The Seoul Journal of Medicine
Vol. 32, No. 3: 131-137, September 1991

Bioavailability of Oral Prednisolone

Kyeong-Hun Lee

Department of Pharmacology, Seoul National University College of Medicine
Clinical Pharmacology Unit, Seoul National University Hospital, Seoul 110-460, Korea

=Abstract=**To assess the bioavailability of a oral prednisolone preparation, prednisolone crossover pharmacokinetics were studied in eight healthy male volunteers following intravenous infusion of prednisolone sodium phosphate 81 mg (equivalent to prednisolone 60 mg) solution over a period of 5 minutes, and oral administration (60 mg) of prednisolone tablets. On two study days, 3 weeks apart, 8 healthy subjects received two prednisolone preparations in random order. Plasma samples were collected over a 24 hr study period and analyzed for prednisolone concentration by high-pressure liquid chromatography, and protein binding was assessed using equilibrium dialysis at 37℃.**

Oral data demonstrated a time to peak concentration of 2.3 ± 0.5 hours (SD), mean residence time of 5.6 ± 0.5 hours, and absolute bioavailability (oral/i.v.) of 58.5 ± 12.2%. The estimated terminal half-life was 3.0 ± 0.4 hours, the total body clearance was 10.9 ± 3.5 L/hr.

Infusion data demonstrated a significantly ($P < 0.05$) shorter mean residence time, 3.4 ± 0.4 hours, with no significant difference in terminal half-life, 2.7 ± 0.3 hours, and total body clearance 12.1 ± 2.1 L/hr.

With respect to free prednisolone, oral data demonstrated a significantly ($P < 0.01$) longer mean residence time than that of infusion data, and AUC ratio (AUC_{oral} / $AUC_{i.v.}$) was 0.667 ± 0.091.

Key Words: *Prednisolone, Bioavailability, Pharmacokinetics*

INTRODUCTION

Prednisolone (11β, 17-dihydroxy-21-(phosphonooxy) pregna-1,4-diene-3,20-dione) is a synthetic adrenocortical steroid used primarily for its anti-inflammatory activity in several diseases (Tse and Welling 1975).

It is cleared from the body predominantly by hepatic metabolism; only about 10% of orally dosed compound is excreted unchanged in urine.

Studies in humans yielded peak serum prednisolone levels at 1-2 hr following oral doses and a serum half-life of about 2.2 hr (Gilman *et al.* 1991; Sullivan *et al.* 1974, 1975).

Although the bioavailability of prednisolone was reported in foreign countries (Gilman *et al.* 1991), no information was available on prednisolone bioavailability in Korean.

The present study was undertaken to determine the bioavailability and pharmacokinetics of this oral prednisolone preparation in healthy Korean subjects.

MATERIALS AND METHODS

Subjects: Eight healthy male volunteers participated in this study. Their age range was from 20 to 21 years, and their weight range was 56 to 73 kg (mean 62.3 kg).

Each subject was examined within 14 days of the first study day. Criteria for admission to the study included a normal medical history, physical examination, and laboratory screening tests (complete blood count, urinalysis, and blood chemistries). Subjects were excluded for any history of long-term alcohol consumption, gastrointestinal or cardiovascular disorders, and the presence of infection. Potential subjects were also excluded if they received corticosteroids within 60 days of the study or if they received any other medication within 7 days prior to initiation of the study. Informed written consent was obtained prior to the study.

Study Design: Prednisolone pharmacokinetics were evaluated in each subject with two study formulations. On two separate study days, the subject received, in random order, one of the following: 60 mg of oral prednisolone tablet and 81 mg of prednisolone sodium phosphate (equivalent to prednisolone 60 mg) as a 5 min i.v. infusion. The intravenous dose was administered in the arm contralateral to the sampling site. The study days were separated by a 3 wk interval.

