# Monitoring glucocorticoid therapy: A pharmacokinetic approach

**Although glucocorticoid therapy is essential for the treatment of severe inflammatory disorders, there is no systematic approach to patient variables that may affect availability of a steroid dose. After the development of a data base of pharmacokinetic parameters, we examined glucocorticoid pharmacokinetics in 54 patients between 2 and 70 years of age using 70 pharmacokinetic studies after administration of intravenous methylprednisolone ($n$ = 25), oral methylprednisolone ($n$ = 15), intravenous prednisolone ($n$ = 18), and oral prednisone ($n$ = 12). Eleven patients had unusually rapid methylprednisolone elimination (clearance, 565 to 837 ml/min/1.73 m$^2$; population mean, [±SD] 380 ± 100 ml/min/1.73 m$^2$) without an identifiable cause. Incomplete absorption of methylprednisolone and prednisone was observed in three patients and one patient, respectively. Evaluation of glucocorticoid pharmacokinetics in children aged 1 year 8 months to 18 years demonstrated a significant inverse correlation ($r$ = 0.88; $p < 0.001$) between prednisolone clearance and age. It is therefore important to consider age in the interpretation of pharmacokinetic data. To simplify measurement of prednisolone clearance, a single-dose single-point method was developed. This was based on a highly significant relationship between the 6-hour postdose prednisolone concentration and prednisolone clearance (log prednisolone clearance = 2.66 + [6-hour postdose concentration] [−0.00167]; $r^2$ = 0.96; $p < 0.0001$). Evaluation of glucocorticoid pharmacokinetics in the clinical setting can be used to identify abnormalities in absorption, elimination, and patient compliance. This technique can be used to individualize glucocorticoid dosing regimens. (CLIN PHARMACOL THER 1990;48:390-8.)**

**Malcolm R. Hill, PharmD, Stanley J. Szefler, MD, Bruce D. Ball, MD,[a] Maryanne Bartoszek, MD,[a] and A. Manon Brenner, MD** *Denver, Colo.*

Glucocorticoids are used extensively as anti-inflammatory and immunosuppressive agents.[1] Oral prednisone (the inactive precursor of the active glucocorticoid prednisolone) and the active glucocorticoid methylprednisolone are commonly selected medications. Occasionally, improvement is not observed or an unexplained deterioration in clinical status may occur in certain patients despite high-dose and long-term glucocorticoid therapy. This may be related to overwhelming disease severity, poor compliance, abnormalities in glucocorticoid disposition such as rapid metabolism or poor absorption, glucocorticoid resistance,[2,3] or a glucocorticoid receptor or postreceptor abnormality.[4]

Unfortunately, there is no system available to measure variables influencing glucocorticoid disposition in individual patients. Anticonvulsants such as phenytoin, carbamazepine, phenobarbital,[5] and rifampin[6] markedly enhance prednisolone and methylprednisolone elimination. Alternatively, glucocorticoid elimination is impaired by other medications. Oral contraceptives have been shown to decrease prednisolone clearance,[7] and ketoconazole inhibits both methylprednisolone and prednisolone clearance.[8,9] Macrolide antibiotic agents such as erythromycin[10] and troleandomycin selectively inhibit methylprednisolone metabolism and have no effect on prednisolone elimination,[11,12] contributing to the beneficial effect observed in the treatment of patients with severe glucocorticoid-requiring asthma.[13,14] Clinical response correlates with changes in glucocorticoid

From the Ira J. and Jacqueline Neimark Laboratory of Clinical Pharmacology in Pediatrics, Departments of Pediatrics and Medicine, National Jewish Center for Immunology and Respiratory Medicine, and the Departments of Pediatrics and Pharmacology, Schools of Pharmacy and Medicine, University of Colorado Health Sciences Center.

Received for publication May 8, 1990; accepted July 19, 1990.

Reprint requests: Malcolm R. Hill, PharmD, Department of Pediatrics, National Jewish Center for Immunology and Respiratory Medicine, 1400 Jackson St., Denver, CO 80208.

[a]Fellows in Allergy and Clinical Immunology, Department of Pediatrics, National Jewish Center for Immunology and Respiratory Medicine, Denver, Colo.

**13/1/23900**

pharmacokinetics because an increase in effect is associated with inhibition of metabolism and a decrease in effect with induction of metabolism. Similarly, development of systemic adverse effects is associated with slower elimination.[15]

The absorption of glucocorticoids has not been evaluated extensively. Complete absorption has been documented in normal volunteers,[16] patients with inflammatory bowel disease,[17] and the nephrotic syndrome.[18] As such, the possibility of poor absorption is not generally considered a factor in poor response to glucocorticoid therapy.

With the multiple factors known to affect glucocorticoid disposition, and concern regarding inadequate clinical response in certain patients, we developed an approach to therapeutic drug monitoring for glucocorticoids in a population of patients with severe asthma. This report will present methods to evaluate glucocorticoid pharmacokinetics in the clinical setting to facilitate an approach to individualizing dosing schemes.

