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# Dietary prescription based on estimated nitrogen balance during peritoneal dialysis

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**Abstract** Protein and energy requirements of children on automated peritoneal dialysis (APD) have still not been sufficiently well defined, although their adequacy is important to maintain a positive nitrogen (N) balance and prevent malnutrition. We carried out 42 studies to estimate N balance in 31 children over 3 years on APD for 19.8±15.7 months. Twenty metabolic studies were performed in patients dialysed for less than 1 year (7.2±3.3 months) and 22 in patients treated for more than 1 year (31.3±13.6 months). The mean estimated N balance of all metabolic studies was 57.5±62.8 mg/kg per day. In only 21 of 42 studies was N balance estimated to be over 50 mg/kg per day, which is considered adequate to meet N requirements for all metabolic needs and growth of uremic children. Estimated N balance correlated significantly with dietary protein intake ($r$=0.671, $P$=0.0001) and total energy intake ($r$=0.489, $P$=0.001). Using the equations of correlation, the values of dietary protein intake [=144% recommended dietary allowance (RDA)] and total energy intake (89% RDA) required to obtain an estimated N balance >50 mg/kg per day were calculated. Significantly lower estimated N balance values were obtained in the studies performed on patients on APD for over 1 year (36.09±54.02 mg/kg per day) than in patients treated for less than 1 year (81.11±64.70 mg/kg per day). In conclusion, based on the values of estimated N balance, we were able to establish adequate dietary protein and energy requirements for children on APD.

**Key words** Dietary protein prescription · Dietary calorie prescription · Estimated nitrogen balance · Automated peritoneal dialysis

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## Introduction

Protein and energy malnutrition are common in patients treated with chronic peritoneal dialysis (CPD) and are associated with increased morbidity and mortality [1–3]; moreover, they may contribute to impaired growth in pediatric patients [4]. Inadequate protein and calorie intake appear to be important causes of malnutrition [3]. Definition of adequate protein and calorie requirements is essential for maintenance of a positive nitrogen (N) balance and prevention of protein wasting. Protein requirements in adults on continuous ambulatory peritoneal dialysis (CAPD) have long been considered higher than those recommended for normal individuals and patients with chronic renal failure, because of protein and amino acid losses with the dialysate [5, 6]. The results of N balance studies [5, 6] suggest that protein needs for adult CAPD patients are 1.2 g/kg per day, although other studies have reported a neutral or positive N balance or an adequate nutritional status with lower protein intakes [7–9].

In children treated with CPD, and particularly in those on automated peritoneal dialysis (APD), which is the prevalent treatment modality in developed countries [4], the optimal nutritional needs, including protein and energy requirements, have not yet been adequately defined. Recommended nutritional intakes vary widely in the literature, irrespective of the age of the patients, and moreover are not easily obtained in clinical practice [4, 10–14]. The very few studies published on N balance in children on CPD [15, 16] have described the pattern of spontaneous protein and calorie intake and N output and balance, but N balance studies have never been performed to establish protein and calorie requirements of patients on PD. The influence of CPD duration on nutritional status and N balance has also been the subject of many studies in recent years, but its role has never been adequately defined [17–19].

The present study was designed to assess dietary protein and calorie intake and estimated N balance in children on APD, to evaluate the influence of treatment du-

ration and age on protein and calorie intake and estimated N balance, and to establish adequate dietary protein and calorie intakes for this population based on estimated N balance studies.

## Patients and methods

We carried out 42 estimated N balance studies on 31 patients on APD, 16 treated with nightly intermittent PD or continuous cycling PD (22 studies) and 15 treated with tidal PD (20 studies). Twenty of the studies were performed on patients dialyzed for less than 1 year (mean treatment duration 7.2±3.3 months) and 22 on patients treated for more than 1 year (mean treatment duration 31.3±13.6 months).

