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Original article

Pharmacokinetics of prednisolone in children with the nephrotic syndrome

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Abstract. The aim of this study was to establish whether the criteria for the clinical effectiveness of steroids are correlated with the pharmacokinetics of prednisolone in children treated with prednisone during an attack of idiopathic nephrotic syndrome (INS). Thirteen patients with nephrosis were included. Prednisolone, prednisone and cortisol levels were measured using a specific high-performance liquid chromatography assay after an oral dose of 1 mg/kg body weight of prednisone taken at the onset of the disease. All the pharmacokinetic parameters, including the conversion of prednisone to prednisolone were similar to the data already published in children with INS. No correlation was found between the values of pharmacokinetic parameters and criteria of clinical effectiveness. Hypo-albuminaemia was significantly correlated with the area under the plasma-concentration curve but not with the elimination half-life of prednisolone. Moreover, the prednisolone elimination half-life correlated with the urinary exretion of 17-hydroxycorticosteroids achieved in the first 6 h. The present study suggests that routine measurements of prednisolone kinetics do not help when assessing the treatment of children with INS.

Key words: Prednisolone – Nephrotic syndrome – Pharmacokinetics – Plasma albumin – High-performance liquid chromatography

Introduction

Prednisone and its pharmacologically active metabolite prednisolone are glucocorticoid compounds commonly used in children to induce remission in the idiopathic nephrotic syndrome (INS). The clinical effectiveness of the treatment and the appearance of unexpected side-effects vary greatly from one subject to another. One reason could be variability in pharmacokinetics among subjects. In adults, published data [1, 2] have shown that patients with the nephrotic syndrome had higher total prednisolone clearance rates and lower mean concentrations of total prednisolone in plasma than healthy volunteers.

Few studies have been performed in children [3, 4]. The purpose of this study was to assess the prednisolone pharmacokinetics in a homogeneous group of children at the onset of corticosteroid treatment during the acute stage of INS, and to investigate whether differences in pharmacokinetic parameters could be correlated with the improvement of the disease in response to corticosteroid treatment.

Patients and methods

This study was performed on 13 children attending the Paediatric Nephrology Unit of Toulouse University Hospital, from November 1985 to June 1987. Parents and children were fully informed of the aims of the study and gave their informed consent.

All children (mean age 8.7 years, Table 1) presented with oedema, heavy proteinuria and hypo-albuminaemia (mean value 347 ± 131 μmol/l); serum creatinine levels and liver function tests were within the normal range. These symptoms corresponded to the INS criteria and all children received prolonged corticosteroid treatment. After more than 6 months follow-up 11 patients could be classified as having steroid-sensitive nephrotic syndrome (SSNS), 5 of whom were also classified as having steroid dependent nephrotic syndrome (SSNS d). Renal biopsy was not performed in these II children as glomerular changes are usually minimal in this situation [5]. The remaining 2 patients had steroid-resistant nephrotic syndrome (SRNS); 1 patient had total SRNS and the other had partial SRNS. Renal biopsy was performed in both patients. In 1 patient the biopsy showed focal global glomerular sclerosis with focal IgM deposits and in the other minimal glomerular changes. Nine children had a primary attack of nephrosis and the trial was performed at the onset of the first dose of oral prednisone treatment. In the other 4 children corticosteroid treatment had been stopped for a minimal period of 10 months prior to the trial. No patient showed severe steroid side-effects during this limited follow-up period and long-term tolerance has not been assessed.

Protocol. The patients fasted from midnight prior to the day of the trial and for 4 h after the dose of prednisone (Cortancyl, Roussel, 97 Rue de Vaugirard, 75279 Paris Cedex 06, France). This was given at a dose of 1 mg/kg body weight at 8 a.m. Venous blood samples (5 ml) were col-

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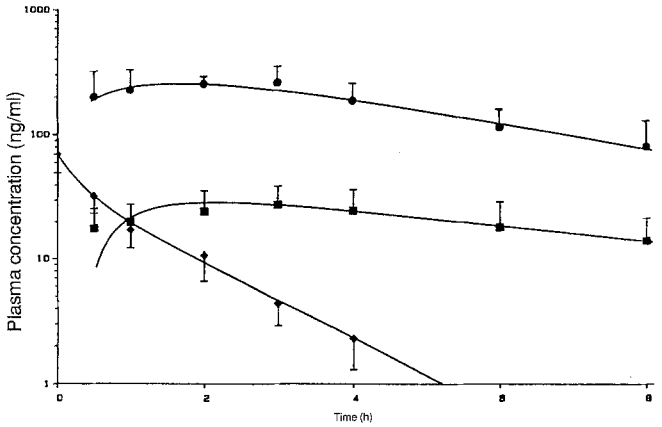

