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Open-label, single dose pharmacokinetic study of prednisolone at steady state in young patients with SLE on prednisone therapy

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Abstract

Background—Current prednisone dosing in the treatment of young patients with childhood-onset systemic lupus erythematosus (cSLE) is largely based on achieving balance between therapeutic efficacy and toxicity, with weight-based dosing a common clinical practice. Despite the widespread use of prednisone, few attempts have been made to improve its clinical dosing regimen and response to prednisone therapy remains variable.

Objectives—To characterize the pharmacokinetics (PK) of prednisolone, the metabolite of the prodrug prednisone, in cSLE patients and explore the relationship between PK and cSLE disease activity.

Methods—Blood samples were taken 1 hour before the morning prednisone dose and at 20, 40, 60, 90 minutes, and 2, 3, 4, 6, and 9 hours from 8 patients (age 12–28 years) after an 8-hour fast. Average weight-adjusted daily prednisone dose, stable at least 30 days pre-study, was 0.29 mg/kg/day. PK analysis of prednisolone was performed using non-compartmental analysis with WinNonlin®. cSLE disease activity was measured using the British Isles Lupus Assessment Group (BILAG) index and Systemic Lupus Erythematosus Disease Activity Index (SLEDAI).

Results—Mean total prednisolone area under the curve (AUC₀₋₉), apparent oral clearance of prednisone at steady state, and half-life were 1094 (range: 467–2404) ng*hr/mL, 11 (range: 6.7–13.7) L/hr, and 2.6 (range: 1.3–3.9) hours. Mean total prednisolone AUC₀₋₉ normalized to

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prednisone dose by weight was 4361 (range: 1136 – 9580) ng*hr/mL/mg/kg. Mean total prednisolone C_{max} normalized to prednisone dose by weight was 1097 (range: 301 – 2211) ng/mL/mg/kg at 1.84 (range: 0.48 – 4) hours (T_{max}). Patients on prednisone had inter-individual variability in prednisolone AUC_{0-9} (coefficient of variation, CV: 61%) and dose-adjusted AUC_{0-9} (CV: 58%).

Conclusions—Inter-individual variability in systemic exposure to prednisolone in cSLE patients was observed.

Keywords

Prednisone; prednisolone; pharmacokinetics; systemic lupus erythematosus; pediatric SLE

INTRODUCTION

Prednisone, a synthetic corticosteroid, has been in use for at least 55 years¹ as therapy in a variety of disease states for its anti-inflammatory and immunosuppressive properties. Corticosteroids, such as prednisone, inhibit the effector functions of several immunologic cells, countering both cell-mediated and humoral autoimmunity, while also altering the genetic expression of proinflammatory cytokines. The therapeutic efficacy of prednisone has been reported in the management of acute systemic lupus erythematosus (SLE).²

Prednisone therapy in SLE is complicated by adverse effects that range in frequency and severity.³ This has made prednisone therapy in SLE problematic, as clinicians avoid high doses and long-term treatment to prevent drug-related toxicity. This is of particular concern when treating cSLE as adverse effects include growth retardation, susceptibility to infections, hypertension, hyperglycemia, hyperlipidemia, osteoporosis, and avascular osteonecrosis⁴. Awareness of these side effects has led to dosing prednisone based on achieving a balance between therapeutic efficacy and toxicity. As a consequence to this practice, maintenance doses of prednisone in cSLE therapy vary widely. Furthermore, based on clinical observations, individual patients differ in the extent of therapeutic response to the same dose of prednisone.⁵

Despite the popular use of prednisone in cSLE therapy and its associated serious adverse effects, there remains a fundamental gap between knowledge of its pharmacokinetic (PK) properties and application of this knowledge to clinical practice. Prednisone is metabolized in the liver by 11- β -hydroxysteroid dehydrogenase to its active form, prednisolone, followed by a complex first-pass metabolism and inter-conversion between both forms. The fraction of recycled prednisone has been estimated at 76%.⁶ Based on our online search of PubMed using the search terms “prednisone/prednisolone pharmacokinetics”, “lupus”, “SLE”, and “pediatric SLE”, there are few prednisone and/or prednisolone PK studies in patients with SLE (one study in adults with SLE⁷ and 2 studies in cSLE^{5,8}) and cSLE. Given its complex pharmacokinetics, we hypothesized that differences in prednisone treatment response in cSLE patients may be partly explained by inter-individual differences in prednisolone PK. The study aimed to characterize prednisolone PK in cSLE patients following dosing with prednisone and explore the relationship between prednisolone PK and cSLE disease activity.