Age, body weight, height, body surface area, primary renal disease, and duration of dialysis of the patients at the time of the study are reported in Table 1, in which patients are divided into four different age groups (3–5 years, >5–10 years, >10–15 years, >15 years). Dialysis adequacy was estimated by weekly creatinine clearance. Mean urinary creatinine clearance was 21.07±27.27 l/week per 1.73 $m^2$ and mean peritoneal creatinine clearance 47.47±21.20 l/week per 1.73 $m^2$. Total creatinine clearance (urinary plus peritoneal) was 66.37±25.91 ml/min per 1.73 $m^2$. No changes in dialysis prescription were made during metabolic studies. Nutritional status and growth at the time of the study were assessed with midarm muscle circumference (MAMC), arm muscle area (AMA), arm fat area (AFA), and height standard deviation score (HSDS). The mean values of these indexes were –0.71±0.85, –0.81±0.76, –0.71±0.83 and –2.2±1.2, respectively. All patients were in a stable clinical conditions, had been free from peritonitis for at least 1 month before the study, and were not receiving recombinant human growth hormone.

Each study lasted for 3 days. Estimated dietary protein (DPI) and energy (DEI) intakes were calculated by a dietitian who examined a 3-day diary kept by the parents. Only children with parents who had already detailed several dietary records before the study and were judged skilled and careful were considered for the study. All children followed the dietary recommendations for patients on CPD [4]. Estimated DPI and DEI were expressed as grams per kilogram per day or kilocalories per kilogram per day and as percentage of the recommended dietary allowance (RDA) for statural age in prepubertal patients and for chronological age in pubertal patients [20]. Energy derived from peritoneal glucose absorption (peritoneal energy intake, PEI) was calculated as the difference between the amount of glucose instilled with the dialysis fluid and the amount drained in the dialysate. Total energy intake (TEI) was calculated as the sum of DEI and PEI. Urine and dialysate were

**Table 1** Patient characteristics

| Group | Patient no. | Age (years) | Height (cm) | Weight (kg) | BSA ($m^2$) | Dialysis modality | Duration of dialysis (months) | Primary renal disease |
|---|---|---|---|---|---|---|---|---|
| 1 | 1 | 3.3 | 87.2 | 11.15 | 0.49 | NIPD | 29 | Drash syndrome |
| | 2 | 3.8 | 85 | 11.8 | 0.51 | NIPD | 34 | HUS |
| 3–5 | 3 | 4.3 | 91.7 | 11.15 | 0.49 | NIPD | 25 | Obstructive uropathy |
| years | 4 | 4.5 | 91.6 | 13.6 | 0.57 | TPD | 3 | Renal hypoplasia |
| | 5 | 4.8 | 98.8 | 15 | 0.62 | TPD | 6 | Jeune syndrome |
| | 6 | 6.5 | 109 | 20.1 | 0.77 | TPD | 8 | Cystinosis |
| 2 | 7 | 7.5 | 109 | 21.4 | 0.79 | CCPD | 17 | PUV |
| | 8 | 7.9 | 110.7 | 20.5 | 0.78 | TPD | 37 | Renal hypoplasia |
| >5–10 | 9 | 8.6 | 113 | 28.7 | 0.91 | NIPD | 28 | Bardet-Biedl syndrome |
| years | 10 | 8.6 | 134 | 26.8 | 1.00 | CCPD | 19 | FGS |
| | 11 | 9.8 | 115.3 | 22.4 | 0.85 | TPD | 46 | PUV |
| | 12 | 9.9 | 122 | 32.7 | 1.00 | TPD | 46 | PUV |
| | 13 | 10.11 | 118 | 19.5 | 0.8 | CCPD | 12 | Renal hypoplasia |
| | 14 | 10.9 | 140 | 33 | 1.12 | CCPD | 30 | FGS |
| 3 | 15 | 11.4 | 133.5 | 37 | 1.16 | TPD | 67 | PUV |
| | 16 | 11.7 | 128 | 29.4 | 1.12 | TPD | 3 | Obstructive uropathy |
| >10–15 | 17 | 12.4 | 145.6 | 38.4 | 1.22 | TPD | 21 | Tubulo-interstitial nephritis |
| years | 18 | 12.5 | 143 | 31.8 | 1.13 | TPD | 7 | Henoch-Schönlein nephritis |
| | 19 | 12.7 | 127 | 29.2 | 0.99 | TPD | 12 | Obstructive uropathy |
| | 20 | 13.4 | 131.4 | 36.5 | 1.12 | CCPD | 6 | Obstructive uropathy |
| | 21 | 13.41 | 151.1 | 39.8 | 1.32 | TPD | 3 | FGS |
| | 22 | 13.6 | 125.1 | 25.2 | 0.94 | TPD | 37 | Renal hypoplasia |
| | 23 | 13.7 | 147 | 35.6 | 1.21 | NIPD | 7.8 | FGS |
| | 24 | 14.3 | 153 | 36 | 1.25 | NIPD | 32.7 | Obstructive uropathy |
| | 25 | 15.4 | 145 | 31.2 | 1.12 | NIPD | 3 | FGS |
| 4 | 26 | 15.8 | 160 | 42.6 | 1.37 | CCPD | 5 | MPGN |
| | 27 | 16.3 | 147.1 | 38.8 | 1.25 | TPD | 14 | FGS |
| >15 | 28 | 16.6 | 144.8 | 35.25 | 1.19 | CCPD | 8 | Obstructive uropathy |
| years | 29 | 17.3 | 163 | 43.8 | 1.44 | NIPD | 24 | MPGN |
| | 30 | 18.5 | 172 | 64 | 1.72 | NIPD | 5 | FGS |
| | 31 | 20 | 143.6 | 38.3 | 1.23 | TPD | 17 | Nephronophthisis |
| Mean±SD | | 11.3±4.4 | 128.6±23.2 | 29.7±11.8 | 1.01±0.3 | – | 19.8±15.7 | – |