Fig. 1. Mean plasma concentrations of prednisolone (●), prednisone (■) and cortisol (◆) after prednisone administration in 13 patients with idiopathic nephrotic syndrome (INS)

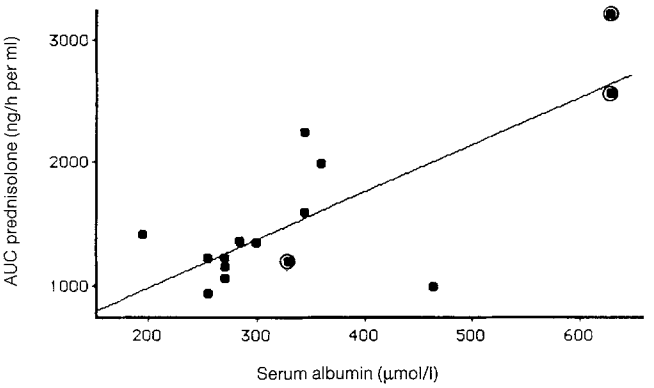

Fig. 2. Relationship between serum albumin and area under plasma concentration curve for prednisolone in (■) 12 patients with INS; (●) 3 additional patients, 2 with lupus nephritis and 1 with a renal transplant, are included in regression analysis, $y = 3.887\,x + 210.301$, $r = 0.599$, $P = 0.02$

lected through an indwelling intravenous catheter prior to and at 0.5, 1, 2, 3, 4, 6 and 8 h after the morning dose of prednisone.

Blood samples were collected in heparinized vacutainers and immediately centrifuged; plasma was separated and stored at –20° C until analysed. Total urine was collected over two time intervals, 0–6 h and 6–24 h.

The urinary excretion of 17-hydroxycorticosteroids (17-OHS) was measured over both periods allowing the fractional excretion (FE) of 17-OHS 6/24 to be calculated. Unchanged prednisolone was not assessed.

Steroid assays. Plasma concentrations of prednisolone, prednisone and endogenous cortisol were determined by the use of a modified high-performance liquid chromatography (HPLC) method previously described [6]. A plasma sample (1 ml) spiked with flumethasone (100 mg) as an internal standard, was extracted into dichloromethane after alkalinization with 0.1 M NaOH (1.0 ml). The analysis was performed on a Waters chromatograph (Waters SA, Toulouse, France) using a mobile phase of dichloromethane, methanol and acetic acid, 94 : 4 : 0.4 (by vol.) at a flow rate of 1.4 ml/min, the wavelength of the UV detector being set at 254 nm.

The elution times were 4.5 and 5.5 min for prednisone and flumethasone (internal standard) and 6.2 and 7.8 min for cortisol and prednisolone, respectively. The sensitivity was 2 ng/ml for all the products.

Analysis of the results. The prednisolone, prednisone and cortisol pharmacokinetic parameters determined include:

1. C_{max} (ng/ml), the observed peak plasma corticosteroid concentrations
2. t_{max} (h), time of C_{max}
3. $t_{1/2}\beta$ (h), the elimination half-life estimated according to 0.693/β. β being the apparent first-order elimination rate constant
4. AUC_0^t (ng/h per millilitre), the area under the plasma concentration curve calculated by the trapezoidal rule.

The results are expressed as mean ± SD. Statistical comparisons were performed using the Student's paired *t*-test. A statistically significant difference was defined as $P < 0.05$.

Results

Blood parameters

The mean plasma concentration curves of prednisolone, prednisone and cortisol are shown in Fig. 1 and their individual pharmacokinetic parameters are summarized in Table 1. Following oral administration of prednisone, the conversion of prednisone into prednisolone was achieved rapidly. As early as 30 min after prednisone administration plasma concentrations of prednisolone were higher than concentrations of prednisone. Both prednisolone C_{max} and AUC (325 ± 69.4 ng/ml, 1330 ± 400 ng/h per millilitre, respectively) were higher than those of prednisone. (30.9 ± 12.0 ng/ml, 149 ± 60 ng/h per millilitre, respectively). The AUC prednisolone/AUC prednisone ratios gave an approximate value of 10. Mean half-lives for prednisolone and prednisone were 2.92 ± 1.06 h and 5.52 ± 2.76 h, respectively.

