

Inhibition of methylprednisolone elimination in the presence of clarithromycin therapy

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Background: Macrolide antibiotics have long been used as steroid-sparing agents in patients with severe steroid-dependent asthma. Their efficacy and their propensity to potentiate glucocorticoid adverse effects have been attributed in part to their ability to delay glucocorticoid clearance.

Objective: We sought to determine whether clarithromycin, a newer macrolide antibiotic, can alter the pharmacokinetic profile of oral glucocorticoids and thereby increase the risk of steroid-induced adverse effects.

Methods: An open-label study in a paired design (before and after treatment) was conducted in a hospital-based outpatient clinic. Participants were 6 adult patients (mean age, 30 years) with mild-to-moderate asthma. Prednisone (40 mg/1.73 m²) and methylprednisolone (40 mg/1.73 m²) were given as single randomized doses on consecutive study days before and on days 8 and 9 of a clarithromycin (500 mg twice daily) course. Twelve-hour pharmacokinetic profiles with measurement of plasma methylprednisolone and prednisolone levels were taken before and after clarithromycin therapy.

Results: Clarithromycin therapy resulted in a 65% reduction of methylprednisolone clearance and significantly higher mean plasma methylprednisolone concentrations compared with preclarithromycin concentrations but had no significant effect on prednisolone clearance or mean prednisolone plasma concentrations.

Conclusions: Clinicians must be aware of potential drug interactions that could place patients at increased risk for steroid-induced adverse effects. Such an effect has been demonstrated between clarithromycin and methylprednisolone, two drugs that may be administered concomitantly in asthma. To avoid potential steroid-enhancing effects, prednisone should be substituted for methylprednisolone during prolonged courses of clarithromycin therapy. (*J Allergy Clin Immunol* 1999;103:1031-5.)

Key words: Glucocorticoids, prednisone, methylprednisolone, clarithromycin, asthma, pharmacokinetics

Macrolide antibiotics, such as erythromycin and troleandomycin (TAO), have a long history of use as steroid-sparing agents in patients with severe steroid-dependent asthma.¹ Clarithromycin, a recently developed macrolide antibiotic, is being used with increasing frequency. Over 10 million prescriptions are written for clarithromycin in the United States each year for the treatment of upper and lower respiratory tract infections. There is an increasing amount of data supporting mycoplasma and chlamydia respiratory infections as factors contributing to poor control of asthma in selected patients.^{2,3} There are also a number of studies demonstrating possible immunomodulatory and anti-inflammatory effects of macrolide antibiotics.⁴⁻⁷ It is therefore not surprising that clarithromycin is being used with increasing frequency in patients with steroid-dependent asthma.

TAO is known to delay the clearance of methylprednisolone by at least 60%, and it has been suggested that the delay in methylprednisolone clearance contributes to its efficacy.⁸ Erythromycin also reduces oral glucocorticoid metabolism, delaying methylprednisolone clearance by 46%.⁹ Unfortunately, the concomitant use of TAO and methylprednisolone has been shown to potentiate corticosteroid adverse effects.¹⁰ We sought to determine whether clarithromycin therapy can alter the pharmacokinetic profile of prednisolone, the active metabolite of prednisone, and methylprednisolone, the two oral glucocorticoids most often used in the treatment of asthma.

METHODS

Six adults with mild-to-moderate asthma (mean age, 30 ± 10 years) who met the American Thoracic Society criteria for asthma¹¹ were studied. None of the patients had a history of chronic obstructive pulmonary disease, liver disease, or renal disease. Patients were not receiving concurrent therapy with medications that could influence corticosteroid clearance, such as anticonvulsants, erythromycin, oral contraceptives, or rifampin. Additional exclusion criteria included viral or other respiratory tract infection within 4 weeks of the study, total inhaled corticosteroid dose of greater than 800 µg/day, abnormal hepatic or renal function, history of smoking, and concurrent pregnancy, lactation, or hormonal replacement therapy.

