Renal water conservation and the volume kinetics of fluid-induced diuresis: A retrospective analysis of two cohorts of elderly men

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Abstract
Renal water conservation after an overnight fast mirrors the habitual intake of liquid. The hypothesis in the present study was that water conservation influences the diuretic response to infusion of two types of crystalloid fluid. Twenty-three elderly male patients (mean age 72 years) underwent a total of 46 intravenous infusions of 1.0 or 1.5 L of either hypotonic non-electrolyte fluid (glycine 1.5%) or isotonic electrolyte fluid (Ringer’s acetate or 0.9% saline). Urine osmolality (used to indicate renal water conservation) and plasma creatinine were measured before the infusions started. A two-volume model was fitted to repeated measurements of the blood haemoglobin concentration and the urinary excretion, using mixed-effects modelling software. Urine osmolality was examined as a potential covariate to the fixed kinetic parameters. The results show that distribution and redistribution of infused fluid occurred twice as fast for the non-electrolyte fluids as for the electrolyte-containing fluids, while the urine flow showed less difference. For both types of fluid, high urine osmolality served as a statistically significant covariate to the rate constant describing urinary excretion. Simulations showed that a high pre-infusion urine osmolality doubled the time required for the kidneys to excrete 50% of a 30-minute infusion. High plasma creatinine independently prolonged the elimination of non-electrolyte fluid. The use of 0.9% saline instead of Ringer’s prolonged the excretion of electrolyte-containing fluid. In conclusion, renal water conservation is a determinant of the diuretic response to crystalloid fluid, regardless of whether the fluid contains electrolytes, and it should be considered in fluid balance studies.

KEYWORDS
fluid therapy, glycine, normal saline, pharmacokinetics, Ringer’s acetate

1 | INTRODUCTION

The diuretic response to infusion fluid has a central role in our understanding of fluid overload in hospital care. There is increasing awareness that the kidneys may be set to excrete or retain water due to variability in the daily habitual intake of water and that this could interfere with the effectiveness of excretion of a fluid load. No correction is made in fluid balance studies to acknowledge the
fact that the kidneys may be set to conserve or excrete water before fluid is administered. This omission probably reflects the assumption that no such influence exists.

This question is addressed in the present report by the use of kinetic analysis that examines whether renal water conservation influences the distribution and elimination of a subsequent intravenous (iv) load of hypo-osmotic non-electrolyte and nearly iso-osmotic electrolyte-containing fluid. The reason for using fluid with and without electrolytes and with different osmolalities was to determine whether any effect would be universal or specific to one type of fluid. A number of mechanisms may be operating in the excretion of a fluid bolus. For example, the elimination of a fluid of low osmolality is facilitated by inhibition of vasopressin secretion, whereas the diuretic response to iso-osmotic electrolyte solutions depends more on improved renal perfusion and increased intravascular hydrostatic pressure.

Renal water conservation can be detected by increased urinary concentrations of metabolic waste products. Several biomarkers have been used, such as urine-specific weight, creatinine, and osmolality. The rationale behind the use of these simple urinary biomarkers is that basal metabolism typically occurs at a fairly fixed rate, regardless of how the renal water conservation is set. In the present study, the concentration of the urine was indicated by measuring the osmolality. The working hypothesis was that concentrated urine before the infusion inhibits fluid excretion after volume loading with both types of fluid.

2 | RESULTS

Twenty-three senior citizens scheduled for benign prostatic hyper trophy surgery due to infravesical obstruction underwent two infusion experiments separated by at least one week, making a total of 46 infusions. The two studied patient cohorts were comparable, with the exception that those who received electrolyte-containing fluids had a higher body weight (Table 1).

2.1 | Non-electrolyte fluids

A two-compartment kinetic model with expandable walls (Figure 1A) was successfully fitted to the 119 measurements of plasma dilution obtained in the course of 20 iv infusion experiments in 10 elderly patients who received 1 L of 1.5% glycine with without electrolytes over 20 minutes (Figure 1B).

Covariate analysis showed that the rate parameter for urinary excretion, \( k_{10} \), attained lower values when plasma creatinine and urine osmolality were high prior to initiation of the infusions. The relationship between \( k_{10} \) and these two significant covariates is shown in Figure 1C,D. Both covariates independently modified \( k_{10} \) for each individual, as follows:

\[
k_{10} = 31.8 \times 10^{-3} \left( P - \text{creatinine}/95 \right)^{-1.9} \left( U - \text{osmolality}/585 \right)^{-0.5}.
\]

where 95 is the mean plasma creatinine concentration and 585 is the mean urine osmolality before the infusion was initiated. All kinetic parameters are shown in Table 2.

