Individuality and responsiveness of biochemical indices of dehydration in hospitalized elderly patients

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Abstract

Background: dehydration is common in elderly patients, but difficult to detect, by either an initial assessment of fluid balance or by monitoring fluid balance over time. In clinical chemistry, population-based reference ranges are only of value for monitoring individual patients if within-subject variability in serial test results over time is larger than between-subject variability. This may have important implications in monitoring fluid balance.

Aim: to assess the within- and between-subject variability of serial laboratory test results in euvolaemia and their responsiveness to dehydration in elderly patients.

Methods: over 16 months, 218 patients were admitted to the geriatric department and 53 consented to participate. Fluid balance was assessed twice a week by physical examination, laboratory tests and weighing. Changes in fluid balance were quantified by measuring total body and extracellular water applying deuterium- and bromide-dilution techniques. Within- and between-subject variability in euvolaemia and responsiveness indexes (RI) for dehydration were calculated for haematocrit, serum sodium, urea and creatinine concentrations and for the urea/creatinine ratio.

Results: during hospitalization 14 patients suffered from dehydration and 27 remained euvolaemic. Data from 12 overhydrated patients were excluded. In a mean study period of 30 days, each patient's fluid balance was assessed 6.3 (1.9) times. This resulted in 1084 laboratory tests and 271 assessments of fluid balance. In all quantities within-subject variability was much smaller than between-subject variability in euvolaemia. Responsiveness of creatinine (mean RI = 2.5) was best and similar to the RI of serial weights (mean RI = 2.9).

Conclusion: population-based reference ranges are of limited value in monitoring fluid balance. Repeatedly measuring plasma creatinine, combined with physical examination and weighing is the best way to monitor fluid balance in elderly patients.

Keywords: clinical chemistry, dehydration, reference ranges, responsiveness, variability

Introduction

Many diseases may disturb fluid balance, which is already compromised by age-related loss of total body water (TBW), renal function and the responsiveness of thirst to dehydration. Signs of dehydration (particularly reduced skin turgor and orthostatic hypotension) are often present in normally hydrated older people [1, 2] and so have a limited sensitivity and specificity in diagnosing mild and moderate dehydration during the initial assessment of new patients [3, 4]. Hence, in research as well as in clinical practice, the diagnosis of dehydration is commonly based on raised serum concentrations of sodium, urea and creatinine, increased urea/creatinine ratio and increased osmolality [3-6]. However, there are important limitations in the use of biochemical indices of dehydration. Firstly, population-based reference ranges (PBRRs) of these indices show clinically relevant changes with increasing age [7] but the PBRRs which are often used in daily practice were determined in a non-aged population. Secondly, diagnosing dehydration simply on the basis of hypernatraemia may be incorrect because hypernatraemia may also be caused by an age-related increase in
osmality [8]. Moreover, it may be unwise to rely on urea and creatinine concentrations or urea/creatinine ratios for the assessment of fluid balance since there may be age- or disease-related loss in renal function [9–11].

As laboratory indices of dehydration in euvolaemic nursing-home patients are highly variable between individuals but stable over time within an individual [12], we questioned whether this individuality in euvolaemic laboratory test results would also be found in hospitalized elderly patients. If this were the case, the interpretation of laboratory tests might be improved by applying subject-specific reference ranges (SSRRs) instead of PBRRs, as has been advocated for healthy elderly subjects [13–15]. Up until now, there have been no reports on constructing SSRRs in geriatric patients, although many physicians perform a similar analysis by intuition when judging serial laboratory measurements.

In monitoring fluid balance the value of the individual laboratory tests is uncertain: in particular, the value of measuring serum urea concentrations has been questioned [6]. In general, diagnostic instruments used in monitoring can be compared quantitatively by their responsiveness to clinically relevant changes [16, 17]. To differentiate between the usefulness of repeatedly measuring haematocrit, serum sodium, urea and creatinine concentrations and urea/creatinine ratios, this study aims to quantify the responsiveness of these factors to dehydration in elderly patients.