Subjects received oral methylprednisolone (Medrol; The Upjohn Company, Kalamazoo, Mich) or prednisone (Roxane, Columbus, Ohio) in random fashion (40 mg/1.73 m²; maximum of 40 mg given as a single dose on study day) on 2 successive days. Baseline phar-

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Supported in part by an American Lung Association Asthma Research Center grant, National Institutes of Health grant number HL-36577, and General Clinical Research Center Grant 5 M01 RR00051.

Received for publication Oct 6, 1998; revised Jan 8, 1999; accepted for publication Jan 12, 1999.

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0091-6749/99 \$8.00 + 0 1/1/97734

Abbreviations used

AUC: Area under the curve
 MRT: Mean residence time
 $t_{1/2}$: Half-life
 TAO: Troleandomycin
 V_{ss} : Steady-state volume of distribution

macokinetic studies were performed by collecting blood by means of a heparinized catheter before and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 hours after the study medication was administered. Plasma was separated, and samples were frozen at -20°C until sample analysis. All studies began between 7 and 9 AM. After the baseline pharmacokinetic studies were completed, patients were given a 9-day course of clarithromycin (Biaxin; Abbott Laboratories, North Chicago, Ill) administered as 500 mg twice daily. Subjects returned for a second set of methylprednisolone and prednisone pharmacokinetic studies on days 8 and 9 of clarithromycin therapy. The pharmacokinetic studies were conducted under identical conditions as the baseline studies except for the concurrent administration of the macrolide antibiotic.

All samples were assayed according to a modification of the highly sensitive and specific HPLC method of Ebling et al.¹² This assay is specific for methylprednisolone, prednisolone, and cortisol; other commonly used corticosteroids, endogenous steroids, and prednisolone and methylprednisolone metabolites did not interfere.

A continuous-flow, constant-volume Hewlett Packard model 1050 HPLC system was used with a Hewlett Packard 3396A integrator. The column used was a DuPont Zorbax silica 4.6×250 mm with a mobile-phase solution containing methylene chloride, *n*-heptane, glacial acetic acid, and ethanol (0.6:0.35:0.035:0.015) with a flow rate of 2.0 mL/min. Betamethasone was used as the internal standard.

Plasma samples were extracted with methylene chloride, and the creamy interface was aspirated. The organic layer was washed with sodium hydroxide, again aspirating the aqueous layer and washing with water. After aspirating the aqueous layer, the remaining organic phase was dried with anhydrous sodium sulfate. The organic layer was then dried under a stream of nitrogen, and the residue was reconstituted with mobile phase to prepare for injection.

Full studies with serial sampling over 12 hours permitted calculation of dose- and time-average pharmacokinetic parameters. Prednisolone and methylprednisolone pharmacokinetic parameters were characterized by noncompartmental pharmacokinetic parameters. The area under the curve (AUC) was calculated by LaGrange polynomial interpolation with the least-squares terminal slope to extrapolate to time infinity.¹³ The first moment of the curve (AUC $\times$ t) was calculated by multiplying each plasma concentration by its time. These values were then used to calculate the plasma clearance (CL) and the steady-state volume of distribution (V_{ss}) as follows:

$$(1) \text{ CL} = \text{dose}/\text{AUC}$$

$$(2) V_{ss} = \text{dose} (\text{AUC}\times t)/(\text{AUC})^2$$

The mean residence time (MRT) of the drug, an indicator of the average duration of time a drug molecule spends in the body before being eliminated, was also calculated. This parameter can be viewed as the time point at which the AUC is equal on both sides of the time axis and is the centroid of the concentration-time curve. It can be determined by means of the following equation:

$$(3) \text{ MRT} = \text{AUC}\times t/\text{AUC}$$

The terminal elimination phase of prednisolone and methylprednisolone is linear and allows calculation of the elimination rate constant and half-life ($t_{1/2}$).