## METHODS

### Patient selection

The 54 patients included in the prospective pharmacokinetic evaluation were patients with severe glucocorticoid-requiring asthma whose clinical response from long-term administration of varying dosage regimens of daily or alternate-day oral prednisone or methylprednisolone was less than desired. Specific clinical indications for these studies included lack of beneficial or adverse glucocorticoid effect ($n = 48$) or concomitant therapy with anticonvulsant agents ($n = 8$) or macrolide antibiotic agents ($n = 14$). Ages ranged between 2 and 69 years. Patients had a wide range in body habitus. All doses administered and final results are uniformly based on total body weight or total body surface area. All patients were also receiving inhaled glucocorticoids, sustained-release theophylline, inhaled β-agonists, and occasionally inhaled atropine sulfate or ipratropium bromide. Systemic side effects of glucocorticoids including cushingoid appearance, posterior subcapsular cataracts, obesity, bone demineralization, and hypertension were absent in approximately 20% of the patients studied. Systemic side effects were present in varying combinations and degrees of severity in the remaining patients. Adrenal suppression (morning cortisol level $<5$ μg/dl) was a more universal finding, occurring in more than 90% of patients studied. Pharmacokinetic studies were performed to determine the degree of systemic glucocorticoid exposure that results from incomplete absorption of oral doses, rapid metabolism, or a change in clearance resulting from concomitant medications that are known or suspected to produce inhibition or induction of glucocorticoid metabolism.

Patient data used for determination of the effect of age on clearance and the single-point clearance estimate were obtained from previously published values listed in Table I.[5,10-12,19]

### Study procedures

***Intravenous studies.*** At approximately 7 AM on the study day an indwelling catheter was placed for serial blood withdrawal. In a contralateral extremity another catheter was placed for infusion of the study drug. The line was flushed with 5 ml saline solution, and the study drug was administered as a bolus over 1 to 2 minutes as close to 8 AM as possible. The line was flushed with another 5 ml saline solution and discontinued. Doses of prednisolone (Hydeltrasol, Merck Sharp & Dohme, West Point, Pa.) were administered as 40 mg/1.73 $m^2$ total body surface area. This dose was selected for all patients to minimize the effects of dose-dependent pharmacokinetics that are observed with this glucocorticoid.[19] Because methylprednisolone (Solu-Medrol, The Upjohn Company, Kalamazoo, Mich.) is generally not affected by dose-dependent pharmacokinetics, doses selected were either the actual dose the patient was receiving clinically or the standardized dose of 40 mg/1.73 $m^2$. Blood samples were obtained before infusion and ½, 1, 1½, 2, 3, 4, 6, 8, 10, and 12 hours after infusion. Blood was placed in heparinized glass tubes and refrigerated immediately. Plasma was separated within 12 hours after the last sample and frozen at $-20°$ C until analysis.

***Oral studies.*** For oral studies, patients fasted from 12 midnight until 1 hour after administration of the study dose. Criteria for dosage selection for prednisone (Orasone, Rowell Inc.) or methylprednisolone (Medrol, The Upjohn Company), as well as other procedures, were identical to those of the intravenous studies.

***Single-point clearance estimation.*** To decrease the number of samples and minimize the technical requirements to determine glucocorticoid clearance in a given patient, we developed methods to predict clearance from a single postdose glucocorticoid concentration. Results from a separate group of 52 studies from 43 patients with an average age of 10 years (range, 2 to 50 years) were evaluated. Of these, 15 patients were receiving concomitant anticonvulsant agents, and all

**Table I.** Glucocorticoid pharmacokinetic parameters assessed from previous reports after administration of 40 mg (adults) or 40 mg/1.73² (adults and children) intravenous prednisolone or methylprednisolone

| *Glucocorticoid/data source* | *CL (ml/min/1.73 m²)* | *$V_{SS}$ (L/1.73 m²)* | *$t_{1/2}$ (hr)* | *Subject category* |
|---|---|---|---|---|
| Prednisolone | | | | |
| Rose et al.[23] | 246 ± 62 | 52.8 ± 14.5 | 2.50 ± 0.5 | Asthmatic children ($n$ = 10) (8-12 yr) |
| Bartoszek et al.[5] | 214 ± 29 | 47.8 ± 5.6 | 2.50 ± 0.41 | Asthmatic children ($n$ = 16) (2-18 yr) |
| Rose et al.[22] | 201 ± 54 | 50.8 ± 11.7 | 3.33 ± 0.71 | Asthmatic ($n$ = 7) |
| | 198 ± 38 | 53.5 ± 13.5 | 3.25 ± 0.58 | Adult volunteer ($n$ = 13) |
| Methylprednisolone | | | | |
| LaForce et al.[10] | 380 ± 101 | 82.4 ± 19.1 | 2.34 ± 0.52 | Asthmatic children ($n$ = 7) (9-18 yr) |
| Szefler et al[11] | 406 ± 139 | 78.4 ± 28.4 | 2.46 ± 0.75 | Asthmatic children ($n$ = 10) (11-15 yr) |
| Szefler et al.[19] | 384 ± 56.2 | 91.0 ± 9.9 | 2.58 ± 0.19 | Adult volunteer ($n$ = 7) (25-35 yr) |
| Szefler et al.[12] | 380 ± 155 | 68.2 ± 17.1 | 2.02 ± 0.38 | Asthmatic adult ($n$ = 5) |