Each study dose was preceded by an 8 hr fast. The oral medications were administered with 200 ml of water, and fasting continued for an additional 4 hrs after the dose. An angiocatheter with a heparin lock was inserted into a peripheral vein in the forearm for blood sampling. Serial blood samples were drawn at 0, 15, 30, 45, 60, 90, 120, 150, 180, 240, 300, 360, 480, 600, 720, and 1440 minutes after oral administration, and at 0, 2, 5, 10, 15, 30, 45, 60, 90, 120, 180, 240, 300, 360, 480, 600, 720, and 1440 minutes after intravenous infusion. Urine was collected for 24 hrs after dose. Blood samples were centrifuged to separate plasma immediately. Plasma and urine samples were stored at -20℃ until analysis.

Materials: Prednisolone tablets (Nisolone 5 mg; Kuk Je Pharmaceutical) were purchased from a pharmacy. Prednisolone sodium phosphate (Hydeltrasol 20 mg/ml; Merck Sharp and Dohme, lot No. 7577X) was supplied by the manufacturer.

Measurement of Plasma and Urine Prednisolone Concentrations: Plasma and urine concentrations of prednisolone were measured by modification of the HPLC method of Rose and Jusko (1979).

For the extraction of prednisolone from plasma or urine, 6 ml of methylene chloride were added to samples of plasma or 20-fold diluted samples of urine (1 ml). The internal standard, dexamethasone (120 ng) was then added and the glass culture tubes were shaken for 20 min. The tubes were centrifuged and the aqueous layer and creamy interface aspirated. The organic phase was then washed with 1 ml of 0.1 N sodium hydroxide and subsequently with 3 ml of water. After aspirating the aqueous phase, 1 g of anhydrous sodium

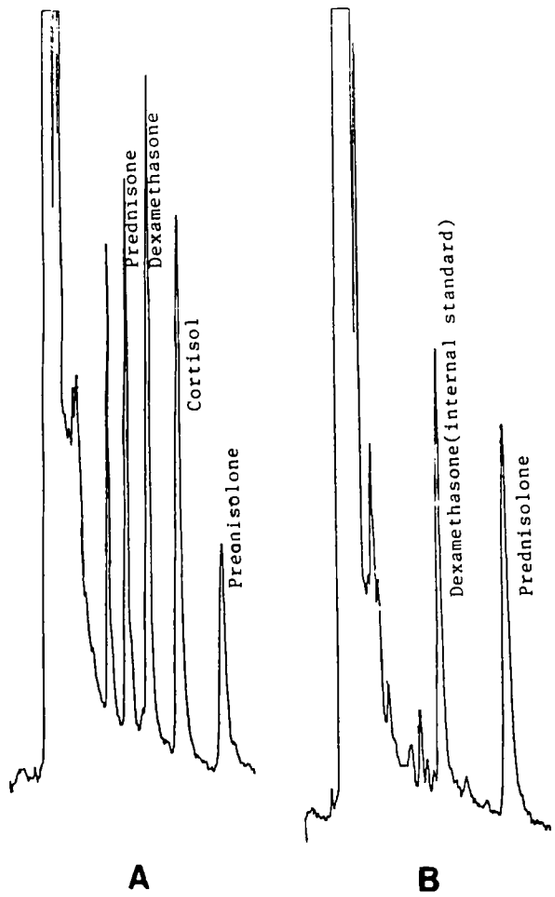

Fig. 1. Chromatogram of (A) extracted standard plasma sample containing prednisolone, prednisone, and cortisol 125 ng/ml, respectively; (B) extracted plasma sample after oral administration of 60 mg prednisolone. The retention times of prednisone, dexamethasone (internal standard), cortisol, prednisolone were 5.3, 6.1, 7.7, 9.1 minutes, respectively.