2.2 | Electrolyte fluids

The two-compartment kinetic model was fitted to 429 measurements of plasma dilution based on blood samples obtained in the course of 26 iv infusion experiments in 13 elderly patients who received 1.5 L of crystalloid fluid (Ringer’s acetate and 0.9% saline) over 45 minutes (Figure 2A).

The fixed parameters for distribution and redistribution (\( k_{12} \) and \( k_{21} \)) attained mean values only half as high as those for the non-electrolyte fluids.

The covariate analysis identified four individual-specific variables that affected the fixed kinetic parameters. The use of saline was associated with a lower rate of elimination as compared to Ringer’s.

Elevated plasma syndecan-1 was associated with slower distribution (Figure 2B).

Due to data scattering, concentrated urine was evaluated as a categorical variable and was taken as urine osmolality above the mean (682 mosmol/kg) and/or urine creatinine above the mean (9.5 mmol/L). In doing so, concentrated urine was associated with lower estimates of both \( k_{12} \) and \( k_{21} \); that is, with slower redistribution from the extravascular space and with slower elimination. Plasma creatinine levels were close to being a significant covariate, but were not included in the final model.

**TABLE 1** Baseline characteristics of the two cohorts of patients

|                  | Non-electrolyte fluids | Electrolyte-containing fluids |
|------------------|------------------------|-------------------------------|
| Patients (N)     | 10                     | 13                            |
| Infusions (N)    | 20                     | 26                            |
| Age (years)      | 71 (57-79)             | 72 (66-79)                    |
| Body weight (kg) | 74 (6)                 | 82 (7)*                       |
| Plasma creatinine(µmol/L) | 95 (23)       | 81 (10)                       |
| Urine osmolality (mosmol/kg) | 585 [218]       | 624 [158]                     |
| Serum osmolality (mosmol/kg) | 292 (6)           | —                             |

*Different from the non-electrolyte group by \( P = .01 \).
Figure 3 illustrates how the inclusion of covariates improved the ability of the kinetic model to predict the dependent variables (plasma dilution and urinary excretion).

Figure 4 shows that the slower excretion associated with 0.9% saline was due to an effect on the kidneys ($k_{10}$), whereas much of the inhibitory effect of concentrated urine on the diuretic response to fluid was due to slow redistribution; that is, the $k_{21}$ was low.

“Saline” and “Concentrated urine” were related to the fixed parameters in the form of exponential covariate models, whereas syndecan-1 was entered as a power model. The covariates affected the fixed parameters as follows:

$$k_{12} = 47.8 \times 10^{-3} \left( P - \text{syndecan} - 1/40.6 \right)^{-0.21}$$

$$k_{21} = 14.8 \times 10^{-3} e^{-0.57 \left( \text{concentrated urine} - 1 \right)}$$

$$k_{10} = 26.3 \times 10^{-3} e^{-0.38 \left( \text{concentrated urine} - 1 \right)} e^{-1.12 \left( \text{Ringer} - 0, \text{Saline} - 1 \right)}$$

where 40.6 is the mean plasma concentration of syndecan-1. In the exponential models, only saline and concentrated urine changed the fixed parameter value (because $e^0 = 1$).

### 2.3 Simulations

Graphical computer plots were used to compare the half-lives of the infused fluid in the body. After infusing 1 L of non-electrolyte fluid over 30 minutes, half the volume would be excreted after 75 minutes if the pre-infusion urine was dilute (osmolality 300 mosmol/kg) and at 130 minutes if the urine was concentrated (osmolality 900 mosmol/kg). The difference was due to a renal effect ($k_{10}$) only (Figure 5A).

An infusion of the same volume of electrolyte fluid (Ringer’s) resulted in excretion of half the volume after 90 minutes if the pre-infusion urine was dilute, and after 175 minutes if the urine was concentrated (Figure 5B). Simulations further showed that only half of this prolongation was due to a renal effect and the rest was due to covariance with $k_{21}$. This implied that more fluid accumulated in the extravascular space, where it was unavailable for excretion.

The half-lives are considerably shorter if considering only the excess fluid residing in the plasma volume, which can be derived mathematically as $\ln 2 \cdot (0.693/k_{10})$. The half-lives corresponding to the values given above then become 18 and 23 minutes for the non-electrolyte fluids and 26 and 32 minutes for the electrolyte fluids.