PATIENTS AND METHODS

Patients

With approval of the institutional review board at Cincinnati Children’s Hospital, patients diagnosed with cSLE⁹ (i.e., SLE with diagnosis prior to or at age 16 years) were studied prospectively after consent and assent had been obtained. To be included in the study, patients were required to have normal renal and hepatic function and have regular and

unchanged dosing regimen for other medications for at least 30 days prior to study participation. Medical records were reviewed by two pediatric rheumatology physicians for relevant demographic data and information such as body weight, cSLE features including disease activity and medication regimens.

Sampling for Pharmacokinetic Measurements

To obtain an accurate medication history as possible, patients completed a drug diary for three days prior to the PK sampling visit. During the study visit, oral prednisone (tablet form) was administered after a fast of at least 8 hours followed by standardized meals 1 hour after the morning dose (low-fat breakfast) and 4 hours later (lunch of patient's choice according to hospital and prescribed standards). Food intake was prohibited during the first hour after prednisone administration. After breakfast, patients were not to receive additional food until 4 hours after prednisone administration.

Serial blood samples were collected over a nine-hour time period, starting between 7 and 8:00 a.m. Blood samples for prednisolone PK testing were taken 1 hour before the morning prednisone dose (trough) and at 20, 40, 60, 90 minutes, and at 2, 3, 4, 6, and 9 hours afterwards. PK blood samples were obtained from an indwelling peripheral line or by direct venipuncture (using a gauge 23 catheter or needle, respectively). Institutional standard operating procedures were followed for drawing blood from an indwelling catheter. The gauge of the IV catheter used, site, number of intravenous access attempts made, and time of access were recorded. 2–3 mL of waste was drawn and discarded prior to blood sample collection for each sampling time point. The indwelling IV line was flushed with heparin in between blood draws according to institutional standard operating procedures. The total amount of blood drawn for research purposes during the study visit could not exceed 50 mL, as based on a minimal body weight of 30 kg, which does not exceed 5% of the total blood volume. During each sampling time point, 3 mL of blood was collected in tubes containing potassium EDTA (Vacutainer® tubes). Tubes were inverted 2 to 3 times immediately after blood collection to afford mixing and were immediately placed on ice until centrifugation. Blood samples were placed within 1 hour after collection in a centrifuge at 2000g (approximately 4000 rpm) for 10 minutes at 4°C. Separated plasma was then immediately aliquoted into a plastic freezer tube/cryotube which was capped with a polypropylene stopper. A new, clean, disposable pipette was used for each sample. The sample was stored within 1 hour of centrifuging at –70°C. Each sample was to be properly labeled with the analyte to be assayed, investigator name, subject number, date of sample collection, scheduled and actual time of sample collection. Specimen collection/harvesting logs were accomplished for all samples. Samples were analyzed at The University of Western Ontario, London, Ontario, Canada.

Monitoring for adverse events was continuous during the PK sampling visit. A physical exam and measurement of disease activity was conducted by a physician prior to the initiation of the visit. Vital signs (i.e., blood pressure, heart rate after sitting or lying supine for at least 5 minutes, resting respiratory rate, and temperature, with weight and height) were measured before the initiation of PK blood sampling. During the visit and afterwards, heart rate, respiratory rate, and blood pressure were measured and recorded every 2 hours throughout PK sampling. If a steady increase in heart rate of 20% above baseline was observed, this was reported to the investigators and physicians and PK blood sampling was aborted.