RESULTS

The mean values for the methylprednisolone and prednisolone pharmacokinetic parameters are presented in Table I. Clarithromycin therapy resulted in a significant reduction in methylprednisolone clearance with a mean value of 369.6 ± 30 (mean $\pm$ SEM) mL/min/1.73 m² before clarithromycin therapy compared with 121.5 ± 10 mL/min/1.73 m² during clarithromycin therapy (Fig 1). This represents a 65% reduction in clearance ($P = .004$, as determined by Student's *t* test). Mean plasma methylprednisolone concentrations in the presence of clarithromycin were significantly higher ($P < .05$) than those in the preclarithromycin studies at 1.5 hours after dosing and thereafter (Fig 1). Clarithromycin had no effect on prednisolone clearance, with mean values of 233.3 ± 15 before clarithromycin therapy compared with 216.0 ± 23 mL/min/1.73 m² during clarithromycin therapy (Fig 2). MRT increased significantly ($P < .002$) for methylprednisolone in the presence of clarithromycin, with mean values of 4.3 ± 0.27 hours before and 6.47 ± 0.2 hours during clarithromycin therapy. This represents a mean increase of 50% from the baseline values. Mean $t_{1/2}$ increased by 125% ($P < .019$) and mean V_{ss} decreased by 50% ($P < .0069$) for methylprednisolone in the presence of clarithromycin. Clarithromycin therapy did not result in significant changes in prednisolone elimination, MRT, $t_{1/2}$, and V_{ss} .

DISCUSSION

Investigators have recognized a potential role for macrolide antibiotics in the treatment of asthma for over 30 years. Several studies have shown significant improvements in FEV₁ in asthmatic patients who were treated with macrolide antibiotics.^{14,15} Erythromycin has also been shown to improve bronchial responsiveness, with a 10-week course of the antibiotic resulting in an increase in PC₂₀ from 0.13 to 0.35 mg/mL.¹⁶

There is an increasing body of evidence demonstrating anti-inflammatory/immunomodulatory effects of macrolide antibiotics. It has been suggested that the clinical improvement seen in asthmatic patients receiving macrolide antibiotics is a result of these anti-inflammatory and immunomodulatory effects. TAO, for example, has been shown to inhibit the lymphocyte proliferative response to mitogens in vitro and to potentiate the inhibition of this response with methylprednisolone.^{4,5} TAO has also been shown to decrease the neutrophil counts in bronchoalveolar lavage fluid after the intratracheal instillation of chemotactic agents in a rabbit model of inflammation.⁶ Furthermore, roxithromycin, a newly developed macrolide, has been shown to inhibit IL-5 production by murine spleen cells.⁷

Several investigators have suggested a role for chronic *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* in the pathogenesis of chronic, severe asthma. Evidence for mycoplasma infection, either by change in antibody titer or by culture, has been noted in 20% to 25% of

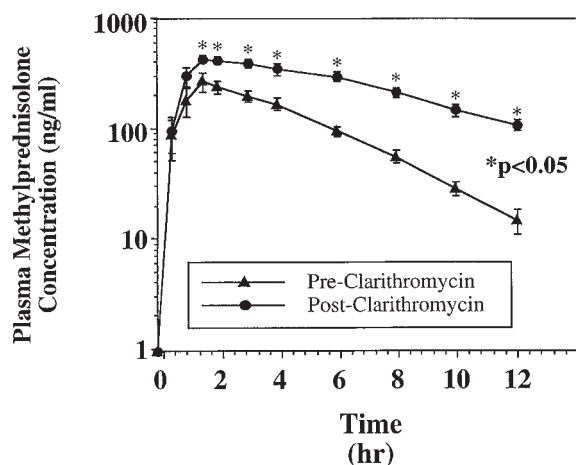


FIG 1. Effect of clarithromycin on methylprednisolone pharmacokinetic profile. Six adult asthmatic patients received oral doses of methylprednisolone (40 mg/mL/1.73 m²) before and after 7 days of clarithromycin therapy. Data are presented as means $\pm$ SEMs.

