures were obtained at various time points throughout the study periods.

Findings. Single doses of MK-886 significantly reduced LTB₄ synthesis, with maximal reductions of 40 to 60% of baseline observed at 1 to 2 hours postdose. Significant suppression persisted for 6 hours postdose. A significant dose effect was observed between 250 and 500 mg and 250 and 750 mg, however no significant difference was seen between 500 and 750 mg. No differences in maximal MK-886 plasma concentrations (Cₘₐₓ), time to maximal plasma concentration (tₘₐₓ), or area under the plasma concentration versus time curves (AUC) were present between treatments. There appeared to be a correlation between LTB₄ inhibition and plasma concentration at 1 and 2 hours postdose with 500 mg. After multiple dosing, maximal inhibition of LTB₄ synthesis occurred 2 hours postdose, and a dose-response effect was observed. It appeared that maximal effects were attained after 4 days of treatment (63 ± 23% of baseline synthesis for 100 mg TID, and 48 ± 42% for 250 mg TID), however, further inhibition was measured at 11 days in the 250 mg of TID-treated group (38 ± 22% of baseline). When plasma MK-886 concentrations after days 1 and 11 are compared, Cₘₐₓ and AUC demonstrated an accumulation of 144%. A dose effect was also observed, as the AUC for 250 TID was 220% of that for 100 mg of TID.
TIMING OF PREDNISONE AND ALTERATIONS OF AIRWAYS INFLAMMATION IN NOCTURNAL ASTHMA

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