Quantitation of Prednisolone in Plasma

Plasma prednisolone concentrations were determined using high performance liquid chromatography- tandem mass spectrometry. Plasma samples (50 µL) were spiked with 10

μL dexamethasone ($1 \mu\text{g/mL}$ in acetonitrile). After addition of $150 \mu\text{L}$ of ice-cold acetonitrile and vortexing, the precipitated protein was pelleted by centrifugation at $14000g$ at 4°C for 10 min. To $100 \mu\text{L}$ of resulting supernatant, $100 \mu\text{L}$ of Mobile Phase A (5 mM ammonium acetate in water, $\text{pH } 4$ with acetic acid) was added and $50 \mu\text{L}$ of this mixture was injected into the liquid chromatograph (Thermo Aria TLX1, Agilent 1200, San Jose, CA). Standard curve samples were prepared from control plasma ($50 \mu\text{L}$) spiked with prednisolone ($0 - 2000 \text{ ng/mL}$ final concentration) and dexamethasone as above. Prednisolone and dexamethasone were sourced from Sigma (St. Louis, MO).

Analytes were separated using reverse phase chromatography using a Thermo Hypersil Gold C_{18} column ($50 \times 5 \text{ mm}$; $5 \mu\text{m}$) with a Javelin Hypersil Gold (3 mm) pre-column. Mobile phase was delivered at a flow rate of 0.5 mL/min with gradient flow with Mobile Phase A and acetonitrile. For the first 30 seconds, the mobile phase consisted of 20% acetonitrile then increased linearly to 90% acetonitrile over 4 min. After 1 minute at 90% acetonitrile, there was a linear decrease to 20% acetonitrile which was held for an additional 30 seconds. The retention times for prednisolone and dexamethasone were 2.8 and 3.2 minutes, respectively.

Analytes were detected by tandem mass spectrometry on a Thermo TSQ Vantage triple quadrupole instrument equipped with heated electrospray ionization probe (HESI-II) set with probe voltage (3000 V), vaporizer temperature (350°C), ion transfer tube temperature (350°C), sheath gas (8 arbitrary units) and auxiliary gas (4 arbitrary units). The following multiple reaction monitoring transitions were used with detection in negative mode and collision gas (1.5 mTorr): prednisolone ($419.0 \rightarrow 329.1 \text{ m/z}$), dexamethasone ($451.0 \rightarrow 361.3 \text{ m/z}$) with collision energy at 20 V , and 19 V , respectively. Precursor ions represent $[\text{M} + \text{acetate}]^-$.

Standard curves were linear ($R^2 > 0.99$) over the concentration range of $25 - 2000 \text{ ng/mL}$ for prednisolone. On the basis of signal-to-noise response greater than 5, the estimated limit of detection is 5 ng/mL prednisolone.

Intraday assay precision (% CV) and accuracy (% bias) were 9.5%, 3.5%, 4.7% and 10.0%, 11.2%, 3.9% for prednisolone quality control samples at 50, 200 and 1000 ng/mL , respectively. Interday assay precision and accuracy were 13.4%, 14.9%, 9.2% and 16.5%, 10.3% and 13.5% for prednisolone at 50, 200 and 1000 ng/mL , respectively.

Data and Statistical Analysis

For general clinical and demographic data, numerical variables were summarized as mean $\pm$ standard deviation (SD). Binary and categorical variables were summarized by frequency (in %)¹⁰. Descriptive analysis was done using medians and interquartile ranges for non-normally distributed numeric data. Means and standard deviations were used for normally distributed numeric variables. Accordingly, frequencies (percentages) were determined for nominal and categorical data.

Pharmacokinetic Analysis

PK analysis of prednisolone maintenance (steady-state) plasma concentration data was conducted using standard non-compartmental analysis (WinNonlin[®], version 5.1, Pharsight, Mountain View, CA) for determining the following PK parameters: time to peak prednisolone concentration (T_{max}); peak prednisolone concentration (C_{max}); 9-hour area under the curve (AUC_{0-9}); and apparent oral clearance (CL/F : total body clearance divided by bioavailability, which is the extent or rate at which the active drug reaches its target tissues). Both absolute and dose-normalized and weight-normalized values were determined. Numerical variables were summarized as mean $\pm$ SD.