BSA, Body surface area; FGS, focal glomerulosclerosis; HUS, hemolytic uremic syndrome; MPGN membranoproliferative glomerulonephritis; PUV, posterior urethral valves; NIPD, nightly intermittent peritoneal dialysis; TPD, tidal peritoneal dialysis; CCPD, continuous cycling peritoneal dialysis

collected by the parents in graduated containers over 24-h periods for 3 consecutive days. The volumes were measured daily, and samples were taken after mixing and frozen for measurement of N, urea, creatinine, glucose, and other compounds. N was measured in dialysate and urine with the Kjeldahl technique [21].

All feces were collected for 3 consecutive days. An enema was given before the collection period and at the end of the period, if required. The samples were refrigerated immediately and stored deep frozen until analysis, which was performed according to Kjeldahl. A blood sample for urea and creatinine determinations was obtained at the beginning and end of the study.

Daily estimated N balance was calculated as the difference between estimated dietary N intake (DNI), i.e., DPI/6.25, and total N losses, i.e., the sum of fecal, urinary, and dialysate nitrogen output. Estimated N balance was adjusted for changes in body urea N, but not for unmeasured N losses from skin, respiration and flatus, and in blood samples. In this study a value of 50 mg/kg per day was considered adequate to guarantee metabolic and growth requirements in children given PD: a N balance value of 40 mg/kg per day is considered to meet N requirements for all metabolic needs and growth in normal children [22–24]; unmeasured N losses can be estimated at about 10 mg/kg per day in uremic children, as adults have unmeasured N losses of 575 mg/day (=8.2 mg/kg per day in an adult of 70 kg body weight) [25]; children generally have a higher metabolic rate than adults. Results are expressed as mean±SD. Student's *t*-test, chi-squared test, and linear regression analysis were used to evaluate the results. The level of significance was set at $P<0.05$.