Methods

This study was part of a larger non-therapeutic research project aimed at the validation of diagnostic measures in monitoring fluid balance in geriatric patients. The research protocol was approved of by the local committee on human experimentation. All 218 patients admitted to the 22-bed department of geriatric medicine of the University Hospital Nijmegen between 1 September 1994 and 31 December 1995 were screened for eligibility. Only subjects who were judged capable of giving informed consent (n = 89; Clinical Dementia Rating scale ≤1 [18]) and were not terminally ill were included in this non-therapeutic study. Patients with an acute confusional state on admission were reassessed for capacity to consent after delirium had resolved. Written informed consent was obtained from 53 (68%) of the 78 invited eligible subjects.

Fluid balance assessment

During hospitalization a geriatrician assessed each patient’s fluid balance twice a week, based on a standardized physical examination, weighing, laboratory tests, relevant data from medical history and the observations of the nurse in charge of the patient. Two geriatricians assessed fluid balance, but individual patients’ assessments were carried out by a single geriatrician. These geriatricians were unaware that this study focused on within- and between-subject variability of biochemical indices. Physical examination consisted of determining the Boston heart failure score [19] and the assessment of the indicators of dehydration that correlate with dehydration regardless of age: tongue dryness, longitudinal tongue furrows, dryness of the mucous membranes of the mouth, upper body muscle weakness, confusion, sunken eyes and axillary moisture [3, 4]. Venous blood samples were drawn twice a week under identical conditions (in the morning, just after waking and before clinical assessment). Serum sodium, urea and creatinine concentrations and the haematocrit were measured on each occasion, but results only were available 1 day after clinical examination. Following this rigorous clinical assessment each patient was judged as dehydrated, overhydrated or euvolaemic.

Dehydration and overhydration were defined as conditions characterized by a clinically relevant shortage or overload of TBW, indicating a need for therapeutic adjustments (rehydration and diuretic drugs, respectively) and resulting in a change in clinical signs, weight and/or laboratory values. In the absence of dehydration or overhydration, a patient was judged as euvolaemic. Fluid balance assessments were reconsidered after monitoring the effects of therapy, because this judgement over time is probably the most sensitive indicator of dehydration [20].

Body composition analysis

Body composition analysis was carried out twice per patient by using deuterium oxide- and potassium bromide-dilution techniques to quantify clinically relevant changes in TBW and extracellular fluid (ECF). It was carried out 1 day after obtaining informed consent and repeated whenever a patient’s fluid balance changed from euvolaemia, dehydration or overhydration. In patients who stayed euvolaemic during hospitalization, body composition analysis was carried out again just before discharge.

For each analysis a cocktail of 10.0 g deuterium oxide and 900 mg potassium bromide was given orally. After 3.5 h dilution time a venous blood sample was drawn. After sublimation of the plasma, the deuterium concentration was determined in the sublimate by infrared spectroscopy analysis [21]. TBW was calculated from the given dose and the tracer concentration determined in plasma, using a correction of 5% for non-aqueous dilution [22]. Bromide in plasma was determined after ultra-filtration by high pressure liquid chromatography [23]. A correction of 5% was used for the Donnan effect (i.e. the unequal distribution of ions at living cell membranes because of the intracellular presence of impermeate anion proteinates) and a correction of 10% for non-extracellular dilution
Analytical measurement errors in bromide- and deuterium-dilution methods, as measured by within-run and between-run variability in two pairs of identical blood samples, were 2.2% and 2.5%. The validity of these dilution methods in measuring body fluid compartments is similar to that of other dilution methods [22].

Statistical methods

All statistical analyses were performed using SPSS for Windows, version 6.1. All the variables studied are often used in PBRRs since 'normality' holds true. In some cases a log-transformation was applied to obtain a more normal distribution. Standard deviations (SD) are presented in parentheses, unless indicated otherwise. Significance of changes in TBW and ECF was tested with paired t-tests. Serial laboratory tests of the dehydrated subjects were split into test results obtained in dehydrated and in euvolaemic state. Results obtained in a period in which no clear clinical assessment could be made were excluded from the analysis. All euvolaemic test results and the initial values of the dehydrated period were used in further analysis.