Data are presented as mean values ± SD.
CL, Clearance; $V_{SS}$, steady-state volume of distribution; $t_{1/2}$, half-life.

were on antiasthma regimens consisting of oral theophylline, oral and inhaled glucocorticoids, and inhaled β-agonists. Patients received 40 mg/1.73 m² intravenous prednisolone ($n$ = 40) or oral prednisone ($n$ = 12). Study procedures were followed as outlined above. Least-squares linear regression was applied to derive the correlation and regression equation between the 6-hour postdose plasma prednisolone concentration and the actual clearance. The regression equation was then applied to the individual 6-hour postdose plasma prednisolone concentrations to determine the accuracy of this relationship. Finally, this method was tested prospectively in 12 additional subjects.

***Assay methods.*** All samples were assayed according to a modification of the highly sensitive and specific HLPC method of Ebling et al.,[20] described in detail by Bartoszek et al.[5] This assay is specific for methylprednisolone, prednisolone, and endogenous cortisol. There was no interference from inhaled glucocorticoids (or metabolites) such as beclomethasone diproprionate or triamcinolone acetonide or from metabolites of prednisolone or methylprednisolone. The lower limit of detection was 10 ng/ml, and the intraday percent coefficient of variation was less than 5% at 50 and 400 ng/ml.

***Estimation of pharmacokinetic parameters.*** Model-independent pharmacokinetic parameters for prednisolone and methylprednisolone were calculated as follows: The area under the plasma concentration–time curve (AUC) was determined by LaGrange polynomial interpolation and integration with the least-squares terminal slope ($k_{el}$) to extrapolate to time infinity.[21] The first moment of the curve, area under the moment curve (AUMC), was calculated similarly after each plasma concentration was multiplied by its time. These values permitted calculation of the average time a molecule of glucocorticoid remained in the body, or mean residence time (MRT):

$$MRT = AUMC/AUC$$

Total body clearance (CL) was calculated as follows:

$$CL = dose/AUC$$

Steady-state volume of distribution ($V_{SS}$) was calculated as follows:

$$V_{SS} = (CL)\ (MRT)$$

These calculations assume total availability of systemically administered glucocorticoid, minimal alterations in the degree of reversible metabolism to inactive metabolites, and a predominantly linear elimination pattern, and important variations in plasma protein binding do not occur.

The percent of a dose of orally administered glucocorticoid (F) was calculated by the AUC ratio corrected for the dose and elimination rate:

$$F = \frac{AUC_{oral} \times dose_{IV} \times k_{e,oral}}{AUC_{IV} \times dose_{oral} \times k_{e,oral}} \times 100$$

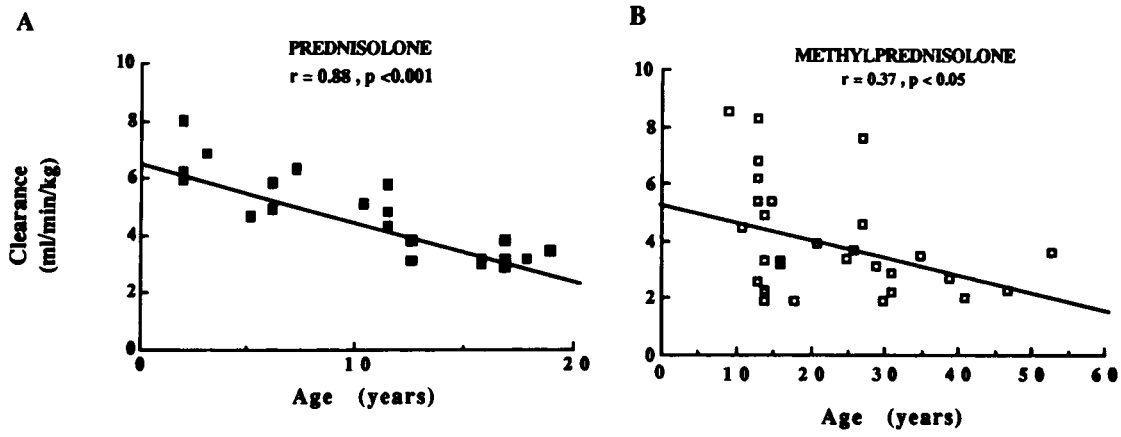


**Fig. 1.** Relationships between age and clearance are shown for prednisolone (**A**) and methylprednisolone (**B**).

### Data analysis

Clearance data from all patients who were not receiving any medications known to alter elimination of prednisolone or methylprednisolone were normalized to total body weight to enhance any age-related differences. Individual clearance values were then compared to age with linear regression. All results are expressed as mean ± SD. Glucocorticoid clearance in patients younger than 12 years of age was compared with clearance in patients older than 12 years with the unpaired $t$ test. The difference was considered significant at $p < 0.05$. The age of 12 years was selected on the basis of the projected onset of puberty and experience in previous studies.[22,23] Values for predicted prednisolone clearance were compared with actual values by calculation of precision (accuracy of a particular estimate) and bias (a measure of tendency to overpredict or underpredict) as described previously.[24]

## RESULTS

To establish population averages and ranges for the various pharmacokinetic parameters, data from previously published studies were pooled (Table I).

