Protein nitrogen appearance in CAPD patients: what is the best formula?

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Abstract Background. The protein equivalent of nitrogen appearance is an indirect index commonly used to assess dietary protein intake in patients on CAPD. Moreover it has been suggested that the ratio between nitrogen appearance and dietary nitrogen intake (fractional urea synthesis) can predict nitrogen balance in uraemic patients. Several formulae to directly calculate the protein equivalent of nitrogen appearance have been published. It has not been established, however, what formulae give the most appropriate estimate of protein intake and nitrogen appearance.

Study design. Nitrogen balance studies were carried out in seven stable patients on CAPD. All of the patients were receiving a diet whose protein content (1.2 g/kg/body wt/day) and calorie content (35 kcal/kg/body wt/day) were rigorously controlled. Six formulae for calculating protein equivalent of nitrogen appearance and nitrogen appearance were tested and the agreement of the estimating formulae was evaluated by means of the Bland and Altman method.

Result. Net nitrogen balance was 1.68±0.9 g/N day, protein intake (g/day) 81±19, protein intake (g/kg) 1.05±0.17. Differences in protein equivalent of nitrogen appearance of up to about 20% were found. The smallest differences between protein equivalent of nitrogen appearance and protein intake were obtained by the formulae of Bergstrom (1±7 g, limits of agreement —12 and +15 g) and Blumenkrantz (—2±5 g, limits of agreement —11 and +7 g). The formula of Bergstrom most closely estimated nitrogen appearance (—0.35±0.89 g). Using such formula, the fractional urea synthesis was 54±12%, giving evidence of positive nitrogen balances.

Conclusion. For the routine monitoring of protein equivalent of nitrogen appearance in CAPD patients, we recommend Bergstrom’s formula with the determination of dialysate protein losses.

Key words: PNA; protein intake; nitrogen balance; CAPD

Introduction

The term protein equivalent of nitrogen appearance (PNA) has replaced the previously used term of protein catabolic rate (PCR), which is considered inappropriate for dietary protein intake (DPI) in patients on CAPD [1,2]. PNA depends on the amount of nitrogen removed with 24 h dialysate and urine, and together with the Kt/V index and blood urea nitrogen with which it is correlated, is considered one of the criteria for evaluating the adequacy of dialysis [3].

Although PNA is routinely determined in CAPD patients, controversy remains as to what formula to use, whether or not to quantify the protein losses from the dialysate, and the way in which PNA should be normalized [4]. Moreover it has been suggested that the ratio between nitrogen appearance and dietary nitrogen intake (fractional urea synthesis) can predict nitrogen balance in uraemic patients [5–7].

The aim of this study was to compare dietary protein intake with the PNA estimated using six different formulae [1,3,8–10] and to assess the accuracy of the formulae in predicting the estimated nitrogen appearance.

Subjects and methods

We studied seven male patients, aged 54±7 years, who had been undergoing peritoneal dialysis therapy (CAPD) for between 12 months and 3 years. Body weight, total body water (TBW), body mass index (BMI), drained dialysate, blood urea nitrogen (BUN), renal, dialysis and total clearances of urea and weekly KprT/V urea are presented in Table 1. None of the patients had any systemic disease or recent infective episodes, and all were capable of complying with the requirements of a metabolic study. The patient’s dietary intake, 2 weeks prior to admission to the ward, calculated from dietary diaries and recall interviews, was estimated to provide 1.17±0.18 g/kg/body wt/day and 30±4 kcal/kg/body wt/day. This intake does not include additional energy derived from glucose absorbed from peritoneal dialysate.
The six formulae used for the calculation of PNA are:

Gotch [3] \[ 0.04 \times \text{KprT/V} \times \text{BUN} + 0.17 \]
Bergstrom (I) [1] \[ 19 + (7.31 \times \text{UNA}) + \text{DPL} \]
Bergstrom (II) \[ 19 + (7.62 \times \text{UNA}) \]
Randerson [5] \[ 10.76 \times (\text{UNA}/1.4 + 1.46) \]
Blumenkrantz [6] \[ 6.25 \times (0.93 \times \text{UNA} + 5.47) \]
Teehan [7] \[ 6.25 \times ((\text{UNA} + 1.81 + 0.031 \times \text{BW}) + \text{DPL}) \]

where DPL = dialysate protein losses.