Measurement of cSLE Disease Activity

Disease activity was measured using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)¹¹ and British Isles Lupus Activity Group (BILAG)¹² index. Both SLEDAI and BILAG are among the most commonly used valid and reliable clinical indices for the assessment of SLE^{11,12}. Both have likewise been shown to be valid in the study of cSLE¹³. The SLEDAI is a one-page weighted scale index composed of 24 items. These items include both clinical and laboratory manifestations which are considered to most frequently contribute to disease activity, and are scored according to the presence or absence of the items within 10 days of the evaluation¹⁴. The score may be between 0 and 105, and provides an estimate of cSLE global disease activity, taking into account disease activity in organ systems that may be involved in cSLE. The SLEDAI includes only objective, rather than subjective, disease manifestations that can be reliably scored retrospectively as was necessary for this study¹⁵. A SLEDAI score of ≥ 6 is generally considered to represent active SLE disease activity which requires treatment¹⁶.

The BILAG scores disease activity based on specific clinical and laboratory findings involving eight specified organ systems over the preceding month. A numeric score ranging from 0 to 72 can be calculated with again higher scores representing higher cSLE disease activity. This instrument employs a Likert scaling of cSLE manifestation per organ system that is founded on an intent-to-treat principle¹⁴. Because of this intent-to-treat approach, i.e., a change of BILAG score is expected to be clinically meaningful, this index has been recommended by the FDA for use in assessing the efficacy of drugs for the treatment of SLE¹⁷. A BILAG score of > 5 has been used to define active disease¹⁸.

The investigators who analyzed the samples for prednisolone PK did not have access to the study participants' clinical data. Members of the Lupus Research Team at Cincinnati Children's Hospital Medical Center reviewed the charts to determine patients' eligibility for participation in the study. The clinicians who performed disease activity measurements, although unblinded to the study aims and drug dosing, perform disease activity measurements as standard of care for all cSLE patients seen in the clinic. Although this was an open trial, this was potentially a limitation of the study that could influence the outcome.

RESULTS

Full nine-hour PK concentration-time profiles of total prednisolone were drawn from eight cSLE patients. Table 1 summarizes the demographic and clinical characteristics of these patients. There were 7 females and 1 male (African-American: 6/8, Caucasian: 2/8; all 8 were non-Hispanic). Age range was 12 to 28 years, with a median age $\pm$ SD of 16.5 ± 5.3 years. Patients' duration of cSLE disease ranged from 0.3 to 13.2 years (median $\pm$ SD: 1.8 ± 4.4 years). The average daily dose of prednisone for all patients was 19.4 ± 11.5 mg/day, with doses ranging from 5 to 40 mg/day. All eight patients were also on mycophenolate mofetil, with doses ranging from 1,000 to 2,000 mg/day (mean $\pm$ SD: 1625 ± 518 mg/day).

As summarized in Table 2, concomitant medications of the study patients included: hydroxychloroquine (n=6), nonsteroidal anti-inflammatory drugs (NSAIDs) (n=4), and antihypertensives and/or diuretics (n=5). Table 2 also provides information about the specific organ involvement of each patient, along with the disease duration. Previously discussed demographic characteristics are also specified according to each patient.

The results of the PK analysis for total prednisolone are summarized in Table 3. Table 4 lists the values of selected pharmacokinetic parameters for each patient. There was evidence of inter-individual variability in prednisolone PK parameters despite adjustments for patient's weight and weight-based prednisone dose. This is shown by the mean AUC₀₋₉ value for all

patients (coefficient of variation [CV]: 61%) in Figure 1 and Table 3. Dose-adjusted peak prednisolone concentrations ranged from 301 – 2211 ng/mL/mg/kg and occurred between 29 minutes and 4 hours after the administration of prednisone. On average, the daily prednisone dose by weight was 0.29 ± 0.16 mg/kg/day (mean $\pm$ standard deviation [SD]), resulting in an average observed weight-based, dose-normalized prednisolone AUC_{0-9} of 4361 ± 2511 ng*hr/mL/mg/kg (range, 1136 – 9580). Inter-individual variability in AUC_{0-9} was still observed after adjustments were made for prednisone dose, as shown by a CV of 58%). Variability (CV: 62%) was also noted in the time (T_{max}) at which the maximum plasma concentration (C_{max}) of prednisolone was reached, which ranged from 29 minutes to 4 hours. The mean $\pm$ SD of the C_{max} of prednisolone among the study patients was 1097 ± 607 ng/mL/mg/kg (CV: 55%). PK parameters for all patients are given in Table 3. A descriptive PK profile averaged for all patients illustrating mean prednisolone concentration (ng/mL) over time (hr) is shown in Figure 1. Full PK profiles for each individual patient are in Figure 2.