### Effect of age on glucocorticoid elimination

To investigate the relationship between age and clearance, linear regression between age and glucocorticoid clearance was performed. For prednisolone, there was a significant inverse relationship between age and clearance ($r = 0.88$; $p < 0.001$; Fig. 1, *A*), with children younger than 12 years of age having a higher clearance (5.52 ± 1.18 ml/min/kg; $n = 12$) compared with the clearance of older children and adults (3.70 ± 1.0 ml/min/kg; $n = 9$; $p < 0.005$). For methylprednisolone, however, the relationship between age and clearance was poor ($r = 0.37$; $n = 30$; $p < 0.05$), although clearance did tend to decrease as age increased (Fig. 1, *B*).

### Evaluation of individual glucocorticoid pharmacokinetic studies

A total of 70 intravenous or oral pharmacokinetic studies was performed in 54 patients. Thirty studies were performed with prednisolone (18 studies with intravenous prednisolone and 12 studies with oral prednisone) and 40 with methylprednisolone (25 studies with intravenous methylprednisolone and 15 studies with oral methylprednisolone). Eleven patients had unexplained rapid methylprednisolone clearance (range, 565 to 837 ml/min/1.73 $m^2$). In four of these patients prednisolone pharmacokinetic study results were within the normal range. An additional three patients demonstrated poor bioavailability of methylprednisolone (range, 22.6% to 65.3% absorbed). Only one patient with incomplete availability of prednisolone from oral prednisone was identified (Fig. 2, *A*), in whom complete absorption of methylprednisolone was subsequently demonstrated. Prednisolone clearances were markedly elevated within the range described previously[5] in patients receiving concomitant anticonvulsant therapy with phenytoin (407.3 to 595.5 ml/min/1.73 $m^2$; $n = 3$) and combination phenytoin-phenobarbital therapy (493.4 and 1015.0 ml/min/1.73 $m^2$; $n = 2$). One patient receiving concomitant phenytoin was subsequently treated with valproic acid. In this patient a decrease in prednisolone clearance from

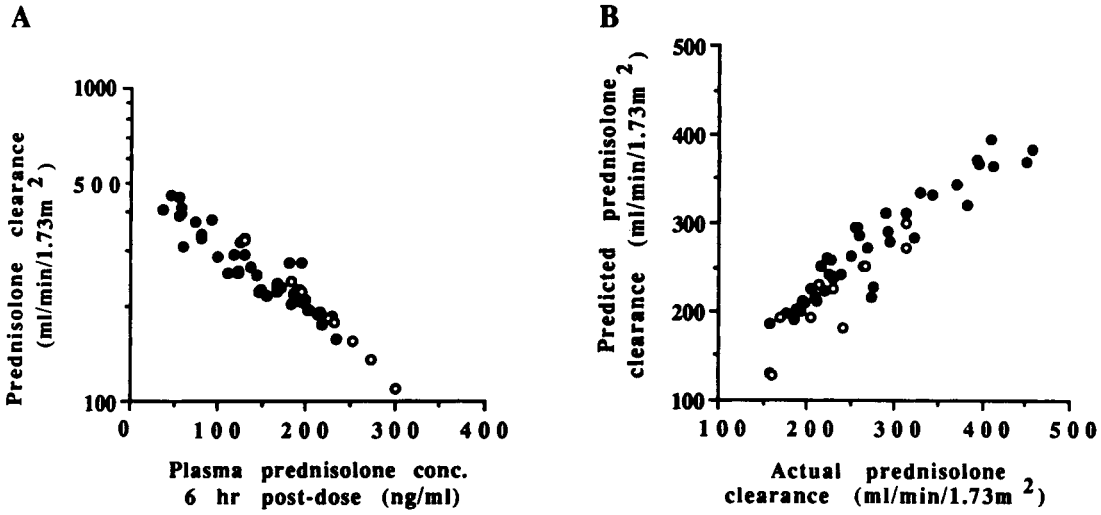


**Fig. 2.** The 6-hour postdose plasma prednisolone concentration is highly correlated with prednisolone clearance **(A)**. Application of the regression equation demonstrates excellent agreement between actual and predicted prednisolone clearances **(B)**. *Solid circles,* Prednisolone; *open circles,* oral prednisone.

539.3 to 296.2 ml/min/1.73 $m^2$ occurred after 10 days of valproic acid therapy. Finally, prednisolone clearance was 192.5 ml/min/1.73 $m^2$ in a patient receiving concomitant valproic acid therapy. There was no obvious relationship between presence or absence of glucocorticoid-associated adverse effects and clearance values. This was primarily because of the wide array in magnitude and duration of glucocorticoid therapy before investigation, as well as the variety in presentation of visible and metabolic adverse effects.