**Table 2** Estimated protein, nitrogen (N), and energy intakes, N output, and estimated N balance in 42 studies performed on 31 children on automated PD

| | |
|---|---|
| Estimated dietary protein intake (g/kg per day) | 1.55±0.38 |
| Estimated dietary protein intake (% RDA) | 150±34 |
| Estimated dietary energy intake (kcal/kg per day) | 54.70±23 |
| Estimated dietary energy intake (% RDA) | 79.67±22.23 |
| Peritoneal energy intake (kcal/kg per day) | 9.08±4.13 |
| Estimated total energy intake (kcal/kg per day) | 63.7±22 |
| Estimated total energy intake (% RDA) | 95±25 |
| Dialysate N loss (g/kg per day) | 0.131±0.045 |
| Urinary N loss (g/kg per day) | 0.03±0.03 |
| Fecal N loss (g/kg per day) | 0.02±0.008 |
| Estimated dietary N intake (mg/kg per day) | 240±61 |
| Total N loss (mg/kg per day) | 190±50 |
| Estimated N balance (mg/kg per day) | 57.5±62.87 |

RDA, Recommended dietary allowance

## Results

Estimated DPI, DNI, and DEI, urinary, dialysate, fecal, and total N output and estimated N balance determined in the 42 metabolic studies are reported in Table 2. Estimated dietary intakes and N balance in the different age groups are shown in Table 3. DPI and DEI values and N balance were higher in the youngest children (3–5 years) than in the older ones. Estimated N balance was positive (more than zero) in 36 studies, but was over 50 mg/kg per day only in 21 studies (50%). Estimated DPI, DEI, TEI, and N balance were significantly higher in the studies with N balance more than 50 mg/kg per day than in those with N balance less than 50 mg/kg per day (Table 4).

Table 5 shows estimated DPI, DEI, and N balance values according to APD duration. Estimated N balance values were significantly lower in the 22 studies performed on patients given APD for over 1 year than in the

**Table 3** Estimated protein and energy intakes (DPI, DEI) and estimated N balance according to age

| Group | Age (years) | DPI | | DEI | | N balance (mg/kg per day) |
|---|---|---|---|---|---|---|
| | | (g/kg per day) | (% RDA) | (kcal/kg per day) | (% RDA) | |
| 1 | 3–5 | 1.89±0.23 | 158.6±19.7 | 95.77±17.8 | 95.3±18.2 | 112.5±66.2 |
| 2 | 5–10 | 1.49±0.4 | 128.2±31.7 | 54.44±17.4 | 62.2±16.5 | 23.2±34.8 |
| 3 | 10–15 | 1.63±0.33 | 162.4±34.1 | 52.27±13.4 | 87.5±24.2 | 69.1±66.5 |
| 4 | >15 | 1.23±0.28 | 145.7±39.1 | 32.12±4.6 | 75.4±11.9 | 37.2±52.9 |

$P<0.05$; DPI, group 1 vs. group 2; N balance, group 1 vs. group 2; N balance, group 1 vs. group 4
$P<0.001$; DPI (g/kg per day), group 1 vs. group 4; DEI (kcal/kg per day), group 1 vs. group 2
$P<0.0001$; DEI (kcal/kg per day), group 1 vs. group 3; DEI (kcal/kg per day), group 1 vs. group 4

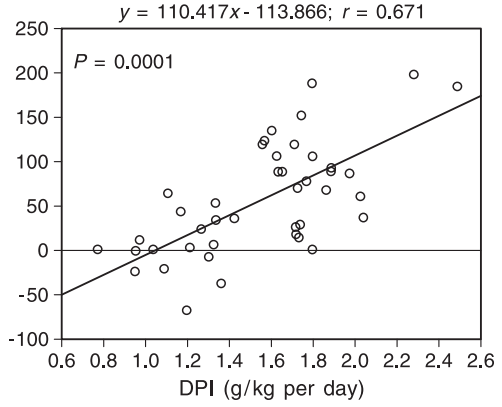
**Table 4** Estimated dietary protein intake, dietary and total energy intakes, and N balance according to N balance cut-off of 50 mg/kg per day