The initial endogenous plasma cortisol concentration decreased and, as expected, tended to cancel the administered steroid until its disappearance 4 h after administration.

Urinary parameters

The mean urinary excretion of 17-OHS measured in 9 patients was clearly higher than physiological elimination with regard to age (9.16 ± 4.27 mg/24 h; min 5.2, max. 17.9). The mean FE 17-OHS 6/24 was 65.13 ± 23.73% with a great variability ranging from 13.3% to 89%. The urinary excretion of 17-OHS during the following 24 h represented 30.4 ± 6.8% of the prednisone dose administered.

Correlations

There was a significant linear correlation between hypo-albuminaemia and AUC prednisolone ($P = 0.02$, $r = 0.60$ Fig. 2) and between hypo-albuminaemia and C_{max} prednisolone ($P = 0.01$, $r = 0.72$); but there was no correlation between hypo-albuminaemia and $t_{1/2}\beta$ prednisolone.

The 17-OHS/6-h urinary excretion was significantly correlated ($P = 0.05$, $r = -0.58$) with the elimination half-

Table 1. Clinical, biological and pharmacokinetic parameters in patients studied

Patient no.	Age (years)	Sex	Serum creatinine (μmol/l)	Serum albumin (μmol/l)	Prednisone			Prednisolone			Cortisol	
					C_{max} (ng/ml)	AUC (ng/h per ml)	$t_{1/2}\beta$ (h)	C_{max} (ng/ml)	AUC (ng/h per ml)	$t_{1/2}\beta$ (h)	C_{max} (ng/ml)	$t_{1/2}\beta$ (h)
Steroid-Sensitive												
1	3.9	F	30	270	33.8	179.05	4.0	278.8	1056.0	2.03	95.4	0.59
2	13.2	M	50	300	32.0	195.23	9.30	291.8	1337.5	2.27	31.8	0.40
3	6.0	F	50	360	27.3	107.55	9.33	389.32	1980.0	3.45	97.9	0.50
4	13.6	F	60	345	32.8	203.20	–	462.8	2238.2	4.27	77.6	0.39
5	5.8	F	54	465	42.5	131.20	3.47	328.6	983.6	1.72	66.5	1.08
6	6.6	F	50	195	14.5	59.80	2.91	284.0	1409.5	3.78	65.6	0.48
(Mean)	(8.2)		(49)	(322)	(31)	(146)	(5.8)	(339)	(1500)	(2.9)	(72)	(0.49)
Steroid-Dependent												
7	15.8	M	65	270	43.2	161.45	3.58	348.9	1214.2	2.82	41.5	0.48
8	12.0	M	20	345	42.2	257.50	5.55	337.5	1580.4	2.12	62.4	0.80
9	15.1	M	40	270	49.9	213.90	1.27	269.6	1147.5	2.05	72.7	0.82
10	4.5	M	35	285	26.8	138.70	3.24	446.8	1349.2	2.19	93.1	1.26
11	4.3	F	30	255	12.2	78.30	7.75	276.8	923.5	4.84	35.9	0.63
(Mean)	(10.3)		(38)	(285)	(35)	(170)	(4.3)	(336)	(1243)	(2.8)	(61.2)	(0.8)
Steroid-Resistant												
12	10.5	M	30	–	31.0	139.0	7.66	271.1	864.4	2.18	62.6	0.63
13	1.6	F	30	255	13.8	69.30	7.93	247.7	1209.1	4.22	100.4	0.81
(Mean)	(6.0)		(30)		(22)	(105)	(7.8)	(259)	(1035)	(3.2)	(81)	(72)
Mean ± SD	8.6		42	301	30.9 ±12.0	149 ±60	5.52 ±2.76	325 ±69.4	1330 ±404	2.92 ±1.06	69.5 ±23.3	0.68 ±0.26

C_{max}, observed peak plasma concentration; AUC, area under plasma concentration curve; $t_{1/2}\beta$, elimination half-life

life of prednisolone; a high 17-OHS/6-h urinary excretion was associated with a short $t_{1/2}\beta$ prednisolone. Likewise, we observed a significant correlation ($P = 0.05$, $r = 0.58$) between the given dose of prednisone and the 17-OHS urinary excretion occurring in 24 h.