The within-subject variability in the repeated laboratory test results of the observations during euvolaemia was expressed as the within-subject SD (SDw), pooled over all patients. Before calculating the within-subject variability, the precondition that SDw should not be related to the magnitude of the measurement was checked by calculating Kendall's test [24]. In variables showing proportionality of within-subject SDs, log transformation was carried out (and proportionality was checked again afterwards) [25]. Subsequently, within-subject variability was calculated by using analysis of variance (ANOVA). The within-subject variability was expressed relative to the mean euvolaemic level by presenting within-subject coefficients of variation (CVw in %). Between-subject variability was calculated using the mean-squares of the same ANOVA procedures in which the subjects were the source of variation. Between-subject variability was also presented in coefficients of variation (CVb).

The ratio of within- and between-subject variability (CVw/CVb) is called the index of individuality (I1) [26]. A low I1 means high individuality. If I1 is <0.6, the PBRR will be almost always insensitive to statistically significant changes from an individual's own mean value [27]. As I1 increases above 0.6, the probability that such a deviation will fall outside the PBRR increases until for I1 > 1.4; this probability is very high (P > 0.95) [27]. These criteria are based on the assumption that an individual's serial test results will show a normal distribution. This assumption is generally satisfied for measurements such as plasma urea, creatinine and urea concentrations and for haematocrit where some sort of homeostatic control exists [28]. Sensitivity and specificity of the laboratory tests in detecting dehydration were calculated applying the PBRR of our hospital [sodium, 137-144 mmol/l; urea, 3.0-7.0 mmol/l; creatinine, 60-110 µmol/l (male), 50-90 µmol/l (female); haematocrit, 0.39-0.51I/l (male), 0.34-0.46I/l (female)].

For patients in whom an episode of dehydration occurred during hospitalization SSRRs were constructed. SSRRs can be calculated based on a subject's mean value of the euvolaemic tests performed so far and the group's within-subject variability in euvolaemia. Adapting formulae developed by Fraser et al. to this study [13], SSRRs were calculated, when the upper and lower limits of the SSRR were required (for sodium), as:

\[ m_k \pm 2 \times SD_w \times \sqrt{[(k + 1)k]} \]

and, when only the upper limits were required (for urea, creatinine, urea/creatinine ratio and haematocrit), as:

\[ m_k + 1.64 \times SD_w \times \sqrt{[(k + 1)k]} \]

where k is the number of euvolaemic measurements on which the subject's mean, \( m_k \), was based.

The assumption of normality that underlies this formula is usually satisfied in patients' serial biochemical and haematological analyses [28]. These SSRRs could only be calculated realistically in subjects in whom a period of euvolaemia preceded dehydration.

To be able to use all dehydration episodes in the comparison of the selected analyses, responsiveness indexes (RIs) were calculated. An RI is the clinically relevant change (\( \Delta \)) relative to the SD of changes among stable subjects

\[ RI = \Delta/\sqrt{(2 \times MSE)} \]

where MSE is the mean square error [16, 17].

In this study, the differences between the first observation (in the case of dehydration) and the mean of a subject's observations (in the state of euvolaemia) were seen as the clinically relevant changes. The sign test was used to determine whether RIs were significantly >1, which means that the clinically relevant changes were larger than noise level in euvolaemia.

Results

Of the 53 subjects included in the study, 27 (51%) were euvaloeic during their stay. Of the 14 (26%) patients who had had an episode of dehydration during the study period, 10 were dehydrated on admission and four were euvaloeic on admission. Data for the remaining 12 overhydrated subjects were not analysed.