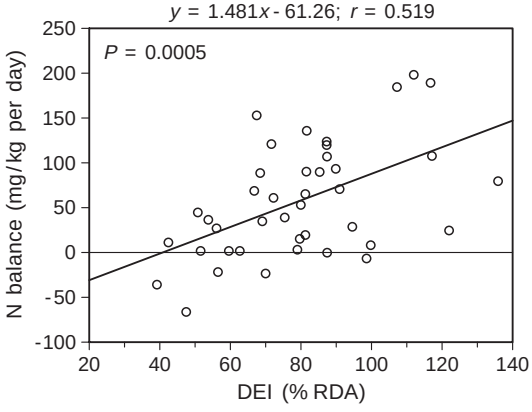
| | N balance | | *P* |
|---|---|---|---|
| | <50 mg/kg per day | ≥50 mg/kg per day | |
| Estimated dietary protein intake | | | |
| (g/kg per day) | 1.33±0.34 | 1.76±0.29 | <0.0001 |
| (% RDA) | 129.4±27.2 | 170.8±29.2 | <0.0001 |
| Estimated dietary energy intake | | | |
| (kcal/kg) | 47.31±17.6 | 62.06±26.15 | <0.05 |
| (% RDA) | 70.39±21.5 | 89.4±18.9 | <0.005 |
| Estimated total energy intake | | | |
| (kcal/kg) | 56.7±17.2 | 70.83±25.24 | <0.05 |
| (% RDA) | 86.09±25.16 | 105.3±21.8 | <0.01 |
| Estimated N balance (mg/kg per day) | 6.21±27.11 | 108.84±42.9 | <0.0001 |

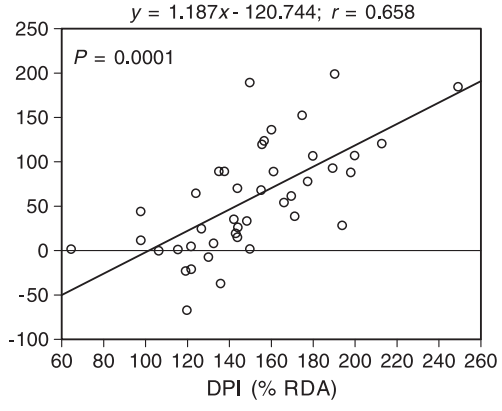
**Table 5** Dietary protein and energy intakes and estimated N balance in 42 metabolic studies of 31 children treated with automated PD (APD) for less than or more than 1 year

| | APD duration | |
|---|---|---|
| | ≤1 year | >1 year |
| Estimated dietary protein intake (g/kg per day) | 1.63±0.43 | 1.48±0.33 |
| Estimated dietary protein intake (% RDA) | 162±36* | 140±31* |
| Estimated dietary energy intake (kcal/kg) | 55.05±21.93 | 54.36±24.9 |
| Estimated dietary energy intake (% RDA) | 85.52±15.7 | 74.1±26.2 |
| Estimated N balance (mg/kg per day) | 81.11±64.7* | 36.09±54.02* |
| Number of negative N balance studies | 3/20 | 3/22 |
| Number of N balance studies <50 mg/kg per day | 3/20 | 12/22** |

* $P<0.02$ ($t$-test); ** $P<0.01$ ($\chi^2$)



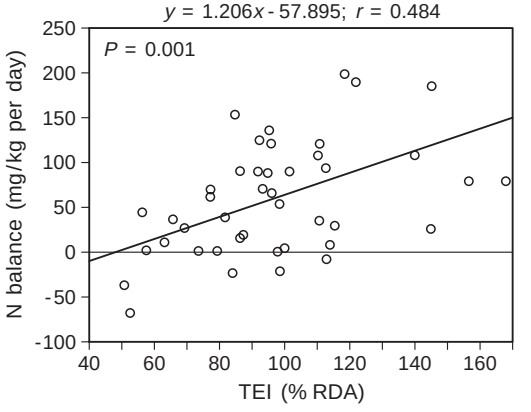




**Fig. 1** Correlation between dietary protein intake (*DPI*) [expressed as g/kg per day and % recommended dietary allowance (*RDA*)] and nitrogen (*N*) balance in 42 studies on 31 children on automated peritoneal dialysis (*APD*)

