Pharmacokinetics of Prednisolone and Its Impact on Cortisol Kinetics in the Blood Serum of Apparently Healthy Human Subjects

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Individual characteristics of prednisolone and cortisol pharmacokinetics in five young healthy subjects administered prednisolone in a single oral dose of 25 mg are described. The results suggests that prednisolone inhibits the glucocorticoid function of the adrenal cortex. It is concluded that the pharmacokinetics of prednisolone can be assessed from the reductions in serum cortisol concentration which it causes.

Key Words: *prednisolone; cortisol; pharmacokinetics*

The widespread utilization of synthetic glucocorticoids in clinical practice reflects the need for achieving a balance in the concentrations of glucocorticoids present in blood serum. Information on serum levels of cortisol (CS) is of value in assessing the hormonal and immune statuses of healthy and ill individuals and in determining to what extent and how long the glucocorticoid function of the adrenal gland is inhibited or stimulated by particular drugs according to their dosage, length of treatment, and the time of the day when they are given [5,6,10,13-15].

The amount of detailed information available so far on the pharmacokinetics of prednisolone (PN) and on how this synthetic glucocorticoid influences CS kinetics in blood serum is obviously insufficient. Thus, it has not been established which of the existing PN preparations is least inhibitory to the pituitary-adrenal axis [12]; data on circadian PN binding by plasma proteins are inadequate [11], and the appropriateness of administering steroids on alternate days remains unproven [4]. It should also be noted that the radioimmunoassays widely used until recently to separate endogenous and exogenous glucocorticoids fall short of the demands now being made on the measurements of their concentrations, for such assays lack the requisite specificity [4,8,9]. In the past two decades, the introduction of high performance (high pressure) liquid chromatography (HPLC) into clinical medicine has helped to solve problems involved in the separation of endogenous from exogenous glucocorticoids and in the study of their kinetics in blood serum [4,7,10].

Pharmacokinetic studies of PN can assist in the development of rational approaches to the selection of its doses and dosage regimens and in the identifications of the effects exerted on this ligand by other drugs, while the study of CS kinetics in the presence of PN is important for evaluating the glucocorticoid function of the adrenal gland. More detailed information on PN and CS kinetics is clearly required if appropriate therapeutic schemes are to be developed.

The foregoing considerations prompted us to undertake a study of PN pharmacokinetics in relation to CS kinetics in healthy subjects.

MATERIALS AND METHODS

The subjects were five apparently healthy males aged 23-24 years who were five- or six-year students of the Pediatrics Department at the Medical Academy in Nizhni Novgorod and had given informed con-

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TABLE 1. Pharmacokinetic Parameters of Prednisolone in Healthy Subjects After Its Oral Intake at 25 mg

Subject	C_o, ng/ml	k_{el}, per hour	k_{abs}, per hour	$t_{1/2}$, h	$t_{1/2,abs}$, h	C_{max}, ng/ml	t_{max}, h	V_{sp}, liter/kg	Cl_t, liter/h	AUC, g×h/ml
1st	442.52	0.1060	6.3376	6.54	0.109	412.77	0.667	0.77	5.99	2043
2nd	683.98	0.2638	1.2037	2.63	0.576	446.70	1.600	0.59	9.64	1995
3rd	462.73	0.1645	1.8834	4.21	0.368	366.42	1.433	0.90	8.89	1755
4th	554.09	0.1884	1.8519	3.68	0.374	427.73	1.367	0.75	8.50	1979
5th	621.61	0.2533	2.2839	2.74	0.303	472.44	1.067	0.57	10.19	1922

sent to participate in the study. None of them smoked or was taking any medicines either before or during the study.

The subjects were each given five 5-mg PN tablets (25 mg) which they swallowed at a time with water (50 ml) on an empty stomach at 09:30; at 11:30 they received a light breakfast and 3 h later the restriction on food intake was lifted. Blood was sampled from an elbow vein before and at 20 min and 1, 2, 3.5, and 6.5 h after PN intake.

Serum steroids were measured with HPLC in a Millikhrom microcolumn chromatograph (Nauchpribor Co., Orel, Russia); for the analysis, 1-ml serum samples with a standard substance (dexamethasone) added to them were used. Glucocorticoids were isolated by extraction from alkalinized serum. The dry sediment was dissolved in the eluting mixture and the resulting solution was placed in the chromatograph. Chromatography was carried out under the following conditions: eluent flow rate, 200 μl/min; wavelength, 254 nm; 64×2 mm stainless steel column filled with Silosorb (5 μ); detection limit, 5 ng/ml with an ultraviolet spectrophotometric detector.

Parameters of PN pharmakokinetics were measured using a one-compartment model of absorption [3]. The computational algorithm allowed determination of approximate parameter values by sequential logarithm taking, followed by their precise determination through minimization of the "difference" functional between the experimental and theoretical points [1].

CS kinetics was described using the empirically derived function: $C(t)=C_o/(1+k_{el}t)$, where $C(t)$ is the CS concentration at a current moment of time (t) after PN intake, C_o is the CS concentration before PN intake ($t=0$), k_{el} is the elimination rate constant for CS, and t is the time.

The k_{el} parameter was determined by the method of least squares from the data for each subject, after which the elimination half-time and the area under the concentration—time curve were calculated from the theoretical elimination curve.

The results were statistically analyzed using a STADIA software package [2]. Calculations showed the validity of the proposed model [1] and of the experimental data; the significance level of the hypothesis establishing concordance between the original data and the mathematical model was found to be no greater than 0.0004 and the coefficient of determination, no less than 0.95 for each subject.