On admission, TBW in dehydrated subjects was lower than in overhydrated and euvaloeic subjects (Table 1). Based on findings from clinical examination
Table 1. Physical characteristics in means and standard deviations of euvolaemic and dehydrated patients as measured at admission

<table>
<thead>
<tr>
<th></th>
<th>Euvolaemic</th>
<th></th>
<th>Dehydrated</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>No. of subjects</td>
<td>20</td>
<td>7</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Age (years)</td>
<td>78.4 (5.7)</td>
<td>78.7 (5.8)</td>
<td>82.9 (6.1)</td>
<td>80.9 (2.5)</td>
</tr>
<tr>
<td>Hospitalization (days)</td>
<td>35 (30)</td>
<td>34 (19)</td>
<td>55 (39)</td>
<td>39 (17)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>158 (6)</td>
<td>167 (6)</td>
<td>155 (5)</td>
<td>169 (4)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>63.5 (9.8)</td>
<td>64.8 (10.5)</td>
<td>52.2 (7.7)</td>
<td>60.4 (8.9)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.4 (5.2)</td>
<td>23.2 (3.5)</td>
<td>21.7 (2.5)</td>
<td>21.1 (3.0)</td>
</tr>
<tr>
<td>Total body water (l)</td>
<td>32.9 (4.4)</td>
<td>37.0 (4.6)</td>
<td>27.6 (4.1)</td>
<td>26.8 (4.3)</td>
</tr>
<tr>
<td>Extracellular fluid (l)</td>
<td>16.2 (2.7)</td>
<td>19.7 (1.7)</td>
<td>15.0 (4.0)</td>
<td>18.0 (4.3)</td>
</tr>
</tbody>
</table>

Comparison of euvolaemic and dehydrated patients within each sex by t-tests: *P < 0.01; bP < 0.001.

Individuality and responsiveness of laboratory tests

In total, 1084 laboratory test results were analysed. The mean study period was 29.9 (13.1) days, during which on average 6.3 (1.9) euvolaemic measurements were carried out per subject. Clinical investigations interfering with the study logistics prevented 14.4% of planned fluid assessments being performed. For creatinine and urea, SD was significantly related to the individual means; this proportionality disappeared following log transformation.

In the euvolaemic group, the overall means of the individual mean values of the serial test results were all within the PBRR (Table 3). However, these individual euvolaemic means showed a large between-subject variability. Within-subject variability in euvolaemic subjects was much smaller than between-subject variability for all analyses, resulting in an I of <0.6 for sodium, urea, creatinine, haematocrit and the urea/creatinine ratio. Figure 1 illustrates that individual values for urea often exceeded the upper limit of the PBRR, while within-subject variability in plasma urea concentrations was much lower than this PBRR. Data for creatinine, sodium and haematocrit showed a

Table 2. Increases in extracellular fluid (ECF) and total body water (TBW) following rehydration in 14 dehydrated geriatric patients, subdivided according to the aetiology of the dehydration episode

<table>
<thead>
<tr>
<th>Cause of dehydration</th>
<th>n</th>
<th>ECF Value (l)</th>
<th>ECF P</th>
<th>TBW Value (l)</th>
<th>TBW P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>14</td>
<td>1.9 (1.9)</td>
<td>0.002</td>
<td>3.4 (1.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Insufficient water intake</td>
<td>5</td>
<td>0.1 (0.6)</td>
<td>0.767</td>
<td>2.3 (0.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>More than one factor</td>
<td>9</td>
<td>2.9 (1.6)</td>
<td>0.001</td>
<td>4.1 (1.9)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*By paired t-tests.
Serial laboratory tests for monitoring fluid balance

Table 3. Characterization of 180 repeated laboratory test results in 27 euvoalaemic geriatric patients.

<table>
<thead>
<tr>
<th></th>
<th>Sodium (mmol/l)</th>
<th>Urea (mmol/l)</th>
<th>Creatinine (μmol/l)</th>
<th>Haematocrit (l/l)</th>
<th>Urea/creatinine ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>140.1 (2.6)</td>
<td>6.5 (1.9)</td>
<td>82.6 (15.0)</td>
<td>0.38 (0.04)</td>
<td>78.9 (22.3)</td>
</tr>
<tr>
<td>Coefficient of variation (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Between subjects</td>
<td>3.8</td>
<td>67.0</td>
<td>44.5</td>
<td>22.0</td>
<td>59.0</td>
</tr>
<tr>
<td>Within subjects</td>
<td>1.3</td>
<td>20.0</td>
<td>7.0</td>
<td>10.0</td>
<td>28.2</td>
</tr>
<tr>
<td>Index of individuality</td>
<td>0.34</td>
<td>0.30</td>
<td>0.16</td>
<td>0.37</td>
<td>0.47</td>
</tr>
</tbody>
</table>