sulfate was added to dry the organic phase. The latter was evaporated at 45℃ with a SVC 100H Speed Vac Concentrator (Savant Instruments Inc., Farmingdale, NY, U.S.A.). The residue was reconstituted with approximately 50 μl of mobile phase, and the reconstituted 20 μl aliquot was injected directly into the sample loop. Chromatographic analysis was done by the HPLC system using a Gilson model 302 pump, variable UV detector (Gilson, France) set at 246 nm with C-R 6A chromatopac integrator (Shimatzu, Japan) and a six-port rotary value injector (Model 7125, Rheodyne, Cotati, California, U.S.A.) with a 20 μl sample loop. The chromatographic separations were achieved using a normal phase liquid-solid 30 cm X 1.9 mm I.D. stainless-steel Silica Column (5 μm particle size, Gilson, France) with methanol-methylene chloride (32 : 968) as a mobile phase. The solvent flow rate was 1.6 ml/min. Under these conditions, the retention times of prednisolone, prednisone, and internal standard, dexamethasone, were 9.1, 5.3, and 6.1 minutes, respectively (Fig. 1). A plot of the height ratio of steroid: dexamethasone was linear over the 0 to 2000 ng/ml steroid concentration range. The measurement limit for routine analysis was about 5 ng/ml.

Measurement of Unbound Prednisolone Concentrations: Plasma protein binding of prednisolone was evaluated at 37℃ by equilibrium dialysis with [^{3}H]-prednisolone. Details of protein binding technique and data analysis were presented previously (Bergrem 1983).

Pharmacokinetic Analysis: To analyze the plasma concentration time course for each study, noncompartmental analysis was performed. Model-independent pharmacokinetic parameters of prednisolone and prednisone were determined as follows. The area under the plasma steroid concentration (AUC) was estimated by linear / log trapezoidal rule. The first moment of the curve (AUMC) was calculated similarly after multiplying each plasma concentration by its time. These values permitted calculation of the total body clearance (Cl):

$$Cl = \text{Dose} / AUC$$

Renal clearance (Cl_R) of prednisolone was calculated from the amount excreted unchanged during the experimental period ($Ar_{o\to t}$) divided by the area under the plasma prednisolone concentration that time period ($AUC_{o\to t}$):

$$Cl_R = \frac{Ar_{o\to t}}{AUC_{o\to t}}$$

the mean residence time (MRT) of the drug, which represents the average residence of a molecule in the body

$$MRT = AUMC / AUC$$

and the steady-state volume of distribution (Lassen and Perl 1979):

$$V_D^{ss} = Cl \cdot MRT$$

With regard to the Cl and V_D^{ss} parameters determined from oral dosing, these parameters may be influenced by the bioavailability of the dosage form. Thus the parameters are referred to as apparent Cl and apparent V_D^{ss} and are equivalent to Cl / F and V_D^{ss} / F.

The relative bioavailability of the oral prednisolone preparation was determined by comparison of its AUC to the intravenous prednisolone preparation:

$$F = \frac{AUC_{oral}}{AUC_{i.v.}}$$

It was assumed that the intravenous formulation was totally bioavailable. The absolute bioavailability is presented in corrected form for terminal elimination differences:

$$F_{corr} = \frac{AUC_{oral}}{AUC_{i.v.}} \cdot \frac{\lambda_{2\ oral}}{\lambda_{2\ i.v.}}$$

where, λ_2 was the terminal slope or elimination rate constant (Gibaldi and Perrier 1982).

The paired observation t test was utilized to compare the two prednisolone preparations for the various pharmacokinetic parameters: p values $<$ 0.05 were considered significant.

RESULTS

Mean plasma prednisolone and prednisone concentration time data are presented in Table 1 and Fig. 2. After a 60 mg oral dose, prednisolone peak plasma concentration is attained within two and half hours. Prednisone formed after the oral dose peaked before one and a half hours.