## DISCUSSION

The kinetic analysis shows that the presence of concentrated urine before an infusion is important for the diuretic response to volume loading in elderly men. Renal water conservation is apparently retained, at least for some time, when the body is rapidly loaded with fluid.
regardless of whether the fluid contains electrolytes. Plasma creatinine was a statistically significant predictor of the diuretic response following infusion of electrolyte-free fluids but not of electrolyte fluids. This difference probably arose because fewer patients who received electrolyte fluids had elevated plasma creatinine values.

The electrolyte-free fluids were distributed, redistributed, and excreted faster than the electrolyte fluids. Furthermore, accumulation of infused fluid in the extravascular space appeared to be similar in importance to renal fluid retention as an explanation of why the

**FIGURE 2** Electrolyte fluids. A, The final curve-fit. Lines are the model fitted to the data; points are individual measurements. B, Covariate analysis showing the inverse relationship between the rate constant for distribution \(k_{12}\) vs the plasma concentration of syndecan-1.

**FIGURE 3** Electrolyte fluids. Comparison between the measured and model-predicted plasma dilution and urinary excretion when covariates were not included (A, C) and when they were included in the model (B, D)

**FIGURE 4** Covariate analysis of electrolyte fluids. Distribution of the three rate constants that determine the distribution of infused fluid \(k_{12}, k_{21}, k_{10}\) depending on whether patients had concentrated urine (left column) and whether they had received Ringer’s or saline for infusion (right column).
urine output was low in response to electrolyte-containing fluids in patients with concentrated urine.

Previous data show that the kidneys are fairly slow to adjust their sodium excretion. They are normally set to excrete urine that is half-isotonic with regard to sodium, but when fluid is infused that is isotonic with regard to sodium (such as Ringer’s), the kidneys require some time to increase their sodium excretion.13

The present study challenges this situation by showing that how the kidneys are pre-set to excrete or conserve fluid is relevant even when the infused fluid contains no sodium at all.

The present study evaluated, without success, other variables for possible covariance with the urinary excretion. Body weight was a top candidate because the infused volumes were given in fixed doses and not per kilogram of body weight. Age was another possible factor, but it played only a secondary role, which probably reflects the limited age span of the patients. Therefore, concentrated urine remains a key determinant of the diuretic response to volume loading in the elderly.

Concentrated urine is used as a sign of acute dehydration in sports medicine.3,4 Urine osmolality might be the most widely accepted biomarker, but it correlates closely with urine-specific weight, urine creatinine, and urine colour.6 In the general population, concentrated urine correlates best with the habitual intake of water if measured in the morning urine.15 By contrast, spot samples taken at daytime poorly reflect the fluid status.

The mechanism explaining concentrated urine in the general population is still somewhat unclear. Vasopressin, which is a water-sparing hormone acting on the renal tubules, has been implicated. Johnson et al2 reported a minor elevation of the plasma vasopressin concentration in females with concentrated urine, but this finding was not supported by a study of our hospital staff.6 Vasopressin is a short-acting hormone, and concentrated morning urine seems to mirror long-term corrections of the fluid balance (>1 week).14 Mechanisms involving the outer and inner medulla,15 which are the main sites for renal conservation of water, might then be more likely to be responsible for the renal water conservation that forms the basis of the present study. Plasma vasopressin was even measured in the study of non-electrolyte fluid, and without elevations.7

No role has yet been established for concentrated urine in clinical medicine, although several studies implicate its importance. For example, concentrated urine is associated with a high 30-day mortality in acute geriatric care,16 with more complications after hip fracture surgery,17 and with a higher likelihood of having a rise in plasma creatinine after surgery.18 Some evidence also indicates that

| Covariate            | Best estimate | 2.5% CI  | 97.5% CI | CV%  |
|----------------------|---------------|---------|----------|------|
| Kinetic parameter    |               |         |          |      |
| $k_{12}$ ($10^{-3}$ min$^{-1}$) | – | 47.8 | 32.8 | 62.9 | 16.0 |
| $k_{21}$ ($10^{-3}$ min$^{-1}$) | – | 14.8 | 9.1 | 20.4 | 19.4 |
| $k_{10}$ ($10^{-3}$ min$^{-1}$) | – | 26.3 | 14.1 | 38.5 | 23.5 |
| Covariate effect     |               |         |          |      |
| $k_{12}$ Syndecan-1  | –0.21         | –0.30   | –0.13   | –19.9 |
| $k_{21}$ Concentrated urine | –0.57 | –0.87 | –0.27 | –27.1 |
| $k_{10}$ Concentrated urine | –0.18 | –0.25 | –0.12 | –18.2 |
| $k_{10}$ Saline      | –1.12         | –1.69   | 0.56    | –25.7 |

Note: Syndecan-1 and P-creatinine are used as power models, the other covariates as exponential models.

