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Disposition of Pulse Dose Methylprednisolone in Adult and Paediatric Patients with the Nephrotic Syndrome

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Summary. The disposition of a large pulse-dose of methylprednisolone was examined in paediatric and adult patients with the nephrotic syndrome. Plasma concentrations and urinary excretion rates were measured by high performance liquid chromatography. Most of the dose was metabolized, as indicated by urinary recovery of less than 10 percent of the dose. There was only slight age-dependence of the plasma clearance and volume of distribution of the steroid, although the $T_{1/2}$ and mean transit time were shorter in younger patients. The pharmacokinetic parameters of the large doses (12–20 mg/kg) were similar to low dose (0.5–1 mg/kg) data from asthmatic patients. The limited variability of the pharmacokinetics of methylprednisolone suggests that tissue sensitivity may be a more important indicator of drug dosage needs in nephrotic syndrome.

Key words: methylprednisolone, nephrotic syndrome; high pulse dose, pharmacokinetics adults, children

Corticosteroids are the primary mode of therapy for most types of nephrotic syndrome in adults and children. Their use is complicated by a high incidence of adverse reactions and the frequency of relapse. Methylprednisolone (MP) pulse therapy has recently been proven to have beneficial effects in different kidney diseases [1–2]. Its use is supposed to make it possible subsequently to maintain the patient on a lower dose of steroid than was previously required.

We have been exploring the use of MP pulse therapy for the treatment of the nephrotic syndrome in adults and children. This part of the investigation involves study of the kinetics of the drug in a group of patients of different ages. The role of pharmacokinetic factors in selecting efficacious and non-toxic dosage regimens of steroids is not known. The need for such studies is indicated by the following considerations. Dose-dependent kinetics has been shown for a related compound, prednisolone, which exhibits increased clearance at high doses [3]. Large doses of MP cause haemodynamic changes [4], which may, in turn, alter the disposition of the drug. Thus, data obtained from low dose studies of MP might not be valid at higher doses. Altered disposition of steroids in the nephrotic syndrome might be caused by diminished protein binding resulting from hyperlipidaemia and hypoproteinaemia, by changes resulting from the oedematous state, and by increased or decreased urinary excretion due to by the nephrosis [5]. Age, too, may be a determinant of drug disposition, as shown for numerous compounds [6], and might play a similar role in MP kinetics.

Materials and Methods

Patients and Assays

Fourteen patients were selected for the study. The diagnosis was based on the presence of oedema, hypoalbuminaemia and heavy proteinuria. Criteria for children were serum albumin 2.5 g/100 ml or less and urinary protein excretion not less than 40 mg/h/sq.m. body surface area [7]. Two children (CL and MO) were "frequent relapsers" and were included in the study because of heavy relapsing proteinuria. The adults included in the study all had proteinuria exceeding 3.5 g/24 h/1.73 m^2. In 11 cases biopsy had been performed, and had revealed minimal change disease in 5 cases, diffuse proliferative glomerulonephritis in 4 cases and focal glomerular lesions in 2 cases. Consent was obtained from every patient or the parents. The study was approved by the Commission on Human Investigation of Regione Lombardia. All the work was conducted in the hospital. Patient data and their clinical characteristics are given in Table 1. Serum biochemical values were determined by the hospital laboratory.

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Table 1. Details of the nephrotic patients

Patient	Sex	Age [years]	Weight [kg]	Dose [mg/kg]	BP [mmHg]	Serum Albumin [mg/dl]	Urinary Protein [mg/h/m^2]	Serum Creatinine [mg/dl]	Serum Cholesterol [mg/dl]
MU	M	2 5/12	16.2	15.7	130/95	2.5	132	0.5	483
SP	M	3 3/12	12.8	12.9	105/80	2.2	312	0.56	441
RU	M	3 3/12	15	14.6	100/70	2.5	60.5	0.5	395
CR	M	3 7/12	15.9	14.4	110/80	2.5	40	0.4	276
TI	M	6 5/12	19.5	14.6	130/80	2.1	81	0.8	500
CL	M	9 7/12	27	14.8	110/70	3.0	75	0.42	321
PO	F	9 11/12	25	15	110/80	2.1	344	0.5	212
MO	F	12 7/12	34.9	14.3	120/75	2.8	366	5.1	170
CI	M	13	36	15	115/70	2.3	356	0.5	700
MA	M	13	45.4	19	120/70	2.2	260	0.6	513
OL	M	15 11/12	45.5	15	125/70	2.4	272	0.42	218
LU	M	16	54	18	130/80	2.2	270	0.9	283
SG	F	26	37	20	125/75	2.5	309	0.7	279
PE	F	48	48.6	20	145/85	1.9	295	0.7	652
BR	F	48	54	19	150/85	2.2	259	1.6	265

Table 2. Methylprednisolone: Percentage excreted unchanged in the urine and its apparent mean renal clearance

Patients:	Young [< 13 years]	Older [> 13 years]
Percentage unchanged in urine	6.5 (3.5)[a]	4.0 (2.5)
Mean renal clearance [ml/min/kg]	0.99 (0.72)	0.53 (0.63)

[a] mean ± SD

Methylprednisolone sodium succinate (Solumedrol, Upjohn) in doses of 12–20 mg/kg was infused over 15–25 min.

Following the infusion, (2 ml) blood samples were collected at time 0 (end of infusion) and after 0.25, 0.5, 0.75, 1, 2, 4, 6, 8, 10 and 12 h. Urine was collected at 2 h intervals for 12 h, and also over the 12–24 h interval as well. All samples were kept frozen (−20 °C) until analysed. The samples were assayed for methylprednisolone by high pressure liquid chromatography following solvent extraction from plasma, using the method of Rose and Jusko [8]. This method, when applied to assay of methylprednisolone, has been found to be specific in the presence of methylprednisone and methylprednisolone sodium succinate. The latter is not extracted into organic solvents; it is stable in human blood in vitro under the conditions of handling and storage. The within-day coefficient of variation of the assay is less than 3% and the minimum level of detection of methylprednisolone in plasma is 10 ng/ml (Ebling, Szefler and Jusko, to be published).

The pharmacokinetic parameters of methylprednisolone were compared with data from asthmatic patients examined by Szefler et al. [9]. They comprised adults and children, aged 11–53 years, who received methylprednisolone 0.5 to 1.0 mg/kg during treatment of asthma. All the patients concomitantly received theophylline and, on occasion, oral or inhaled sympathomimetics.

Pharmacokinetic Analysis

The decline in the post-infusion serum concentrations of methylprednisolone (Cp) as a function of time (t) were characterized by a biexponential equation:

$$Cp = C_1 \cdot e^{-\lambda 1 t} + C_2 \cdot e^{-\lambda 2 t} \quad (1)$$

where C and λ are the intercept and slope coefficients. These values, corrected for the infusion period, permitted calculation of the model-independent physiological parameters. The systemic clearance (Cl) was obtained from the area under the curve (AUC):

$$AUC = \frac{C_1}{\lambda_1} + \frac{C_2}{\lambda_2} \quad (2)$$

from:

$$Cl = Dose/AUC \quad (3)$$

The mean residence time ($\bar{t}$) was calculated from:

$$\bar{t} = \left(\frac{C_1}{\lambda_1^2} + \frac{C_2}{\lambda_2^2}\right)/AUC \quad (4)$$

which was used to obtain the steady-state volume of distribution (Vss):

$$Vss = Cl \cdot \bar{t} \quad (5)$$