Table 1. Plasma prednisolone concentration vs time data for the oral prednisolone tablet and intravenous prednisolone sodium phosphate

Time	Plasma prednisolone concentration(ng/ml)	
(hr)	Oral (mean±SD)	Infusion (mean±SD)
0	0	0
0.25	116.2 ± 45.1	1578.2 ± 221.7
0.50	115.1 ± 97.3	1127.9 ± 214.8
0.75	227.2 ± 129.9	921.2 ± 194.5
1.00	281.6 ± 145.9	805.2 ± 244.8
1.50	380.9 ± 115.4	724.0 ± 116.7
2.00	520.0 ± 69.7	639.1 ± 156.0
3.00	446.2 ± 78.0	545.3 ± 143.5
4.00	391.1 ± 63.4	402.3 ± 85.6
5.00	317.4 ± 50.4	270.4 ± 28.2
6.00	259.5 ± 47.2	259.2 ± 78.3
8.00	164.6 ± 28.7	137.4 ± 18.1
10.00	99.6 ± 22.5	85.9 ± 23.2
12.00	49.1 ± 13.4	42.3 ± 17.0

Pharmacokinetic parameters derived from oral prednisolone preparations are summarized in Table 2. Total AUC of prednisolone was 3224.2 ± 364.9 ng/ml · hr, and mean residence time was 5.6 ± 0.5 hours. The terminal half-life averaged 3.0 ± 0.4 hours, and mean peak concentration and time to peak were 558.6 ± 79.7 ng/ml and 2.3 ± 0.5 hours, respectively. The volume of distribution was 1.08 ± 0.12 L/kg and average total body clearance was 10.94 ± 3.51 L/hr.

Pharmacokinetic parameters derived from intravenous prednisolone are also presented in Table 2. Mean total AUC was 5071.1 ± 786.7 ng/ml · hr, and mean residence time was 3.4 ± 0.4 hours. Terminal half-life at elimination phase was 2.7 ± 0.3 hours. Volume of distribution was 0.66 ± 0.12 L/kg and mean total body clearance was 12.11 ± 2.10 L/hr.

$AUC_{oral/i.v.}$ represents the relative bioavailability for a comparison of the tablet and infusion preparations. Individual subject data are presented in Table 3. The relative bioavailability ($F_{oral/i.v.}$) was 64.3 ± 7.6%, and absolute bioavailability (F_{corr}) was 58.5 ± 12.2%. Comparison of the data for the two preparations shows no significant differences in the elimination rate constant, clearance, and half-life. Evaluation of clearance on successive study

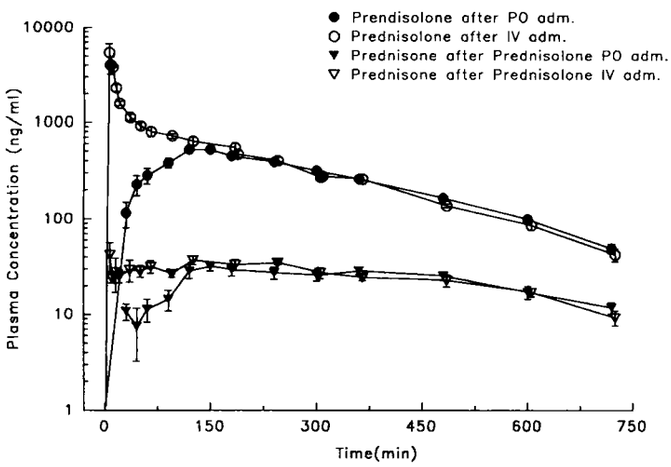

Fig. 2. Mean plasma prednisolone and prednisone concentration time curves for 8 subjects after 60 mg oral prednisolone and 81 mg prednisolone sodium phsophate (equivalent to 60 mg prednisolone) in a 5 min intravenous infusion.