similar distribution around the PBRR. Specificity of PBRRs for euvoalaemia for all euvoalaemic test results in these euvoalaemic subjects was 82% for sodium, 64% for urea, 85% for creatinine and 100% for the haematocrit. Because of the absence of disturbances of fluid balance, the sensitivity of PBRRs for dehydration could not be calculated in this group.

The laboratory results of euvoalaemic episodes in dehydrated subjects showed a similar pattern: for all quantities the l was much lower than 0.6 (Table 4). Initial dehydrated values for urea were all outside the PBRR (Figure 2), resulting in a sensitivity of 100%. However, for six subjects all euvoalaemic values were outside the PBRR and for another four subjects some of them were outside. Therefore, specificity of the PBRR was very low, resulting in 57% false-positives (Table 4).

PBRR for serum sodium and creatinine concentrations only proved to be moderately sensitive and specific for dehydration. Dehydration could be excluded safely when the haematocrit did not exceed the upper limit of the PBRR, but this cut-off point resulted in a very low sensitivity for the occurrence of dehydration.

SSRR could only be calculated in four patients who had had an episode of dehydration which was preceded by an episode of euvoalaemia. This number is too small to calculate the sensitivity or specificity of the SSRR. In two of these patients SSRRs were equally sensitive and in two patients SSRRs were more sensitive than PBRRs in judging the measured creatinine concentrations. The data from one of these patients (Figure 3) illustrate that SSRRs result in a rather narrow reference range that becomes even narrower as more euvoalaemic measurements are performed.

Only for serum creatinine concentrations were the individual changes during transition from dehydrated to euvoalaemic state significantly larger than the noise level in the euvoalaemic state (i.e. RI > 1; P = 0.012).

Discussion

This is one of the few studies that has prospectively addressed the important problem of dehydration in elderly patients. To our knowledge, it is the first in which dehydration severity was measured directly by dilution techniques. The results demonstrate a high individuality in euvoalaemic laboratory test results. Individuality of the biochemical indices of fluid balance was caused by a small within-subject variability compared with a much larger between-subject variability. PBRRs had a limited diagnostic value in detecting dehydration in these patients, which is in agreement with this high individuality. Subsequently, it was shown that serum creatinine concentrations were most responsive to dehydration.

Although there have been prospective studies investigating the incidence of hypernatraemia in elderly subjects [29, 30], there are few prospective studies which have tried to determine the overall prevalence and incidence of dehydration in older people. Lavizzo-Mourey noted a prevalence of dehydration of 39% among nursing-home patients who went into hospital [31]. In our study dehydration was present in 26% of the subjects. However, the prevalence of dehydration in the whole group of patients might have been different because of the high exclusion rate (dehydration was mentioned in the letter of discharge in 18% of the 165 patients who did not participate in the study). The dehydration episodes studied were mostly caused by a combination of several factors, which resulted more often in a loss of water and electrolytes than in pure water loss.
Table 4. Characteristics of 91 serial laboratory test results obtained in dehydrated and euvoelaemic episodes of 14 elderly patients