### Single-point clearance estimation

There is a highly significant ($r^2 = 0.80$; $p < 0.0001$) correlation between log actual prednisolone clearance and the 6-hour postdose plasma prednisolone concentration (Fig. 3, *A*). Accuracy of results obtained from oral prednisone did not differ from those of intravenous prednisolone. The equation for the regression line is:

log prednisolone clearance = 2.66 + [6-hour prednisolone concentration] [−0.00167]

There is a slight bias of 5.3 ml/min/1.73 $m^2$. Precision is 30 ml/min/1.73 $m^2$, or less than 12% of the mean actual prednisolone clearance. There is a tendency to underpredict prednisolone clearance in patients with an actual clearance of greater than 350 ml/min/1.73 $m^2$. This predictive method did not give a result in the normal range in any subject with an actual prednisolone clearance of greater than 300 ml/min/1.73 $m^2$. Results from the prospective evaluation to test the derived equation yield a similarly strong correlation between actual and predicted prednisolone clearance ($r^2 = 0.96$; $p < 0.0001$). The absolute value of the percent difference between actual and predicted prednisolone clearance was 7.3% (range, 16.4% to 22.0%).

## DISCUSSION

The application of systemic glucocorticoids has been used successfully for many years for a wide variety of inflammatory disorders and their generalized immunosuppressive effects. Typically the dosage regimen is highly individualized, with the goal of obtaining the maximal benefit with minimal risk of adverse effects. Many patients with asthma require glucocorticoids for control of the signs and symptoms of chronic asthma. This need is usually manifested as a short course of high-dose oral prednisone. There is a subset of patients who require maintenance oral glucocorticoids in addition to maximal bronchodilator therapy and inhaled glucocorticoids. Of this subset, there are patients who have difficulty maintaining acceptable pulmonary function and quality of life despite long-term aggressive oral glucocorticoid therapy.[25] Failure to respond to glucocorticoid therapy is poorly understood and can involve severe disease, noncompliance, a cellular aberration, or end-organ nonresponsiveness. In an attempt to examine these patients from a pharmacokinetic aspect, we