No statistical difference was found for prednisolone kinetics between patients with SSNS, SSNS d and SRNS.

Discussion

Few pharmacokinetic studies of glucocorticoids have been undertaken in children because micromethods were not available. Hence there are few studies concerning children suffering from nephropathy [3, 7, 8], and in particular from INS [4, 9]. However, there are more studies of adults with nephrotic syndrome [1, 2, 10].

The present study reports on the pharmacokinetics of glucocorticoids in children suffering from INS. The patient group was as homogenous as possible, i.e. most patients were studied during a primary attack of nephrosis but a few were studied long after any prior prednisone therapy. Unfortunately we were unable to make up a control group.

Our pharmacokinetic data were in accordance with those previously found in nephrotic children and adults [2, 9, 11]. In particular, a great inter-subject variability was noticed, which is probably due to complex factors determining the corticosteroid behaviour (e.g. the dose-dependent kinetics owing to the non-linearity of the binding to plasma proteins). The conversion of prednisone into prednisolone occurred rapidly, with the peak plasma concentrations of the two compounds both occurring at about 2 h after prednisone administration.

The prednisolone plasma concentrations were 10–12 times higher than the corresponding prednisone levels. These results are similar to those obtained in adults [12–14] and children without INS [3]. It is therefore likely that an attack of nephrosis does not modify prednisone absorption and its conversion into prednisolone. This result is in accordance with the studies of Rocci et al. [4]. However, Frey and Frey [2] showed that the total prednisolone concentrations in adult nephrotic subjects were lower than in healthy volunteers due to a higher unbound fraction of prednisolone. This higher free fraction in the plasma is due to lower concentrations of transcortin and albumin [4]. In our study this phenomenon was reflected by the significant linear correlation between AUC prednisolone and hypo-albuminaemia. This indicated that the elimination of prednisolone was increased when albuminaemia was decreased. Although we could not establish the volume of distribution, Bergrem [1] showed a significant negative-linear correlation between the serum albumin concentration and the volume of distribution at steady state in patients with nephrotic syndrome.

The $t_{1/2}\beta$ prednisolone tends to be correlated with the 17-OHS/6-h urinary excretion. The same results were found in children after renal transplant by Perignon et al. [15]. These data justify the measurement of the 17-OHS/6-h urinary excretion in order to estimate the elimination rate of the drug. Like other studies [9] we did not find a correlation between blood or urinary pharmacokinetic values and criteria of clinical effectiveness. These parame-

ters, and especially the $t_{1/2}\beta$ prednisolone and the 17-OHS/6-h urinary excretion did not appear to differ between patients with SSNS, SSNS d or SRNS. Moreover, we failed to establish a correlation between the pharmacokinetics and the rapidity of the response, i.e. the delay required for the suppression of proteinuria from the onset of corticosteroid treatment (7.9 ± 2.3 days; min. 3, max. 10. in 11 SSNS patients).

Within the 6-month follow-up period none of our patients presented any signs of drug intolerance. Thus we cannot argue for or against the higher frequency of prednisolone-related side effects observed in patients with the nephrotic syndrome [16]. In one study corticosteroid intolerance and growth retardation were correlated with FE of 17-OHS in subjects treated by methyl prednisolone pulse [17]. The dependence of prednisolone side-effects upon hypo-albuminaemia reported by Lewis [18] has not been confirmed by Frey and Frey [2] or Baron et al. [9] and anyway it is not clear whether less albumin binding increases or decreases the accessibility of prednisolone to target cells.

In conclusion it is difficult to correlate corticosteroid responsiveness and the occurrence of side-effects with modifications of prednisolone pharmacokinetics in children with INS. Owing to the difficulties of undertaking exhaustive glucocorticoid pharmacokinetic studies, measurement of plasma prednisolone levels is not helpful in assessing the treatment of children suffering from INS. It is likely that other factors influence the efficacy of glucocorticoids in INS, such as hitherto uninvestigated pharmacodynamic mechanisms or an heterogeneity in the pathogenesis of the disease.

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