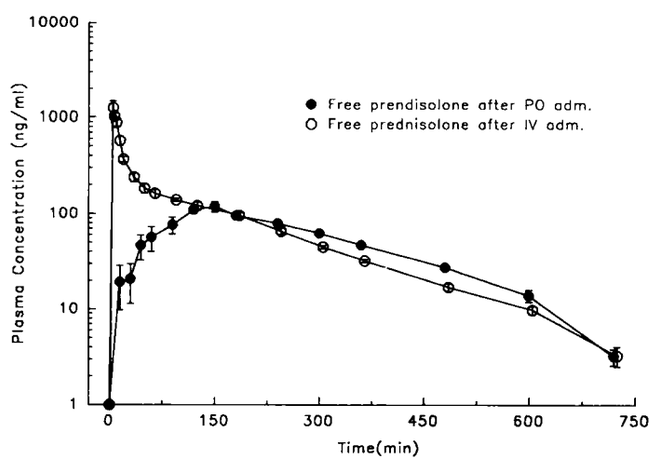

Fig. 3. Mean plasma free prednisolone concentration time curves for 8 subjects after 60 mg oral prednisolone and 81 mg prednisolone sodium phsophate (equivalent to 60 mg prednisolone) in a 5 min intravenous infusion.

Table 2. Pharmacokinetic parameters of prednisolone after a 60 mg dose to humans in the fasting state

Parameter	Oral (mean ± SD)	Infusion (mean ± SD)	Statistical difference (p value)
AUC-total (ng/ml · hr)	3224.2 ± 364.9	5071.1 ± 786.7	< 0.01
λ_2(hr^{-1})	0.233 ± 0.034	0.259 ± 0.028	NS
Cl (L/hr)	10.94 ± 3.51	12.11 ± 2.10	NS
Cl_R (L/hr)	1.38 ± 0.55	2.18 ± 0.98	NS
V_D^{ss} (L/kg)	1.08 ± 0.12	0.66 ± 0.12	< 0.01
MRT (hr)	5.6 ± 0.5	3.4 ± 0.4	< 0.01
Half-life (hr)	3.0 ± 0.4	2.7 ± 0.3	NS
Bioavailability (AUC_{oral} / $AUC_{i.v.}$)	0.643 ± 0.076		
Bioavailability (F_{corr})	0.585 ± 0.122		

λ_2 : elimination rate constant
Cl : apparent total body clearance
Cl_R : renal clearance of prednisolone
MRT: mean residence time
NS : not significant

Table 3. Individual subject bioavailability of oral prednisolone tablet as compared to intravenous infusion

Subject	F_{corr} (oral / i.v.)	AUC_{oral} / $AUC_{i.v.}$
A	0.701	0.744
B	0.777	0.692
C	0.466	0.661
D	0.505	0.555
E	0.662	0.681
F	0.590	0.669
G	0.553	0.635
H	0.423	0.509
Mean	0.585	0.643
SD	0.122	0.076

days supports the assumption that there was no apparent time related trend in clearance.

The ratio of the partial AUC (up to 6 hours) of prednisone and prednisolone after the prednisolone dose was significantly ($P < 0.01$) higher in the oral preparation.

Mean free prednisolone concentration data are presented in Table 4 and Fig.3. After a 60 mg prednisolone oral dose, unbound prednisolone peak concentration is attained within two hours.

Pharmacokinetic parameters of free prednisolone from oral prednisolone are summarized in Table 5. Total AUC of unbound prednisolone was 598.9 ± 96.0 ng/ml · hr, and mean residence time was 4.9 ± 0.4 hours. The terminal half-life averaged 2.4 ± 0.5 hours, and mean peak concentration and time to peak were 126.6 ± 32.8 ng/ml and

Table 4. Plasma free prednisolone concentration vs time data for the oral prednisolone tablet and intravenous prednisolone sodium phosphate