Abbreviations: CI, confidence interval; CV, coefficient of variation.
concentrated urine necessitates the use of more fluid to perform fluid optimization before surgery.\(^{19}\)

The population (mixed effects) kinetics used here is an industry standard tool for evaluating the kinetics and drugs and their dependency on individual-specific factors, such as age and gender.\(^{12}\) The micro-constant model detects a “wall” between a central space, where fluid equilibrates very rapidly with the site of infusion, and a more remote peripheral space. The exchange of infused fluid between these two body fluid spaces is determined by the rate constants \(k_{12}\) and \(k_{21}.\) The space with fast equilibration very likely represents the plasma volume.

The exploratory analysis of syndecan-1 yielded an unexpected finding. Syndecan-1 is a component of the endothelial glycocalyx layer, and elevated concentrations in plasma, according to the “Revised Starling Principle,” are believed to imply increased capillary permeability.\(^{20}\) In volume kinetics, the rate constant \(k_{12}\) represents the rate of fluid that leaves the plasma in all extra-renal tissues. The covariate plot in Figure 2B does not support this hypothesis; instead, it suggests that less fluid is distributed when plasma syndecan-1 is on the high side. A similar result has been found previously.\(^{21}\)

Limitations of this study include that the present report is a secondary publication to two previously published studies, albeit with similar protocols but a different focus. Both series of experiments were well controlled. Each patient received two infusions of fluid having similar characteristics.

The cohorts are likely to have a hydration status representative of patients arriving at the hospital to undergo elective surgery. Blunt dehydration was prevented after fasting overnight and waiting to undergo the experiments by allowing our patients to ingest one glass of liquid at least 2 hours before coming to the hospital. A second limitation is that this practice might have added somewhat to the variability of the urine osmolality, although the osmolality in the morning urine rests mainly on the habitual intake of water over a longer period of time.\(^{15}\) In any event, the average urine osmolality found here was quite similar to the morning urine that was collected just after they woke up in the morning.\(^{15}\)

All studied patients suffered from prostatic enlargement, but they were not debilitated and showed no clinical indications of being dehydrated or having an unstable fluid balance. All urine was collected via a bladder catheter at precisely timed intervals. The haemodynamics was not included in the present evaluation, as all patients were in their conscious state with intact cardiovascular systems. In the original publications, no abnormal arterial pressures were reported.\(^{7,8}\)

In conclusion, the urine osmolality measured prior to fluid loading with an electrolyte-free or electrolyte-containing solution is a key variable that determines the subsequent diuretic response.

### 4 | METHODS

This study is a secondary publication for two open-label, randomized, parallel clinical trials that were performed in a similar way.\(^{7,8}\) Twenty-three senior citizens scheduled for benign prostatic hypertrophy surgery due to infravesical obstruction underwent two infusion experiments separated by at least one week, making a total of 46 infusions. The first series of experiments compared plasma electrolytes when electrolyte-free irrigating fluids with glycine (1.5%), with and without 1% added ethanol, was given to 10 patients.\(^{7}\) The second study compared glomerular filtration rates when Ringer’s acetate or 0.9% saline was administered to 13 patients.\(^{8}\) Both studies were approved by the Regional Ethics Committee (Dnr 113/89 and 2008/804-31/2). All patients had given their informed consent for participation.

#### 4.1 | Procedure

The infusions were started in the morning between 8 and 9 am at the Hospital Research Centre. Participants were allowed to ingest one glass of liquid to prevent dehydration before arriving at the hospital. No premedication was given. The patients rested for 30 minutes on a bed to reach a haemodynamic steady state. Fluid was administered intravenously at a constant rate by infusion pumps. Blood (3–4 mL) was withdrawn in a standardized manner at timed intervals from a cannula placed in a cubital vein on the arm not used for infusion. A small discard volume of blood was drawn before each blood collection to preclude any admixture of rinsing solution, and 2 mL of 0.9% saline was then injected to prevent clotting.

Urine was collected from an indwelling bladder catheter at the same points in time as blood was sampled.