Each patient's clinical and laboratory data at the time of the PK study visit were used to measure cSLE disease activity by the SLEDAI and BILAG indices. (Table 5).

DISCUSSION

To the best of our knowledge, this study represents the first descriptive study of prednisolone PK in cSLE. Our results suggest that there is inter-individual variability in the systemic exposure to prednisolone, as measured by the 9-hour concentration-time profile (AUC_{0-9}), indicated by a coefficient of variation (CV) of 61%. This variability was still present when AUC_{0-9} was normalized according to prednisone dose by weight (CV: 58%). In a preliminary analysis, findings from this study also suggest a possible relationship between dose-adjusted AUC_{0-9} and cSLE disease activity as measured by the BILAG index. Results showed that patients with high dose-adjusted AUC_{0-9} values had low disease activity, while patients with low dose-adjusted AUC_{0-9} values had high disease activity. This was, however, not consistently observed when the SLEDAI was used to measure disease activity. A possible reason for this apparent discrepancy may be that the BILAG is a more appropriate measure to use for the assessment of disease response to treatment as it provides a comprehensive evaluation of organ-specific SLE disease activity.^{12,19}

Prednisone and prednisolone PK have been studied previously in patient populations other than those with cSLE. However, our findings may not be directly comparable to these studies given the differences in the study approaches, assay methods, patients of interest, and the PK parameters assessed. Prednisolone PK has been investigated in the renal transplant population. Potter *et al.* sought to utilize area under the curve monitoring in adult renal transplant patients with stable graft function to determine optimal prednisolone dosing that provides clinical efficacy while limiting adverse effects. The study showed a strong correlation between bioavailability, prednisolone exposure (measured using a 6-hour area under the curve), and clinical side effects.²⁰ Another study, also in renal transplant patients, evaluated prednisolone PK parameters with respect to the occurrence of cushingoid side effects. Prednisolone plasma clearance and volume of distribution were found to be significantly lower in patients with a cushingoid habitus, as compared to those who were non-cushingoid, while other PK parameters were comparable between both groups.²¹ This study thus showed a correlation between prednisolone PK and the clinical effects of the drug. Results from another study performed in adult lung transplant recipients suggest a significant inter-individual variability in dose-adjusted AUC_{0-6} and half-life of prednisolone.²² This study recommended therapeutic drug monitoring of prednisolone for this patient population in order to optimize therapy and minimize morbidity.

There have also been studies on prednisone and prednisolone PK performed in various pediatric patient populations, with contradictory conclusions regarding the utility of PK for individualizing prednisone or prednisolone dosing. A previous study performed in children receiving prednisolone for a variety of clinical conditions (i.e., juvenile dermatomyositis, cSLE, nephrotic syndrome, renal transplant, congenital virilizing adrenal hyperplasia, and regional enteritis) evaluated the PK of prednisolone in these patients.⁵ Plasma prednisolone levels were measured at specified time points over a 7-hour time period after ingestion of a single dose of oral prednisolone. Peak prednisolone levels were reached 1–2 hours after ingestion and the mean half-life was 132 minutes. However, marked variability in absorption and metabolism of prednisolone was also noted. Delayed absorption occurred more frequently in patients with juvenile dermatomyositis and prolonged half-life values were noted in cSLE patients. In another study, Hill *et al.* report an inverse correlation between prednisolone clearance and age, suggesting that patient age is an important factor in corticosteroid disposition in pediatric patients with steroid-requiring asthma.²³ The investigators also conclude that measurement of a single 6-hour post-dose concentration allows a precise estimation of prednisolone clearance, which may be utilized as a screening tool to determine which patients require additional PK assessments. Another study comparing the PK of oral prednisolone and intravenous methylprednisolone in patients with juvenile dermatomyositis showed that greater disease activity, manifested by significant vascular compromise (i.e., loss of nailfold capillary end-row loops) correlated with decreased bioavailability of prednisolone, as measured by lower mean AUC₀₋₆ and mean peak concentration of oral prednisolone as compared to intravenous methylprednisolone.²⁴