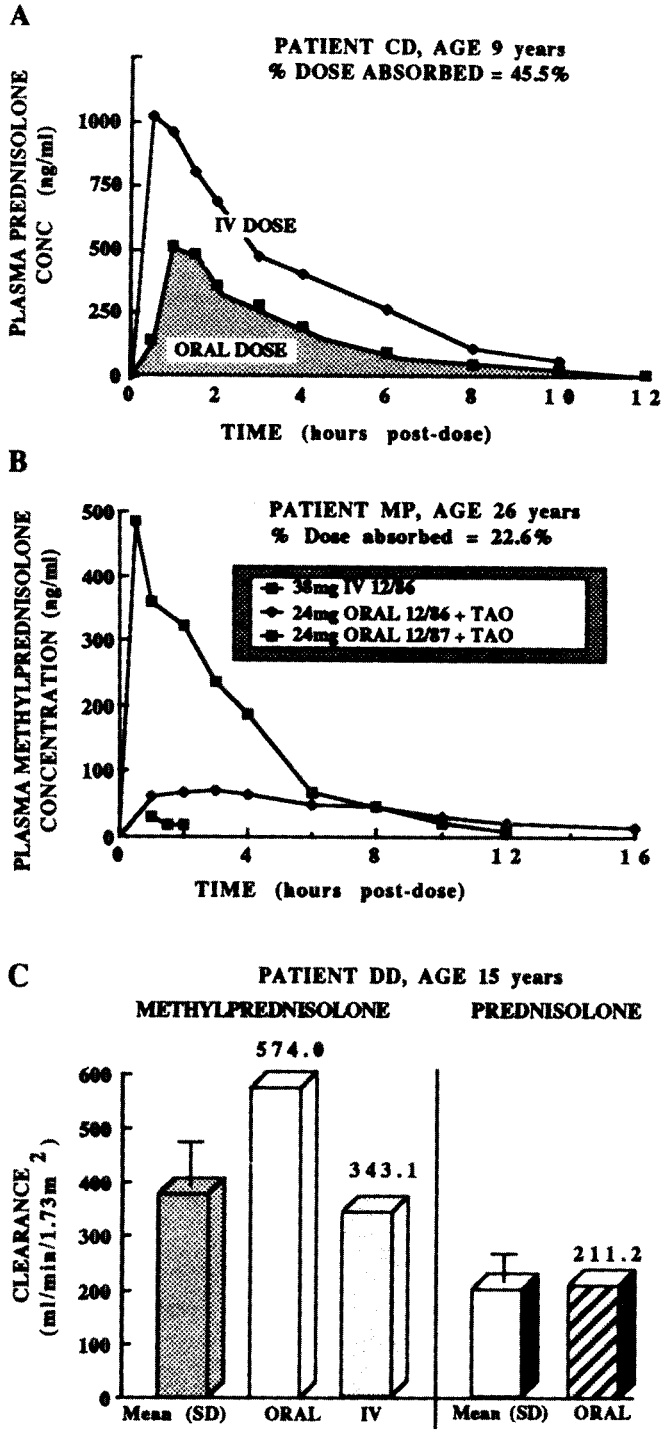


**Fig. 3.** Pharmacokinetic studies from three patients. **A,** Demonstrates incomplete bioavailability of prednisolone from an oral dose of prednisone. **B,** Indicates incomplete absorption of methylprednisolone on two separate occasions. TAO, troleandomycin. **C,** Demonstrates selective abnormalities in pharmacokinetics. This patient demonstrated high apparent oral clearance after oral methylprednisolone (32 mg) and a typical clearance after intravenous (IV) methylprednisolone (38 mg), with a bioavailability of 49.4%. Oral prednisone (35 mg) pharmacokinetics were within the normal range, suggestive of complete absorption of this glucocorticoid.

have developed the following approach. Initially we began with complete pharmacokinetic studies. Because of cost and inconvenience, we attempted to develop a simplified screening method. We have observed a pharmacokinetic basis for nonresponsiveness to systemic glucocorticoid therapy that occurs in some patients. Also, we have developed a single-point method to help identify some of these patients without extensive investigation.

Findings from previous pharmacokinetic investigations are pooled in Table I. This provides the framework for interpretation of studies that are performed in individual patients. The higher values for clearance seen with methylprednisolone compared with prednisolone are consistently observed in the literature, as well as in patients described in this study.[19] The higher value for clearance in conjunction with the larger volume of distribution likely explains the enhanced tissue penetration that is observed with methylprednisolone.[26,27] However, there is a higher degree of interpatient variability in methylprednisolone pharmacokinetic parameters. The reasons for this are not clear but may be the result of different pathways of elimination and protein-binding characteristics that exist for prednisolone compared with methylprednisolone.[19]

Total body clearance of most drugs, whether excreted renally or metabolized by the liver, is higher in children than adults.[28] This is also true for prednisolone (Fig. 1, *A*). To demonstrate the age-related effect, we have normalized clearance to actual body weight rather than body surface area. Although maintenance regimens for glucocorticoids are adjusted based on the minimum dose that achieves a desired therapeutic response, empiric regimens for short-course, high-dose prednisone therapy are often based on body weight (e.g., 2 mg/kg/day). Therefore younger children will receive less systemic glucocorticoid exposure and effect than will older children and adolescents receiving the same dosage regimen. The relationship of age and clearance for methylprednisolone does not correlate as well (Fig. 1, *B*). This is most likely because we did not have the opportunity to evaluate children less than 10 years of age. Although it is likely that this age group, especially those younger than 6 years of age, would have significantly higher clearance values compared with older children, the higher degree of interpatient variability in methylprednisolone pharmacokinetic parameters partially prevents the relationship between age and clearance from appearing as strong as it is for prednisolone. When evaluating glucocorticoid pharmacokinetic parameters, the age of the patient should be taken into consideration, especially in younger children.

As factors that alter glucocorticoid pharmacokinetics have been elucidated, the feasibility and need to evaluate glucocorticoid absorption and elimination in individual patients has evolved. We have developed a scheme to estimate pharmacokinetic parameters with a minimum number of blood samples. Measurement of a single 6-hour postdose prednisolone concentration is sufficiently accurate and precise to predict clearance. This approach is therefore useful as a screening tool to determine which subjects may require further pharmacokinetic evaluation. In this situation, subjects who are determined to be rapid metabolizers (i.e., prednisolone clearance >300 ml/min/1.73 $m^2$) should ideally undergo a complete evaluation. Poor absorption of prednisone or lack of interconversion of prednisone to the active glucocorticoid prednisolone will provide falsely elevated values for predicted prednisolone clearance. These important perturbations tend not to be missed during a complete pharmacokinetic study after intravenous and oral doses. To partially obviate this, we have begun obtaining a series of three blood samples (before dosing, 2 hours after dosing, and the 6-hour postdose sample) to provide a more complete, yet still simple evaluation. The predose sample is useful primarily to document that there is no prednisolone remaining in plasma from previous doses but also to assess endogenous plasma cortisol concentration. The second sample is obtained at the theoretical maximum prednisolone concentration and is useful to estimate the rate and extent of absorption of the oral dose. Typically, this 2-hour postdose prednisolone concentration should be greater than 400 ng/ml. This predictive method cannot isolate aberrations in parameters such as volume of distribution, elimination rate constant, or protein binding. These more detailed parameters must be arrived at through more sophisticated analysis, such as complete oral or intravenous studies. Unfortunately, a similar approach for estimation of methylprednisolone clearance has not proved reliable. Although reasonable relationships exist between 4- and 6-hour postdose concentrations and total body clearance, interpatient variability in rate of absorption of oral methylprednisolone doses rendered predicted clearances unreliable.