<table>
<thead>
<tr>
<th>Dehydration</th>
<th>Sodium (mmol/l)</th>
<th>Urea (mmol/l)</th>
<th>Creatinine (µmol/l)</th>
<th>Haematocrit (l/l)</th>
<th>Urea/creatinine ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>135.6 (8.4)</td>
<td>15.8 (12.5)</td>
<td>165.8 (137)</td>
<td>0.41 (0.06)</td>
<td>95.5 (15.9)</td>
</tr>
<tr>
<td>Range</td>
<td>118-148</td>
<td>8.4-51.7</td>
<td>89-609</td>
<td>0.35-0.54</td>
<td>61.4-121.5</td>
</tr>
<tr>
<td>Mean euvoelaemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coefficient of variation (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Between subjects</td>
<td>6.3</td>
<td>223</td>
<td>246</td>
<td>32</td>
<td>71.6</td>
</tr>
<tr>
<td>Within subjects</td>
<td>1.5</td>
<td>14.0</td>
<td>5.0</td>
<td>6.8</td>
<td>13.2</td>
</tr>
<tr>
<td>Index of individuality</td>
<td>0.24</td>
<td>0.06</td>
<td>0.02</td>
<td>0.21</td>
<td>0.18</td>
</tr>
<tr>
<td>Population-based reference range</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>64</td>
<td>100</td>
<td>57</td>
<td>7</td>
<td>- b</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>68</td>
<td>43</td>
<td>71</td>
<td>96</td>
<td>- b</td>
</tr>
<tr>
<td>Responsiveness index a</td>
<td>0.98 (2.2)</td>
<td>0.14 (0.1)</td>
<td>2.5 (2.0)</td>
<td>1.1 (0.7)</td>
<td>0.13 (0.73)</td>
</tr>
</tbody>
</table>

*Standard deviation in parentheses.

Within-subject variability in euvoelaemia

Within-subject variability in euvoelaemic test results of all laboratory quantities was comparable to results obtained in other studies. Fraser and co-workers measured a similar CV in 27 healthy subjects aged 70-83 years (sodium, 1.1%; urea, 10.6%; creatinine, 5.1%; haematocrit, 2.8%) [14, 15] and demonstrated that age had no effect on the within-subject variability in these quantities. This implies that euvoelaemic within-subject variability of these analyses in geriatric patients is not widened by age or comorbidity.

Based on measurements of the analytical variability

![Figure 2](https://academic.oup.com/ageing/article/27/3/311/17099)

Figure 2. Initial urea concentrations of dehydration episodes (●) and individual means and absolute ranges of urea concentrations of euvoelaemic episodes in 14 geriatric patients. •, upper limit of population-based reference range.

![Figure 3](https://academic.oup.com/ageing/article/27/3/311/17099)

Figure 3. Serial creatinine concentrations from patient no. 30 (a 78-year-old man). —, patient's mean euvoelaemic creatinine concentration; —, patient's upper limit of subject-specific reference range; ...., upper limit of population-based reference range; ■, creatinine concentrations in euvoelaemia; ■ Dehydration, initial creatinine concentration in dehydrated episode.)
at all ages and estimations of the biological within-subject variability, the Central Clinical Chemistry Laboratory of the University Hospital Nijmegen calculated within-subject variability for the most frequently determined analyses. These non-age specific reference values of within-subject coefficients of variation for longer than 1 week are 1.0, 12.3, 15.8 and 4.2% for sodium, urea, creatinine and haematocrit, respectively. These figures are close to the within-subject variabilities found in this study, except for the even lower within-subject variability in creatinine in geriatric patients. Therefore, homeostatic properties of geriatric patients do not seem to be compromised on the basis of these laboratory analyses, provided that data obtained during episodes in which fluid balance was disturbed are excluded.

In our data, $CV_W$ for sodium was smallest, which may be explained by the endocrine system maintaining the sodium level within strict ranges around the individual set point. $CV_W$ values for haematocrit and creatinine were also small, probably because haematological parameters are also subject to homeostatic control mechanisms and the daily creatinine production is relatively constant. However, daily urea formation is highly dependent on the same day's diet and muscle catabolism [10, 36]. The latter may be increased by fever, corticosteroid therapy or muscle damage. Moreover, the presence of blood in the gastrointestinal tract raises the serum urea level, as do glomerular diseases and dehydration. This explains the large within-subject variability found in sodium concentrations and the urea/creatinine ratio.