Thereafter they, except Gotch's formula, have been rearranged to enable the estimation of UNA from protein intake. (e.g. using Bergstrom's (II) formula, UNA = (DPI-19)/7.62.)

Normalized PNA (nPNA) was obtained by dividing it by three standard weights: actual dry body weight (ABW), ideal body weight (IBW) and idealized weight (iBW). ABW was calculated with the peritoneum free of dialysis fluid, IBW according to the table of the Metropolitan Life Insurance [13], iBW by dividing the total body water by 0.58 [14].

### Statistical analysis

One NB value was considered for each patient, representing the mean value of the two studies. The assumption of the gaussian distribution of our data was tested using the Lilliefors and Shapiro-Wilks procedures [15]. No variable showed a statistically significant departure from the null hypothesis. The data are expressed as mean values ± SD, and the range is given. The comparison of groups of data were made using 95% confidence intervals and mean differences.

### Results

The data concerning protein and calorie intake, protein and nitrogen losses, nitrogen appearance, and NB are given in Table 2. Energy derived from glucose absorption was calculated for each exchange as the difference between the amount of glucose in the fresh dialysis fluid and the amount in the drained dialysate. When NB is approximately zero or slightly positive, a patient can be considered stable.

Table 3 shows PNA (g/day) as calculated by the six formulae compared with DPI (g/day). The values derived from the formulae differ by up to 20%, with the formulae of Teehan underestimating DPI by
Table 2. Nitrogen balances

<table>
<thead>
<tr>
<th>Patient</th>
<th>N loss g/day (Urine)</th>
<th>N loss g/day (Dialysate)</th>
<th>UNA (g/day)</th>
<th>Protein N loss g/day (Urine)</th>
<th>Protein N loss g/day (Dialysate)</th>
<th>NUN (g/day)</th>
<th>NB (g/N/day)</th>
<th>DPI (g/kg/day)</th>
<th>DNI (g/kg/day)</th>
<th>DCI PC TCI (kcal/kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.14</td>
<td>3.31</td>
<td>0.04</td>
<td>5.49</td>
<td>0.06</td>
<td>1.15</td>
<td>2.20</td>
<td>1.02</td>
<td>62</td>
<td>0.87</td>
</tr>
<tr>
<td>2</td>
<td>0.88</td>
<td>2.80</td>
<td>0.04</td>
<td>3.64</td>
<td>0.16</td>
<td>1.9</td>
<td>2.17</td>
<td>1.89</td>
<td>61</td>
<td>0.87</td>
</tr>
<tr>
<td>3</td>
<td>0.95</td>
<td>2.62</td>
<td>0.10</td>
<td>3.67</td>
<td>0.03</td>
<td>1.9</td>
<td>2.20</td>
<td>1.96</td>
<td>61</td>
<td>0.86</td>
</tr>
<tr>
<td>4</td>
<td>5.82</td>
<td>6.30</td>
<td>0.12</td>
<td>12.24</td>
<td>0.19</td>
<td>0.8</td>
<td>2.62</td>
<td>0.31</td>
<td>101</td>
<td>1.20</td>
</tr>
<tr>
<td>5</td>
<td>4.37</td>
<td>6.88</td>
<td>0.02</td>
<td>11.27</td>
<td>0.03</td>
<td>1.18</td>
<td>2.67</td>
<td>1.17</td>
<td>102</td>
<td>1.19</td>
</tr>
<tr>
<td>6</td>
<td>4.11</td>
<td>4.55</td>
<td>0.10</td>
<td>8.76</td>
<td>0.05</td>
<td>0.5</td>
<td>2.39</td>
<td>2.86</td>
<td>91</td>
<td>1.18</td>
</tr>
<tr>
<td>7</td>
<td>4.21</td>
<td>4.77</td>
<td>0.10</td>
<td>9.07</td>
<td>0.02</td>
<td>0.66</td>
<td>2.41</td>
<td>2.56</td>
<td>92</td>
<td>1.18</td>
</tr>
<tr>
<td>Mean</td>
<td>3.20</td>
<td>4.46</td>
<td>0.07</td>
<td>7.73</td>
<td>0.08</td>
<td>1.16</td>
<td>2.38</td>
<td>1.68</td>
<td>81</td>
<td>1.05</td>
</tr>
<tr>
<td>SD</td>
<td>1.91</td>
<td>1.67</td>
<td>0.04</td>
<td>3.51</td>
<td>0.07</td>
<td>0.56</td>
<td>0.20</td>
<td>0.90</td>
<td>19</td>
<td>0.17</td>
</tr>
</tbody>
</table>