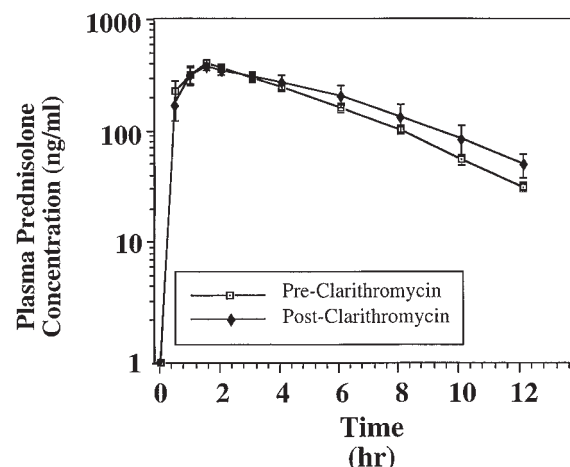


FIG 2. Effect of clarithromycin on prednisolone pharmacokinetic profile. Six adult asthmatic patients received oral doses of prednisolone (40 mg/mL/1.73 m²) before and after 7 days of clarithromycin therapy. Data are presented as means $\pm$ SEMs.

TABLE I. Glucocorticoid pharmacokinetics before and after clarithromycin therapy (mean $\pm$ SEM, n = 6)

	Methylprednisolone			Prednisolone		
	Before	After	P value	Before	After	P value
Clearance (mL/min/1.73 m ²)	369.6 $\pm$ 30	121.5 $\pm$ 10	.004	233.3 $\pm$ 15	216 $\pm$ 22.7	.44
t _{1/2} (h)	2.46 $\pm$ 0.2	5.6 $\pm$ 0.93	.019	3.41 $\pm$ 0.49	4.24 $\pm$ 1.05	.21
MRT (h)	4.30 $\pm$ 0.27	6.47 $\pm$ 0.2	.002	4.61 $\pm$ 0.17	5.22 $\pm$ 0.42	.13
V _{ss} (L/1.73 m ²)	95.55 $\pm$ 10.8	46.71 $\pm$ 3.0	.0069	65.23 $\pm$ 2.9	65.42 $\pm$ 4.2	.97

patients hospitalized with acute asthma exacerbations.^{2,3} Preliminary data from a study by Kraft et al¹⁴ found mycoplasma in bronchoalveolar lavage fluid and/or biopsy specimens by PCR in 9 of 11 asthmatic subjects compared with 0 of 5 nonasthmatic control subjects. After a 6-week course of clarithromycin therapy, subjects receiving clarithromycin displayed less overnight fall in FEV₁ (15.6% $\pm$ 3.6% to 4.5% $\pm$ 2.7% compared with 15.5% $\pm$ 4.4% to 19.3% $\pm$ 2.8% in placebo-treated control subjects; P = .005) and improved baseline FEV₁ (146 $\pm$ 24 mL increase compared with a decrease of 564 $\pm$ 26 mL in placebo-treated control subjects; P = .07). Hahn¹⁷ demonstrated a mean improvement in FEV₁ of 12.5% in patients with chronic asthma and positive serology for *C pneumoniae* after treatment with a macrolide antibiotic. These data suggest a role for macrolide therapy in eradicating a chronic respiratory infection that may be contributing to poor asthma control in selected patients.

The emerging data demonstrating clinical efficacy of macrolide antibiotics in the treatment of asthmatic patients have led to an increased interest in the use of these medications in subjects with severe, often steroid-dependent asthma. More recent data supporting the antimicrobial and anti-inflammatory mechanisms of action have given further credence to the long-term utilization of these medications in the treatment of severe steroid-dependent asthma. It is therefore not surprising

that a more recently developed macrolide, such as clarithromycin, which has an improved side-effect profile, ease of administration, and fewer drug interactions when compared with the older macrolide antibiotics, is being prescribed with increasing frequency for patients with severe asthma.