Time	Plasma free prednisolone concentration(ng/ml)	
(hr)	Oral (mean±SD)	Infusion (mean±SD)
0	0	0
0.25	19.1 ± 13.3	573.1 ± 151.1
0.50	20.7 ± 22.9	239.5 ± 60.3
0.75	46.2 ± 30.6	183.8 ± 45.4
1.00	56.5 ± 40.2	163.0 ± 38.1
1.50	76.6 ± 34.8	140.0 ± 12.7
2.00	110.1 ± 21.5	121.6 ± 22.6
3.00	95.3 ± 17.2	96.7 ± 16.5
5.00	62.5 ± 10.4	65.7 ± 12.4
6.00	47.3 ± 8.3	32.3 ± 3.2
8.00	27.5 ± 5.1	17.1 ± 3.9
10.00	13.9 ± 4.9	9.8 ± 2.4
12.00	3.2 ± 1.3	3.3 ± 1.9

Table 5. Pharmacokinetic parameters of free prednisolone after a 60 mg prednisolone dose to humans in the fasting state

Parameter	Oral (mean ± SD)	Infusion (mean ± SD)	Statistical difference (p value)
AUC-total (ng/ml · hr)	598.9 ± 96.0	948.0 ± 121.1	< 0.01
λ_2 (hr^{-1})	0.300 ± 0.083	0.328 ± 0.049	NS
Cl (L/hr)	69.96 ± 13.85	64.28 ± 9.32	NS
V_D^{ss} (L/kg)	5.25 ± 0.77	2.49 ± 0.54	< 0.01
MRT (hr)	4.9 ± 0.4	2.4 ± 0.4	< 0.01
Half-life (hr)	2.4 ± 0.5	2.2 ± 0.4	NS
AUC_{oral} / $AUC_{i.v.}$	0.667 ± 0.091		

λ_2 : elimination rate constant
Cl : apparent total body clearance
MRT : mean residence time
NS : not significant

2.3 ± 0.5 hours, respectively. The volume of distribution was 5.25 ± 0.77 L/kg and average total body clearance was 69.96 ± 13.85 L/hr.

Pharmacokinetic parameters of free prednisolone derived from intravenous prednisolone are also presented in Table 5. Mean total AUC was 948.0 ± 121.1 ng/ml · hr, and mean residence time was 2.4 ± 0.4 hours. Terminal half-life at elimination phase was 2.2 ± 0.4 hours. Volume of distribution was 2.49 ± 0.54 L/kg and mean total body clearance was 64.28 ± 9.32 L/hr.

AUC ratio of free prednisolone for a comparison of the oral and infusion preparations was 66.69 ± 9.05% (Table 5). Comparison of the data for the two preparations shows no significant differences in the elimination rate constant, clearance, and half-life.

DISCUSSION

Pharmacokinetic analysis of prednisolone is complicated by several factors. Prednisolone is converted to prednisone and thus an interconversion reaction between prednisone and prednisolone is continually taking place *in vivo* (Rose *et al.* 1980; Meikle *et al.* 1975). The biologic activity of corticosteroids is proportional to the free concentration of the drug in biologic fluids. Prednisolone differs from most drugs in that prednisolone free concentration varies with total plasma concentration. This unusual phenomenon also occurs with hydrocortisone and is a result of prednisolone binding to two plasma proteins, albumin and transcortin. Albumin is a low-affinity, high-capacity prednisolone-binding protein and transcortin is a high-affinity, low-capacity prednisolone-binding protein. Saturation of transcortin binding with increasing total plasma prednisolone concentration results in increased prednisolone clearance with increased dose (Rose *et al.* 1981). Although the interconversion and protein binding phenomenon complicate pharmacokinetic analysis, the resultant effect on biologic activity is unknown because of the difficulty in relating pharmacologic effect to the time of corticosteroid administration. Unlike adrenergic agents and theophylline, response to corticosteroids is often not apparent for several hours.

Prednisolone sodium phosphate is known to produce its pharmacological action after being converted to prednisolone in the body (Osol 1970). Phosphate hydrolysis is extremely rapid in rats, rabbits, and dogs, with peak plasma free steriod levels occurring almost immediately following intravenous injection of the ester (Tse and Welling 1975).