\(\Delta\) BUN, variation BUN (see text), UNA, urea nitrogen appearance; NUN, non-urinary nitrogen; NB, nitrogen balance; DPI, dietary protein intake; DNI, dietary nitrogen intake; DCI, dietary calorie intake; PCI, peritoneal calorie intake; TCI, total calorie intake.

Table 3. PNA Calculation

<table>
<thead>
<tr>
<th>Author</th>
<th>PNA (g/day)</th>
<th>Mean difference (g)</th>
<th>Confidence limits (+95%)</th>
<th>Limits of agreement (lower-upper)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gotch</td>
<td>71 ± 28</td>
<td>-11 ± 11</td>
<td>-20 + 1</td>
<td>-32 + 11</td>
</tr>
<tr>
<td>Bergstrom (1)</td>
<td>83 ± 23</td>
<td>± 7</td>
<td>-5 + 7</td>
<td>-12 + 15</td>
</tr>
<tr>
<td>Bergstrom (II)</td>
<td>78 ± 27</td>
<td>-3 ± 9</td>
<td>-12 + 5</td>
<td>-22 + 15</td>
</tr>
<tr>
<td>Randerson</td>
<td>75 ± 27</td>
<td>-6 ± 9</td>
<td>-15 + 2</td>
<td>-25 + 12</td>
</tr>
<tr>
<td>Blumenkrantz</td>
<td>79 ± 20</td>
<td>-2 ± 5</td>
<td>-7 + 2</td>
<td>-11 + 7</td>
</tr>
<tr>
<td>Teehan</td>
<td>69 ± 20</td>
<td>-12 ± 5</td>
<td>-17 + 8</td>
<td>-22 - 2</td>
</tr>
</tbody>
</table>

Mean difference vs DPI (g/day). an average of 12 g, and the formulae of Bergstrom (1) and Blumenkrantz coming closest to actual DPI.

Table 4 shows the estimated nitrogen appearance values obtained using the five formulae. The mean difference between UNA estimated and UNA measured ranges from a minimum of -0.35 ± 0.89 by the equation of Bergstrom (1) to a maximum of 1.40 ± 1.21 by the equation of Randerson. Using the formula of Bergstrom (1) the fractional urea synthesis was 54 ± 12%.

Ideal body weight according to table of Metropolitan Life Insurance was 64.4 ± 2.9 kg, idealized body weight was 70.6 ± 5.1 kg.

Normalized PNA values obtained using the formula of Bergstrom (1) by dividing ABW, IBW, and iBW were respectively 1.06 ± 0.21, 1.28 ± 0.31, 1.16 ± 0.25. The values determined from the normalization differ by up to 21%.