A majority of patients who underwent glucocorticoid pharmacokinetic studies in this investigation had values that were within the normal range. In addition, patients in whom we anticipated induced (as with anticonvulsant[5]) or inhibited (as with macrolide antibiotics[11,12]) elimination of prednisolone or methylprednisolone did indeed have the alterations we expected. However, an important subpopulation of patients was identified. Generally, these were the patients

who did not achieve the desired therapeutic response despite relatively aggressive therapy. We observed unusually rapid metabolism of methylprednisolone in 11 of 40 patients who were evaluated for poor responsiveness to this glucocorticoid. Although this population is a selected and therefore biased group, the fact that greater than 25% of patients evaluated had markedly elevated methylprednisolone elimination is, nonetheless, clinically relevant. One finding that we did not anticipate was incomplete absorption, which was observed in four patients. Studies in volunteers and patients with a variety of disease states have demonstrated complete absorption of prednisone[16-18] and prednisolone.[29] Although incomplete absorption was a less common finding, it can also be of clinical importance in certain individuals (Fig. 2, *B*).

In asthma therapy we commonly use serum theophylline concentrations to individualize treatment regimens. Experience with theophylline has enhanced our appreciation of the dose-response relationship in managing individual patients and the significant influence that age, drug interactions, and variation in absorption have on the clinical response that is observed. We are now approaching an era of understanding the relationship of glucocorticoid pharmacokinetics to the pharmacodynamics of the response.[30] The response is determined by not only the binding of the glucocorticoid to its receptor but also the availability of the drug to the site of action, ultimately determined by the absorption and elimination of the drug. Our clinical experience to date has provided the initial basis for evaluating the pharmacokinetic aspects of the response to glucocorticoids. Information obtained from these studies has provided the opportunity to individualize further the patients' treatment regimens, similar to the approach used with other medications that undergo therapeutic drug monitoring, such as anticonvulsant agents or theophylline. We use this information to verify the presence of a drug-drug interaction and consequently discontinue the implicated medication or attempt alternative glucocorticoid therapy to identify abnormalities in absorption, consider split-dose regimens, or support the addition of troleandomycin therapy. Certainly, applications exist in patients receiving long-term glucocorticoid therapy for immunosuppressive therapy associated with transplantation who are subject to serious sequelae of treatment failure. This particular indication is of increasing importance because of a potential cyclosporine-prednisolone drug interaction.[31]

Compliance with prescribed regimens is also an important feature of determining responsiveness to glucocorticoid therapy. Patient misunderstanding of various prescribed regimens along with devious noncompliance can have important clinical ramifications. A recent report of a prednisone treatment failure in an adolescent with Crohn's disease was attributed to noncompliance after detailed pharmacokinetic studies were employed.[32] In this case, detection of the noncompliance issue was essential for amelioration of the disease and avoidance of surgery. In selected situations we have monitored random blood samples for glucocorticoid concentrations in conjunction with endogenous cortisol concentrations in patients with severe asthma. It has been surprising to us that patients with life-threatening disease will design their own dosage-reduction regimens even under close medical supervision.

Although the majority of patients respond to oral glucocorticoids, there is a subpopulation who will not. Part of the clinical evaluation of these patients should include pharmacokinetic studies to determine if a perturbation is, at least in part, responsible for the persistently unstable asthma or other inflammatory disease.

We thank Maureen Plourd-Sandoval for editorial assistance and Eleanor Brown, MT, ASCP, for technical assistance.

### *References*

1. Fauci AS, Dale DC, Balow JE. Glucocorticosteroid therapy: mechanisms of action and clinical considerations. Ann Intern Med 1976;84:304-15.
2. Kay AB, Diaz P, Carmichael J, Grant IWB. Corticosteroid-resistant asthma and monocyte complement receptors. Clin Exp Immunol 1981;44:576-80.
3. Poznansky MC, Gordon ACH, Douglas JC, Krajewski AS, Wylie AH, Grant IWB. Resistance to methylprednisolone in cultures of blood mononuclear cells from glucocorticoid-resistant asthmatic patients. Clin Sci 1984;67:639-45.
4. Bloomfield CD. Glucocorticoid receptors in leukemia and lymphoma. J Clin Oncol 1984;2:323-8.
5. Bartoszek M, Brenner AM, Szefler SJ. Prednisolone and methylprednisolone kinetics in children receiving anticonvulsant therapy. CLIN PHARMACOL THER 1987;42: 424-32.
6. Buffington GA, Dominguez JH, Piering WF, Herbert LA, Kauffman HM, Lemann J. Interaction of rifampin and glucocorticoids: adverse effect on renal allograft function. JAMA 1976;236:1958-60.
7. Boekenoogen SJ, Szefler SJ, Jusko WJ. Prednisolone disposition and protein binding in oral contraceptive users. J Clin Endocrinol Metab 1983;56:702-8.
8. Glynn AM, Slaughter RL, Brass C, D'Ambosio R, Jusko WJ. Effects of ketoconazole on methylprednisolone and cortisol secretion. CLIN PHARMACOL THER 1986;39: 654-9.
9. Zürcher FM, Frey BM, Frey FJ. Impact of ketoconazole on the metabolism of prednisolone. CLIN PHARMACOL THER 1989;45:366-72.