Since mean residence time includes the time necessary for tablet disintegration, dissolution and absorption, this parameter is significantly higher for the tablet as compared with the intravenous preparation.

AUC for the tablet is 64.3 ± 7.6% as compared with the intravenous solution. Follow-up studies on a large scale will be necessary to determine more accurately the bioavailability of prednisolone tablet in Korean subjects.

REFERENCES

Bergrem H. Pharmacokinetics and protein binding of prednisolone in patients with nephrotic syndrome and patients undergoing hemodialysis. Kidney International 1983, 23: 876-881

DiSanto AR, DeSante KA. Bioavailability of and pharmacokinetics of prednisone in humans. J. Pharm. Sci. 1975, 64: 109-112

Gergitis JW, Flesher KA, Szefler SJ. Bioavailability assessment of a liquid prednisone preparation. J. Allergy Clin. Immunol. 1982, 70: 243-247

Gibaldi M, Perrier D. Pharmacokinetics, in Swarbick J editor: Drugs and the pharmaceutical sciences. Marcel Dekker Inc., New York, 1982

Gilman GA, Rall TW, Nies AS, Taylor P. Goodman & Gilman's the pharmacological basis of therapeutics. Pergamon Press, New York, 1991

Lassen NA, Perl W. Tracer kinetic methods in medical physiology. Raven Press, New York, 1979: pp. 76-80

Meikle AW, Weed JA, Tyler FH. Kinetics and interconversion of prednisolone studied with new radioimmunoassays. J. Clin. Endocrinol. Metab. 1975, 41: 717-721

Osol A. Remington's pharmaceutical sciences. Mack Publishing Co., Easton, Pa, 1970: pp 971-972

Rose JQ, Jusko WJ. Corticosteroid analysis in biological fluids by high-performance liquid chromatography. J. Chromatogr. 1979, 162: 273-280

Rose JQ, Yurchak AM, Jusko WJ. Dose dependent pharmacokinetics of prednisone and prednisolone in man. J. Pharmacokinet. Biopharm. 1981, 9: 389-417

Tse FLS, Welling PG. Prednisolone bioavailability in the dog. Anal. Chem. 1975, 58: 1751-1754

=국 문 초 록=

Prednisolone 정제의 생체이용률

서울대학교 의과대학 약리학교실 및 서울대병원 임상약리학 Unit

이경훈

Prednisolone 정제의 생체이용률을 평가하고자, 8명의 건강한 지원자들에게 prednisolone 60 mg과 동등한 양인 prednisolone sodium phosphate 81 mg 용액을 5분간에 걸쳐 정맥주입하고, 경구 prednisolone 정제 60 mg을 3주 이상의 간격을 두고 무작위 교차투여한 후, 24시간까지의 경시적인 prednisolone 혈장농도 및 24시간 동안 모은 소변의 농도를 HPLC 방법으로 측정하여 약동학적 분석을 시행하였다.

정제의 최대혈장농도 도달시간은 2.3 ± 0.5시간이었으며 mean residence time (MRT) 및 절대 생체이용률(F_{corr})은 각각 5.6 ± 0.5시간 및 58.5 ± 12.2%이었다. 소실기 혈장반감기는 3.0 ± 0.4시간이었으며 총 체내 청소율(Cl)은 10.9 ± 3.5 L/hr이었다.

정맥투여 후 MRT는 3.4 ± 0.4시간으로 정제보다 짧았으며, 소실기 혈장반감기 및 총 체내 청소율은 2.7 ± 0.3시간 및 12.1 ± 2.1 L/hr이었다.

Free prednisolone에 대해서는, 정제가 정맥투여시보다 MRT가 짧았으며 AUC 비(정제/정맥투여)는 0.667 ± 0.091이었다.