Discussion

The calculation of PNA in peritoneal dialysis is based on urea nitrogen appearance and corresponds to the PCR in haemodialysis. It expresses protein intake only under conditions of metabolic balance and for protein intakes ranging from 0.8 to 1.4 g/kg [17]. When catabolic conditions occur it has been shown that the line of best fit between DPI and PNA is usually skewed from the line of identity [18,19]. Most of the studies that have investigated the relationship between DPI and PNA have reported low correlation coefficients [1,2,20,21]; furthermore, using the Bland and Altman method [16], Harty et al. [22] found that the PNA underestimates DPI by up to 59% or overestimates it by up to 32%. The results obtained by a large number of formulae are disappointing and, although some authors [21] have found similar results between formulae, others have found differences of up to 30% [18]. These differences depend on the metabolic status of the patients, the correction factor of urea nitrogen appearance, and whether or not the amounts of both dialysate and urine protein losses are considered. The formula of Bergstrom include the measurement of these protein losses. Bergstrom proposes a simplified formula if protein losses are less than 2–3 g/day. The Randerson and Blumenkrantz formulae have the advantage of requiring only the measurement of urea nitrogen appearance. The formula proposed by Teehan is based on data from haemodialysis patients, with the addition of measured dialysate protein losses. The formula of Gotch is based on a mathematical model, where PNA is a function of the dialytic dose and BUN. In the present study seven patients without infectious or systemic disease underwent 7 days of metabolic nitrogen balance. Their NB were approximately zero or moderately positive, thus suggesting a stable metabolic condition. PNA was calculated according to six
formulae described in the literature in order to evaluate which offers the best agreement with actual DPI. The formula of Bergstrom (1) gave the smallest difference between DPI and PNA (1 ± 7 g), with a confidence interval ranging from -5 to +7 g and with limits of agreement between -12 and +15 g (equal to an underestimate of 15% and an overestimate of 18% of DPI). Bergstrom's simplified formula gave a mean difference of -3 ± 9 g, which can be explained by the fact that the dialysate protein losses (7 ± 3 g/day) of our patients were greater than those estimated by the formula. The formula of Blumenkrantz also offers a good estimate of DPI (mean difference -2 ± 5 g/day), with an underestimate of 14% and an overestimate of 9%, whereas the formula proposed by Teehan gave results that were more than 12 g different from DPI. Finally, the equation applied for the estimation of PNA on average yields values of protein intake lower than those obtained from actual dietary intake. Our results are similar to the findings of Bergstrom, who reported that during metabolic nitrogen balance studies up to 1.6 g/N/day are unaccounted for, reflecting an underestimate of 'true' protein intake by the order of 9 g per day [1].

In the second part of the study we rearranged the formulae to assess their accuracy in predicting the estimated nitrogen appearance. In fact it has recently been reported [5] that you can indirectly estimate nitrogen balance status by the ratio between nitrogen appearance and dietary nitrogen intake. Since in normal subject urea nitrogen appearance represents about the 80% of dietary nitrogen intake [6], a negative nitrogen balance can be assumed in haemodialysis patients if urea nitrogen production exceeds the 85% of nitrogen intake [7]. Therefore from the knowledge of dietary protein intake we can estimate the nitrogen appearance from the rearranged formulae and easily predict nitrogen balance status. Our results show the smallest difference between estimated and measured nitrogen appearance with the formula of Bergstrom (1). With the fractional urea synthesis was 54 ± 12%, giving evidence of neutral or positive nitrogen balances.

To normalize PNA the easiest way is to divide it by the patient's actual dry body weight. This method is often applied, but the protein requirements per kilogram of body weight are probably lower in obese subjects, and furthermore the method gives high nPNA values in malnourished patients with a low body weight [14]. The use of ideal body weight to normalize PNA has been proposed, but the very determination of ideal weight adds further potential problem: the tables described in literature give different results and there is no table at all from studies on the Italian population [23]. An alternative method of normalization is to make a preliminary estimate of total body water using anthropometric formulae and then normalize PNA to 'idealized body weight' [14]. This method is not exempt from criticism either: the anthropometric formulae have not been validated in CAPD patients and it is not correct to consider a value of 0.58 equal for men and for women [24]. Our results have clearly shown difference of up to about 21% in the value of nPNA obtained using different approaches. However they do not show what the method should be applied. Since normalization of PNA is necessary to compare the relative values of groups of patients with different body sizes, we still need a 'consensus' of the best way to normalize PNA.

This study highlights some major pitfalls that may arise when different formulae and different ways of normalizing PNA are used. Differences in PNA of up to 20% were found in our group of stable (nitrogen balanced) patients. Such differences depend on different correction factors present in all formulae. In our opinion, the formulae of Bergstrom and Blumenkrantz most closely reflect protein intake; when the formula of Bergstrom is used, dialysate protein losses should be included.

References


ment between two methods of clinical measurement. *Lancet* 1986; February 8, 307–310


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