RESULTS

Calculations gave the following mean values for PN parameters: C_o=552.7±45.9 ng/ml; k_{el}=0.195±0.02 per h; absorption rate constant k_{abs}=2.71±0.923 per h; elimination half-time $t_{1/2}$=3.96±0.71 h; absorption half-time $t_{1/2,abs}$=0.346±0.075 h; maximum concentration C_{max}=425.0±17.8 ng/ml; time taken to reach that concentration t_{max}=1.227±0.164 h; specific volume of distribution V_{sp}=0.716±0.061 liter/kg; total clearance Cl_t=8.64±0.72 liter/h; area under the curve AUC=1938±50 ng×h/ml.

The mean values of CS parameters were: C_o= 134.8±23.0 ng/ml; k_{el}=3.25±0.57 per h; $t_{1/2}$=0.4± 0.1 h; AUC=136.3±22.2 ng×h/ml.

Both the variation of PN concentration with time (Fig. 1) and the values of PN parameters (Table 1) differed from one subject to another. This suggests the desirability of including pharmacokinetic studies in the individual treatment of patients with PN so as to improve its efficacy and safety. On the other hand, the fact that the mean values of most parameters differ no more than by 10% is an indication that the chromatographic analysis and mathematical model used are reliable.

TABLE 2. Pharmacokinetic Parameters of Cortisol in Healthy Subjects after Oral Intake of Prednisolone at 25 mg

Subject	C_o, ng/ml	k_{el}, per hour	$t_{1/2}$, h	AUC, ng×h/ml
1st	153	2.92	0.35	156.8
2nd	108	1.35	0.75	182.6
3rd	104	3.22	0.32	99.9
4th	92	4.61	0.23	68.5
5th	217	4.16	0.25	173.7

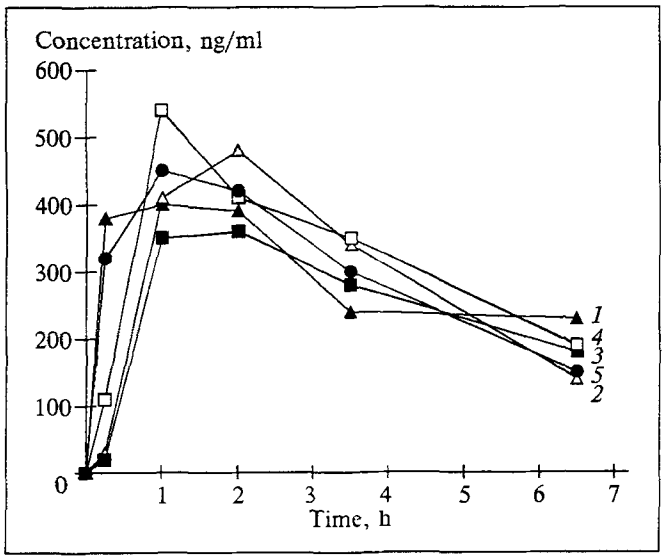

Fig. 1. Variations in serum concentrations of prednisolone in the five subjects (*1*, *2*, *3*, *4*, and *5*) after its oral intake at 25 mg.

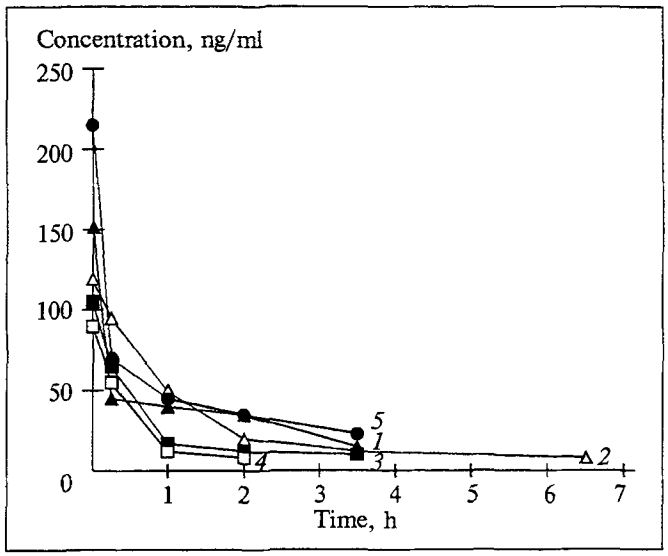

Fig. 2. Variations in serum cortisol concentrations in the five subjects (*1*, *2*, *3*, *4*, and *5*) after oral intake of 25 mg prednisolone.

Serum CS concentrations, which differed from one subject to another before the intake of PN, fell in all five subjects after its intake (Fig. 2); as shown in this figure, CS was undetectable in subject 4 after 3.5 h and was detected only in subject 2 after 6.5 h. Pharmacokinetic parameters are shown for CS in Table 2.

One possible mechanism of serum CS decline under the action of PN was shown to be the substitution of PN for the protein-bound CS, which facilitates the elimination of CS from serum through increased clearance [9,14]. It is also reasonable to attribute the fall of serum CS and its apparent complete disappearance to the PN-induced inhibition of adrenocorticotropic hormone release. This feedback mechanism (suppression of the activity of the hypothalamus-pituitary-adrenal axis by PN) is well known.

This study on healthy subjects has thus provided information on interindividual differences in pharmacokinetic parameters of PN. These differences appear to result from the genetically determined individual metabolic features as well as from the action of many other factors affecting PN pharmacokinetics. Our study has also shown that PN lowers serum CS to levels that may be beyond detection limits of the instruments used to measure them.

As is indicated by the present study, PN pharmacokinetics can be assessed by the reduction in serum CS. Comparison of the experimental and theoretical values demonstrated a good approximation to real values of the calculations performed using a linear mathematical model of absorption, and the model function we obtained, which well describes the variation in CS after a single PN dose, permits calculation of the major kinetic parameters for CS and can facilitate the prediction of changes in its concentration with time in patients.

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