In pediatric patients with nephrotic syndrome, marked inter-individual variability in prednisone and prednisolone AUC was noted by Rostin *et al.*,⁸ whereas Petersen *et al.* found the opposite among children with acute lymphoblastic leukemia, who exhibited low variation in AUC values.²⁵ However, there are also prednisone PK studies in pediatric patients that question the value of PK monitoring. Studies performed in children with nephrotic syndrome demonstrated that prednisolone PK parameters did not correlate with clinical effectiveness⁸ and that PK is unlikely associated with steroid unresponsiveness in children with nephrotic syndrome.²⁶ Another study performed in children with steroid-dependent asthma showed that the PK of prednisolone (administered intravenously in this study) is unrelated to patients' clinical response to therapy.²⁷

Interestingly, our results did not demonstrate the expected dose-dependent PK of prednisolone. The values of some patients' dose-normalized AUC₀₋₉ and prednisone dose do not suggest that there is relationship between either of this and clearance values. However, this does not necessarily mean that a relationship does not exist. It may be that we are currently unable to conclude whether dose-dependent PK of prednisolone occurs in cSLE patients, since our study was not designed to specifically evaluate this, and given the relatively small sample size of the study. Notably, all of the study patients were receiving mycophenolate mofetil (MMF). There are several studies documenting the influence of corticosteroids on MMF metabolism in the renal transplant population that propose corticosteroids decrease MMF clearance due to its general ability to induce uridine diphosphate glucuronosyltransferase, the enzyme responsible for MMF metabolism.²⁸ However, based on our online literature search utilizing PubMed, there do not seem to be studies on the effect of MMF on corticosteroid PK.

The variability in clinical response to corticosteroid therapy may also be attributed to factors other than those directly related to prednisone or prednisolone PK, such as the potential role of known genetic polymorphisms in the MDR-1 gene which have been associated with altered drug disposition.²⁹⁻³¹ P-gp, which is a product of the MDR-1 gene, has been linked to drug resistance by exclusion of intracellular drugs, such as prednisone. Tsujimura *et al.*

identified the overexpression of P-gp on the lymphocytes of SLE patients with high disease activity and related this to the observed resistance of these patients' disease to steroid therapy.³²

To date, there have been no studies addressing the PK of corticosteroids exclusively in SLE. Our results showed inter-individual differences in systemic exposure to prednisolone. Although no statistically significant link was established, there appeared to be a possible relationship between drug exposure and disease activity, as higher dose-adjusted AUC₀₋₉ values were observed in patients with relatively low disease activity based on the BILAG index. The relatively small number of clinically evaluable patients may be construed as a limitation of our study. Given the descriptive and exploratory nature of this study, no specific statistics to estimate group differences were done. Concurrent cSLE medications, which may influence disease activity and response to prednisone were not accounted for. However, potential factors that could affect the absorption and disposition of prednisone, such as body weight, medication adherence, and food intake were controlled for in this study. While our findings have important implications, these will need to be confirmed in larger prospective studies. The potential impact of concurrent medication on prednisolone PK, as well as the potential implication of polymorphisms involving the MDR-1 gene which may account for the observed differences in some PK parameters, will need further evaluation. The complex metabolism of prednisone, specifically the interconversion between prednisone and prednisolone, should also be accounted for in future studies as this phenomenon may present challenges in PK measurements. It would be ideal to measure both prednisone and prednisolone levels for PK analysis. Future studies should take into consideration the total duration of prednisone therapy and should include a more extensive evaluation of cSLE disease activity over a longer period of time. The study design should allow for prospective evaluation of prednisone and prednisolone PK with respect to both disease activity and change of prednisone dosing over time. Measurement of mean time-adjusted disease activity scores^{33,34} may be undertaken and these should be correlated with the concurrent prednisone doses. It may be also worthwhile to correlate PK parameters, such as exposure, not only with therapeutic responses but also with prednisone-related adverse effects. This method may provide further evidence favoring prednisone PK monitoring to aid in dose optimization. A challenge to future studies is the absence of known therapeutic and toxic windows for prednisone and/or prednisolone.³⁵

CONCLUSIONS

Our data suggests inter-individual differences in systemic exposure to prednisolone, as measured by the AUC₀₋₉ and dose-adjusted AUC₀₋₉, in cSLE patients. The PK profiles obtained from eight cSLE patients did not appear to exhibit the expected dose-dependent PK of prednisone, although the present study was not designed to evaluate this.