In both studies, the osmolality of the urine excreted during the 30 minutes awaiting haemodynamic steady state was measured by freezing-point depression. Plasma creatinine and serum osmolality (Hitachi 737) were also measured at baseline.

In the study of electrolyte fluids, the plasma concentration of syndecan-1, which is a biomarker of injury to the endothelial glycocalyx layer,\(^{10}\) was measured with an ELISA test kit from Dianalce (Besancon Cedex) before and just after the infusion.

#### 4.1.1 | Non-electrolyte fluids

Ten men received 1 L of glycine 1.5% (osmolality 180 mosmol/kg) over 20 minutes and a second infusion with glycine 1.5% containing 1% ethanol (350 mosmol/kg) over 20 minutes (both fluids from Baxter). The ethanol was studied as a means of monitoring irrigating fluid absorption during transurethral prostatic resection.\(^{9}\) Blood was withdrawn at 0, 10, 20, 50, and 140 minutes after initiation of the infusion. Volunteers were covered in blankets to ensure good thermal comfort. Half an hour before the infusions started a catheter was placed in the bladder for collection of urine.

#### 4.1.2 | Electrolyte fluids

Ten men aged were given a 45 minutes infusion consisting of 1.5 L of either Ringer’s acetate (Na 130, K 4, Ca 2, Cl 110, acetate
30 mmol/L; osmolality 273 mosmol/kg) or 0.9% saline (Na 154 and Cl 154 mmol/L; 308 mosmol/kg). Blood sampling was performed every 5 minutes during the first 90 minutes of the study, and then at 100, 110, 120, 140, 160, 180, and 240 minutes. Patients already had a bladder catheter inserted to alleviate their outflow obstruction before the study started.

4.2 | Kinetic analysis

A two-volume fluid volume kinetic model was fitted to the dependend variables, which were the frequently measured plasma dilution and urinary excretion, in all experiments performed in each of the two studies.

This kinetic model is the one most commonly used to model fluid shifts, and it agrees well with physiological data showing that crystalloid infusion fluids distribute between two compartments: the plasma and the extravascular fluid space (Figure 1A).

Fluid infused into the plasma (\( V_p \), volume) expands the plasma volume to \( V_p \), and is eliminated by urinary excretion (\( k_{10} \), rate constant), as well as being distributed to (\( k_{12} \), rate constant), and re-distributed from (\( k_{21} \), rate constant), the extravascular space (\( V_e \), volume). All flow rates are proportional, by virtue of the rate constant (\( k_{12}, k_{21}, \) and \( k_{10} \)), to the volume expansion of the respective body fluid space.

The differential equations describing the model are:

\[
\frac{dV_p}{dt} = R_v - k_{10} (V_p - V_e) - k_{12} (V_p - V_e) + k_{21} (V_t - V_c)
\]

\[
\frac{dV_e}{dt} = k_{12} (V_p - V_e) - k_{21} (V_t - V_c).
\]

The haemodilution corrected for the baseline haematocrit was used to represent the dilution of \( V_c \); that is, \( (V_c - V_e)/V_c \). To stabilize the analysis, \( k_{10} \) was obtained as the measured urine volume divided by the area under the curve for \( (V_c - V_e) \) that was estimated during the curve-fitting process.

The influence of various individual-specific covariates on the estimated values of these four fixed model parameters was then tested sequentially, as guided by the goodness-of-fit for the model. The criterion for inclusion was that inclusion of the covariate should decrease the –2 log-likelihood for the model by > 3.8 points (\( P < .05 \)). Moreover, the confidence interval (CI) for the covariate could not include 0 and the inter-individual variability should be <50%.

The following variables were evaluated as a potential covariate once for each type of infusion: age, body weight, type of fluid, serum and urine osmolality, and plasma concentration of creatinine before the infusions started.

The distribution of infused fluid is determined by the rate constants \( k_{12}, k_{21}, \) and \( k_{10} \). The size of \( V_c \) can be estimated, but it serves only as a scaling factor between the plasma dilution and plasma volume expansion. These parameters and their statistically significant covariates, if any, were estimated simultaneously using the Phoenix software for nonlinear mixed effects (NLME), version 1.3 (Pharsight) with the First-Order Conditional Estimation Extended Least Squares (FOCE ELS) as the search routine and the additive model for the random-error variability. Data are presented as the mean (SD). The kinetic data are reported as the best estimate, and 95% CI \( P < .05 \) was considered statistically significant.

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CONFLICT OF INTEREST

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PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data used for the kinetic analysis can be obtained from the author upon request.

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