**Individuality and responsiveness**

In general, most quantities in clinical chemistry have marked individuality, and serial values for an individual span only part of the PBRR [27, 37]. Even in chronic renal failure within-subject variability in 15 biochemical analyses was much smaller than between-subject variability [38]. The individuality for sodium, urea, creatinine and haematocrit in hospitalized geriatric patients found in this study was even more pronounced than that described for healthy elderly subjects [14, 15]. This was caused by a much larger between-subject variability in geriatric patients, which can be explained by the high prevalence of multiple diseases that influence baseline values characteristic of the internal milieu in this population.

The disappointing diagnostic characteristics of PBRRs in this study are in agreement with the limited value of these reference ranges predicted by the low indexes of individuality. However, the alternative—calculating SSRRs—could only be performed in a few subjects. More research is needed to compare the diagnostic properties of SSRRs and PBRRs and to quantify the clinical implications and cost-effectiveness of medical decision-making based on these different types of reference ranges. PBRRs will remain necessary in the initial assessment of the fluid balance of new patients. However, their sensitivity and specificity may be improved by using reference populations consisting of elderly subjects. This may result in raising the upper limits of reference ranges for creatinine and urea and lowering the lower limit for serum sodium concentration [7]. In their prospective study on blood urea levels in the elderly, Bowker et al. reported a PBRR of 1.4–13.2 mmol/l, which is considerably wider than the range applied in this study (3.0–7.0 mmol/l) [10].

Serum creatinine concentrations were most responsive to the development of dehydration. Serum sodium and urea concentrations and urea/creatinine ratios had a very low responsiveness in monitoring fluid balance. This questions the widespread use of sodium and urea concentrations and urea/creatinine ratio as indicators of dehydration in elderly subjects.

**Limitations of this study**

Some caution in interpreting these results is needed because clinical diagnoses were not blinded for patients' laboratory test results, but were partly based on these data. However, more important in clinical assessment was the fact that conclusions about fluid balance could be changed after having monitored the effects of rehydration therapy on the patients' weights and symptoms. Serial examinations in the same patient, as used here, are probably more valid in assessing dehydration than a single examination [20].

It may be argued that the external validity of this study is limited, because only 24% of all patients admitted in the 16 month period were included. However, subjects were excluded primarily because of the restrictions in subject selection dictated by the ethical guidelines for non-therapeutic research. Consequently, the presence of moderate or severe dementia was the main reason for exclusion.

We do not know whether the exclusion of this group of subjects had any effect on our results but have found no clear evidence that the external validity of the study was jeopardized by the high exclusion rate. Gross et al. did not discuss the possible effects of dementia on diagnosing dehydration, although nearly three-quarters of their sample had reduced mental capacity [3]. O'Neill et al. did not find a relationship between mental status and osmolality in elderly female patients in continuing care [8] and we found only one small study ($n = 18$) suggesting that serum osmolality could be more responsive to dehydration in patients suffering from Alzheimer's disease [39].

Finally, responsiveness to minimal relevant changes in fluid balance could not be determined in all patients, although this procedure has been recommended by Guyatt [16]. Instead we calculated responsiveness in detecting a loss of 11% of TBW: this relatively large change may well be the minimally detectable change.
and reflect the difficult clinical assessment of fluid balance in elderly subjects.

Conclusions
We have confirmed that laboratory indices of dehydration in hospitalized geriatric patients are, like those of nursing-home patients [12], highly variable between subjects but stable over time within subjects. This study also introduced the concepts of individuality, responsiveness and reference ranges that are subject-specific. Because of the high individuality in the laboratory analyses studied, it may be profitable to calculate SSRR when repeated laboratory tests are available. Within-subject variability in elderly patients is probably no different from within-subject variability in other populations. Therefore, the within-subject variability measures of elderly subjects available from the literature or variability measures of younger populations measured by the local clinical chemistry laboratory may be used in calculating SSRR.

Dehydration can be diagnosed best by applying reference ranges for serial serum creatinine concentrations that are age- and, if possible, subject-specific and by repeatedly examining and weighing patients.

Key points
- Population-based reference ranges of biochemical indices of dehydration are of limited value in monitoring fluid balance in elderly patients.
- Monitoring individual patients for the development of dehydration should be based on repeated measurements of serum creatinine concentration and weight, combined with physical examination.

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