10. LaForce CF, Szefler SJ, Miller MF, Ebling W, Brenner M. Inhibition of methylprednisolone elimination in the presence of erythromycin therapy. J Allergy Clin Immunol 1983;72:34-9.
11. Szefler SJ, Rose JQ, Ellis EF, Spector SL, Green AW, Jusko WJ. The effect of troleandomycin on methylprednisolone elimination. J Allergy Clin Immunol 1980; 66:447-51.
12. Szefler SJ, Brenner AM, Jusko WJ, Spector SL, Flesher KA, Ellis EF. Dose- and time-related effect of troleandomycin on methylprednisolone elimination. CLIN PHARMACOL THER 1982;32:166-71.
13. Spector SL, Katz FH, Farr RS. Troleandomycin: effectiveness in steroid-dependent asthma and bronchitis. J Allergy Clin Immunol 1974;54:367-79.
14. Eitches RW, Rachelefsky GS, Katz RM, Mendoza GR, Siegel SC. Methylprednisolone and troleandomycin in treatment of steroid-dependent asthmatic children. Am J Dis Child 1985;139:264-8.
15. Kozower M, Veatch L, Kaplan MM. Decreased clearance of prednisolone, a factor in the development of corticosteroid side effects. J Clin Endocrinol Metab 1974; 38:407-12.
16. Georgitis JW, Flesher KA, Szefler SJ. Bioavailability of a liquid prednisone preparation. J Allergy Clin Immunol 1982;70:243-7.
17. Milsap RL, George DG, Szefler SJ, Murray KA, Lebenthal E, Jusko WJ. Effect of inflammatory bowel disease. Dig Dis Sci 1983;28:161-8.
18. Rocci ML, Assael BM, Appiani AC, Edefonti A, Jusko WJ. Effect of nephrotic syndrome on absorption and disposition of prednisolone in children. Int J Pediatr Nephrol 1982;3:161-6.
19. Szefler SJ, Ebling WF, Georgitis JW, Jusko WJ. Methylprednisolone versus prednisolone pharmacokinetics in relation to dose in adults. Eur J Clin Pharmacol 1986;30:323-9.
20. Ebling WF, Szefler SJ, Jusko WJ. Analysis of cortisol, methylprednisolone and methylprednisolone hemisuccinate: absence of effects of troleandomycin on ester hydrolysis. J Chromatogr 1984;305:271-80.
21. Rocci ML, Jusko WJ. LAGRAN program for area and moments in pharmacokinetic analysis. Comput Programs Biomed 1983;16:203-16.
22. Rose JQ, Nickelsen JA, Middleton E, Yurchak AM, Park BH, Jusko WJ. Prednisolone disposition in steroid-dependent asthmatics. J Allergy Clin Immunol 1980; 66:366-73.
23. Rose JQ, Nickelsen JA, Ellis EF, Middleton E, Jusko WJ. Prednisolone disposition in steroid-dependent asthmatic children. J Allergy Clin Immunol 1981;67:188-93.
24. Sheiner LB, Beal SL. Some suggestions for measuring predictive performance. J Pharmacokinet Biopharm 1981;9:503-12.
25. Turner-Warwick M. Clinical patterns of responsiveness to corticosteroids. In: Kay AB, ed. Asthma: clinical pharmacology and therapeutics progress. Blackwell Scientific, 1986:347-55.
26. Braude AC, Rebuck AS. Prednisone and methylprednisolone disposition in the lung. Lancet 1983;2:995-7.
27. Vichyanond P, Irvin CG, Larsen GL, Szefler SJ, Hill MR. Penetration of corticosteroids into the lung: evidence for a difference between methylprednisolone and prednisolone. J Allergy Clin Immunol 1989;84:867-73.
28. Milsap RL, Szefler SJ. Special pharmacokinetic considerations in children. In: Evans WE, Schentag JJ, Jusko WJ, eds. Applied pharmacokinetics: principles of therapeutic drug monitoring. 2nd ed. Spokane, Washington: Applied Therapeutics, Inc., 1986:294-330.
29. Tembo AV, Hallmark MR, Sakmar E, Bachmann HG, Weidler DJ, Wagner JG. Bioavailability of prednisolone tablets. J Pharmacokinet Biopharm 1977;5:257-70.
30. Boudinot FD, D'Ambrosio R, Jusko WJ. Receptor-mediated pharmacodynamics of prednisolone in the rat. J Pharmacokinet Biopharm 1986;14:469-92.
31. Ost L. Effects of cyclosporin on prednisolone metabolism. Lancet 1984;1:425.
32. Milov DE, Hill M, Andres JM, Cynamon HA, Hendeles L. Measurement of plasma prednisolone level to evaluate a prednisone treatment failure in an adolescent with Crohn's disease. J Pediatr Gastroenterol Nutr 1989; 8:404-7.