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Figure 1. Prednisolone concentrations were averaged for all patients and then plotted against specified sampling times. This included within 1 hour before the morning prednisone dose (trough) and at 20 minutes, 40 minutes, and at 1, 1.5, 2, 3, 4, 6, and 9 hours after the morning prednisone dose. Bars indicate standard error (SE). Considerable inter-individual variability is evident based on the SE bars.

Figure 2. Time (hr) vs Prednisolone concentrations figures for each individual patient included in the study. This includes 1 hour before morning dose (trough) sample and blood samples taken 20, 40, 60, 90 minutes, and 2, 3, 4, 6, and 9 hours after the morning prednisone dose. Bars indicate standard error (SE).

Table 1

Demographic and clinical characteristics of patients with childhood-onset SLE included in this study.

	N	Median [§] , Mean* $\pm$ SD	Range
Gender			
Female	7		
Male	1		
Ethnicity			
Non-Hispanic	8		
African-American	6		
Caucasian	2		
Hispanic	0		
Age (years)		16.5 [§] $\pm$ 5.3	12 – 28
Weight (kilograms)		65.5 [§] $\pm$ 9.3	43.4 – 74.5
Disease duration (years)		1.8 [§] $\pm$ 4.4	0.3 – 13.2
Medications			
Prednisone (mg/day)	8	19.4* $\pm$ 11.5	5 – 40
Mycophenolate mofetil (mg/day)	8	1625* $\pm$ 518	1000 – 2000
Hydroxychloroquine	6		
NSAIDs	4		
Antihypertensives/Diuretics	5		

Table 2

Detailed characteristics of patients with childhood-onset SLE included in this study.

Patient	Gender	Age (yr)	Race [†]	SLE Disease Duration (yr)	Major Organ Involvement	Immunosuppressants	NSAIDs [*]	Concurrent Medications	Others
1	F	12	AA	1.8	renal, cutaneous, musculoskeletal	mycophenolate mofetil, hydroxychloroquine	aspirin		
2	M	15	AA	1.2	renal, musculoskeletal	mycophenolate mofetil		lisinopril, nifedipine, chlorothiazide	lansoprazole
3	F	17	C	1.8	renal, cutaneous	mycophenolate mofetil, hydroxychloroquine	naproxen	lisinopril	
4	F	28	AA	13.2	cutaneous, musculoskeletal	mycophenolate mofetil, hydroxychloroquine	aspirin, nabumetone		atenolol
5	F	22	AA	7.0	cutaneous, hematological	mycophenolate mofetil	celecoxib		
6	F	13	C	0.6	renal, cutaneous, hematological	mycophenolate mofetil, hydroxychloroquine		lisinopril, chlorothiazide	
7	F	16	AA	0.3	renal, cutaneous, musculoskeletal, vascular	mycophenolate mofetil, hydroxychloroquine		enalapril	lansoprazole
8	F	16	AA	3.1	renal, cutaneous, musculoskeletal	mycophenolate mofetil, hydroxychloroquine		lisinopril, atenolol, nifedipine, furosemide	lansoprazole

[†] AA – African-America; C – Caucasian

^{*} NSAIDs – nonsteroidal anti-inflammatory drugs

Table 3

Pharmacokinetic parameters of prednisolone in patients with childhood-onset SLE treated with prednisone.

Pharmacokinetic parameters of prednisolone [‡]	Mean ± SD	Coefficient of variation (%)	Range
Maximum serum concentration of prednisolone (C _{max}) [ng/mL]	287 ± 206	72	124 – 712
Maximum serum concentration of prednisolone (C _{max}) normalized to prednisone dose by weight [ng (prednisolone)/mL (serum)/mg (prednisone)/kg (body weight)]	1097 ± 607	55	301 – 2211
Time of the maximum prednisolone concentration (T _{max}) [hr]	1.84 ± 1.14	62	0.48 – 4
9-hour area under the concentration-time curve of prednisolone AUC ₀₋₉ [ng*hr/mL]	1094 ± 664	61	467 – 2404
Dose-normalized prednisolone AUC _{0-9h} [ng*hr/mL/mg of prednisone]	73 ± 49.5	68	18.7 – 172.6
Prednisolone AUC _{0-9h} normalized to prednisone dose by weight [ng (prednisolone*hr)/mL (serum)/mg (prednisone)/kg (body weight)]	4361 ± 2511	58	1136 – 9580
Half-life of prednisolone (T _{1/2}) [hr]	2.57 ± 0.94	36	1.26 – 3.94
Apparent oral clearance at steady state of prednisolone (CL/F) [L/hr]	11.37 ± 2.35	21	6.7 – 13.7

[‡]Units are presented in brackets.