**Fig. 2** Correlation between dietary energy intake (*DEI*) and total energy intake (*TEI*) (expressed as % RDA) and estimated N balance in 42 studies on 31 children on APD

20 studies on patients treated for less than 1 year. Protein and calorie intakes were also lower in the former group than in the latter. The number of studies showing a negative estimated N balance was about the same in the two groups, but the number of those with estimated N balance of under 50 mg/kg per day was significantly higher in the group with longer treatment.

No significant correlation was observed between N balance and nutritional status (as shown by MAMC, AMA, and AFA), HSDS, or dialysis adequacy (as shown by total weekly creatinine clearance). Estimated N balance correlated significantly with DPI (expressed both as g/kg per day and as % RDA) (Fig. 1). Using the equations of correlation reported in Fig. 1, the DPI values (in g/kg per day or in % RDA) required to obtain a desired N balance can be calculated. Thus, a DPI of 1.45 g/kg per day, corresponding to 144% RDA, is required to obtain an estimated N balance of 50 mg/kg per day in children on APD (Fig. 1). Similarly, based on the correlation between estimated N balance and DEI (Fig. 2), a DEI of 75% RDA (48 kcal/kg per day) is required to obtain an estimated N balance of 50 mg/kg per day and, based on

the correlation between TEI and estimated N balance (Fig. 2), the total energy intake required to obtain an estimated N balance of 50 mg/kg per day is 89% RDA (58 kcal/kg per day).

## Discussion

Adequate protein and energy intake is important in the maintenance of positive N balance and prevention of malnutrition, but the precise nutritional intakes required to obtain a positive N balance and to reduce the risk of malnutrition in children treated with CPD have still not been defined. Although some authors have investigated the effect of energy and protein intake on N balance in normal subjects [22–25], a review of the literature reveals surprisingly few studies on the relationship between N balance and dietary requirements in patients on CPD [5–7], particularly those in the pediatric age group [15, 16]. DPI of more than 1.2 g/kg body weight per day has been recommended for adults treated with CAPD to maintain a positive N balance [5, 6], but an adequate nutritional status has also been achieved with lower protein intakes according to other authors [7–9]. Protein and calorie intakes recommended for children treated with CPD vary widely according to age. Recommended protein intakes for children on CPD are generally higher than those for normal children and those on hemodialysis, as they are based on those of normal children of the same statural age but also take into account protein losses in the dialysate [4, 10–14]. However, spontaneous protein and calorie intakes of children on CPD are frequently lower than recommended. Also the most-recent article published on the subject [16] does not clarify this question, as it is simply a description of the pattern of estimated dietary intakes and N balance in childen on CPD.

We adopted a different approach, using estimated N balance as a tool to determine protein and calorie requirements for children on CPD. Protein and calorie intakes can be considered adequate if estimated N balance is at the level required for all metabolic needs and growth, including unmeasured N losses. We performed 42 studies in which estimated protein and calorie intakes and N balance were assessed. Estimated N balance varied widely in our series, as in other series of normal subjects and adults and children on dialysis, [7, 16, 25]. In most of our children, as in those of a recent study [16], nutritional intakes were sufficient to maintain estimated N balance over zero, but this positive pattern is in contrast to the high prevalence of malnutrition and impaired growth reported in children on CPD. Based on a N balance of 50 mg/kg body weight per day, which is deemed adequate in children on CPD, only 21 of 42 estimated N balance values were considered satisfactory (over 50 mg/kg body weight per day), 15 were relatively satisfactory (lower than 50, but over zero), and 6 were completely unsatisfactory, as they were negative. This proportion is in agreement with the reported high percentage of malnourished CPD patients, as shown by methods other than N balance studies [1–3].