Macrolides such as TAO and, to a lesser extent, erythromycin can delay methylprednisolone clearance. In a study of 15 asthmatic children, low-dose TAO therapy (250 mg once daily or on alternate days) resulted in a mean decrease in methylprednisolone clearance of 62% while having no effect on prednisolone clearance.¹⁸ Similar results were observed for erythromycin, with a mean decrease in methylprednisolone clearance of 46% noted when asthmatic children were treated with a 1-week course of erythromycin base (250 mg 4 times daily).⁹ Clarithromycin is not thought to interact with the cytochrome P-450 system to the same degree as erythromycin or TAO, and therefore it is not expected to have the same impact on methylprednisolone clearance.¹⁹ We have demonstrated that clarithromycin therapy results in a reduction of methylprednisolone elimination, as indicated by a significant decrease in clearance and increase in MRT and t_{1/2}. This delay in methylprednisolone clearance with clarithromycin therapy is comparable with that observed with TAO.

Szefer et al⁸ found that delayed methylprednisolone

clearance is associated with enhanced clinical efficacy. Delayed methylprednisolone clearance with concomitant TAO therapy resulted in improved daily pulmonary function, decreased requirement for adrenergic bronchodilators, increased exercise tolerance, and decreased hospitalizations in patients with severe steroid-dependent asthma. The delay in methylprednisolone clearance with clarithromycin therapy may therefore contribute to the beneficial effect observed in patients receiving concomitant clarithromycin-methylprednisolone therapy.

Nelson et al¹⁰ studied patients with steroid-dependent asthma receiving methylprednisolone with and without TAO. Although the TAO group was able to tolerate a greater decrease in oral corticosteroid dose, they found the TAO group to have a significantly greater decline in vertebral body density and serum IgG, as well as a rise in the fasting blood sugar and the serum cholesterol compared with a fall in fasting blood sugar and the serum cholesterol in the placebo group. They concluded that the TAO/methylprednisolone combination was effective, but adverse effects outweighed the benefits gained. The results of our study suggest that the long-term use of clarithromycin in patients receiving chronic methylprednisolone therapy, but not prednisolone therapy, may place those patients at increased risk for steroid-induced adverse effects.

Prednisone and methylprednisolone are the two most commonly used glucocorticoids in the treatment of asthma. Although structurally very similar, these compounds differ in many respects. First, prednisone is an inactive prodrug. Once absorbed, it must be transformed to the active drug, prednisolone, by means of first-pass metabolism. Second, methylprednisolone is more slowly absorbed than prednisone and prednisolone. Its binding to transcortin, a glucocorticoid-binding protein, is reduced as a result of its 6-methyl group.^{20,21} Of note, this modification also changes the susceptibility of methylprednisolone to alterations of its metabolism by other medications.²² Third, because methylprednisolone binds primarily to albumin and not transcortin,²³ it is thought to achieve better lung penetration and a longer retention time within the lung. This combination may represent a therapeutic advantage of this glucocorticoid in the treatment of asthma and other pulmonary diseases.^{24,25} Lastly, methylprednisolone is more susceptible than prednisone to drug interactions. These interactions may result in either reduced or enhanced clearance and consequently an increased risk for adverse effects or a diminished therapeutic response. Anticonvulsants, including phenytoin, phenobarbital, and carbamazepine, cause an increased rate of elimination for dexamethasone, prednisolone, and methylprednisolone,²⁶ with methylprednisolone clearance affected to a much greater degree than prednisolone. As stated above, methylprednisolone also appears to be more susceptible to delayed clearance in the presence of drugs, such as the macrolides erythromycin, TAO, and clarithromycin.

Clinicians must be aware of potential drug interactions that could place patients at increased risk for steroid-

induced adverse effects. We have demonstrated such an effect between clarithromycin and methylprednisolone, two drugs that may be administered concomitantly in asthma, as well as in other diseases. The dose of clarithromycin used in this study was equivalent to that which is recommended for the treatment of minor infections. To avoid potential steroid-enhancing effects, methylprednisolone should be switched to prednisone during prolonged courses of clarithromycin therapy. If the immunomodulatory properties of clarithromycin are to be studied in steroid-requiring patients, these patients should receive oral prednisone therapy in place of methylprednisolone to avoid any compromise in effect due to a clarithromycin/steroid drug interaction.

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