Table 4

Overview of prednisolone pharmacokinetic parameters for each patient.

Patient	Tmax (hr)	Cmax_D [*] (ng/mL/μg/kg)	T1/2st (hr)	Ctrough=C0 (ng/mL)	Clast=C9 (ng/mL)	AUC0-9 [*] (ng hr/mL)	AUC0-9_D [†] (ng hr/mL/mg/kg)	TI/2 (hr)	CL_F (L/hr)	Prednisone Dose (mg)	Weight (kg)	Wt Adjusted Prednisone Dose (mg/kg)
1	1.30	1234.30	9.02	4.4	5	588.67	5109.61	1.26	9.80	5	43.4	0.12
2	1.30	642.41	9.07	2.5	29.5	622.00	2649.71	3.80	13.71	15	63.9	0.23
3	1.30	2211.12	9.00	3.4	26.5	863.08	9580.13	2.51	6.70	5	55.5	0.09
4	0.48	1498.94	9.10	2.5	59.1	1332.09	4962.03	3.94	13.25	20	74.5	0.27
5	3.00	1246.70	9.00	2.5	65.2	2404.11	4207.18	2.07	12.64	40	70.0	0.57
6	1.30	301.08	9.00	5.5	8.4	467.11	1136.01	1.92	10.08	25	60.8	0.41
7	2.00	1090.20	8.59	2.5	81.2	1654.78	4494.37	2.94	12.09	25	67.9	0.37
8	4.00	550.74	9.00	2.5	29.8	819.88	2746.58	2.13	12.65	20	67.0	0.30
N	8	8	8	8	8	8	8	8	8	8	8	8
Mean	1.84	1096.94	8.97	3.2	38.1	1093.96	4360.70	2.57	11.37	19.37	62.88	0.29
SD	1.14	607.41	0.16	1.1	27.5	664.09	2511.06	0.94	2.35	11.48	9.76	0.16
Min	0.48	301.08	8.59	2.5	5.0	467.11	1136.01	1.26	6.70	5	43.40	0.09
Max	4	2211.12	9.10	5.5	81.2	2404.11	9580.13	3.94	13.71	40	74.50	0.57
CV%	61.97	55.37	1.77	35.58	72.16	60.71	57.58	36.35	20.69	59.23	15.53	53.48

^{*}Cmax_D – dose-normalized prednisolone Cmax

[†]AUC0-9_D – weight-based dose-normalized prednisolone AUC0-9h

Table 5

SLE disease activity scores in comparison with prednisolone pharmacokinetic parameters.

Patient	BILAG [†] Score around time of PK Study	SLEDAI [‡] Score around time of PK Study	Wt Adjusted Prednisone Dose (mg/kg)	AUC _{0-9_D} (ng*hr/mL/mg/kg)	Minimum Prednisolone Concentration over dosing interval (ng/mL)	Maximum Prednisolone Concentration over dosing interval (ng/mL)
1	0	0	0.12	5109.61	4.4	142.2
2	18	16	0.23	2649.71	5.0	150.8
3	0	0	0.09	9580.13	3.4	199.2
4	8	7	0.27	4962.03	5	402.4
5	19	5	0.57	4207.18	5	359
6	23	16	0.41	1136.01	5.5	123.8
7	15	18	0.37	4494.37	5	401.4
8	17	14	0.30	2746.58	5	137

[†] A BILAG score of > 5 has been used to define active disease.¹⁸

The BILAG has been recommended by the FDA in a guidance document for the development of drugs for the treatment of SLE, as a change of score using the BILAG would be considered as clinically meaningful.¹⁷

[‡] A SLEDAI score of 6 is generally considered to correlate with active disease requiring treatment.¹⁶