Dietary recommendations for children on APD could also be defined using a series of N balance studies. The correlation between estimated DPI and N balance indicates that a DPI of over 140% RDA is required to obtain an estimated N balance of 50 mg/kg body weight per day or higher. This is therefore the average protein intake that we consider adequate for children of over 3 years on APD. The correlation between estimated dietary and total energy intake and N balance in this study was less significant than that between DPI and N balance. N balance correlates better with DPI than with dietary or total energy intake, as has been reported in other studies [7, 16], but the reason for this is unclear. However, according to our results, it is likely that an average TEI of over 85% RDA is required to obtain an adequate N balance in children on APD. Interestingly, these dietary recommendations based on estimated N balance are in line with published recommendations for dialyzed children of the same age as our series based on other methods [4, 13].

Nutritional intakes varied in our series according to the patient's age. Higher values of estimated N balance were observed in pre-school children, in whom nutritional intakes were more adequate than in older patients. Unfortunately, the number of estimated N balance studies per age group was too small to obtain specific dietary recommendations for each age.

The negative influence of the duration of CPD on estimated N balance should be carefully considered, as the most unsatisfactory N balance values occurred in patients with longer CPD duration, as already reported by Bergstrom et al. [7]. The spontaneous protein and calorie intakes were lower in our patients with longer duration of CPD. The impaired appetite of patients undergoing prolonged PD treatment and other factors interfering with the utilization of dietary protein, probably related to the decline of residual renal function and total creatinine clearance, could result in an unsatisfactory N balance in the long term.

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## LITERATURE ABSTRACT

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### Pharmacokinetics of mycophenolic acid (MPA) and determinants of MPA free fraction in pediatric and adult renal transplant recipients

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Dosage guidelines for mycophenolate mofetil (MMF), an ester prodrug of the immunosuppressant mycophenolic acid (MPA), are still preliminary in children. This study compares the pharmacokinetics of MPA and its major metabolite MPA glucuronide (MPAG) in pediatric renal transplant recipients receiving 600 mg MMF/m2 body surface area twice a day to those of adults on the currently recommended oral dose of 1 g of MMF twice a day. Concentration-time profiles of 18 children (age, 10.7+/–0.72 yr; range, 5.9 to 15.3 yr) and 10 adults were investigated 1 and 3 wk after transplantation. Plasma concentrations of MPA and MPAG were measured by reverse-phase HPLC. Because MPA is extensively bound to serum albumin and only the free fraction is presumed to be pharmacologically active, the MPA free fraction was also analyzed by HPLC after separation through ultrafiltration. The areas under the concentration-time curves (AUC0-12) of total and free MPA throughout the 12 h dosing interval in children were, in general, comparable to the corresponding data in adult patients. The mean AUC0-12 of MPA and free MPA did not change significantly over the first 3 wk after transplantation, but there was substantial intra- and interindividual variation. MPAG-AUC0-12 values in children with primary renal transplant dysfunction were threefold higher than in those with functioning transplants. Renal impairment had no consistent effect on total MPA-AUC0-12 values, but the MPA free fraction in children (median, 1.65%; range, 0.40 to 13.8%) was significantly ($r2$=0.46) modulated by renal transplant function and serum albumin levels. In conclusion, concentration-time profiles of pediatric renal transplant recipients administered 600 mg MMF/m2 body surface area twice a day are comparable to those in adults on 1 g MMF twice a day in the first 3 wk after transplantation. Renal impairment and decreased serum albumin levels led to an increase in the free fraction of MPA and the free MPA-AUC0-12 values. Because the pharmacologic activity of MPA is a function of unbound drug concentration, these findings might be relevant for the pharmacodynamic effects of MPA.