

Modelling of peripheral fluid accumulation after a crystalloid bolus in female volunteers – a mathematical study

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Objective. To simultaneously model plasma dilution and urinary output in female volunteers.

Methods. Ten healthy female non-pregnant volunteers, aged 21–39 years (mean 29), with a bodyweight of 58–67 kg (mean 62.5 kg) participated. No oral fluid or food was allowed between midnight and completion of the experiment. The protocol included an infusion of acetated Ringer's solution, 25 ml/kg over 30 min. Blood samples (4 ml) were taken every 5 min during the first 120 min, and thereafter the sampling rate was every 10 min until the end of the experiment at 240 min. A standard bladder catheter connected to a drip counter to monitor urine excretion continuously was used. The data were analysed by empirical calculations as well as by a mathematical model.

Results. Maximum urinary output rate was found to be 19 (13–31) ml/min. The subjects were likely to accumulate three times as much of the infused fluid peripherally as centrally; $1/\mu = 2.7$ (2.0–5.7). Elimination efficacy, E_{eff} , was 24 (5–35), and the basal elimination k_b was 1.11 (0.28–2.90). The total time delay T_{tot} of urinary output was estimated as 17 (11–31) min.

Conclusion. The experimental results showed a large variability in spite of a homogenous volunteer group. It was possible to compute the infusion amount, plasma dilution and simultaneous urinary output for each consecutive time point and thereby the empirical peripheral fluid accumulation. The variability between individuals may be explained by differences in tissue and hormonal responses to fluid boluses, which needs to be further explored.

Keywords: anaesthesia; fluids; kinetics; modelling; peripheral space

Introduction

Fluid management is an important part of per-operative care. The previous debate whether crystalloids or colloids should be used has changed to focus more on how they can be used in combination. Regardless of what endpoint is chosen for per-operative fluid management, there is an inevitable movement of protein-free fluid to peripheral, functional or

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non-functional parts of the body. Furthermore, if the endothelium is damaged as for instance during trauma and septicemia, there is increased leakage of larger molecules causing protein-rich fluid to escape as well. There is an overwhelming consensus that excessive peripheral fluid accumulation causing weight gain postoperatively is detrimental [1]. Therefore, the clinician should benefit from being able to continuously monitor such fluid accumulation. However, fluid distribution in the body is a very complex matter regulated by a large amount of feedback mechanisms. To cope with this complexity, mathematical models could be useful. One limitation, however, is that the input for such a model consists of blood dilution samples taken from a vein meaning that the analysis at best can be an approximation of the whole body distribution. Volume kinetics [2–7] is an analysing tool built on repetitive analysis of an endogenous tracer, such as haemoglobin, in blood. When fluids are infused intravenously, dilution of the plasma occurs, and by repetitive sampling, it is possible to customize non-linear equations to the sampled data. It is further possible to analyse time-dependent distribution and elimination constants. Particularly, it is possible to predict the fluxes of fluids between different compartments. One and two volume fluid models (V_1 and V_2) can be identified if isotonic solutions are infused [2]. These fluid spaces are to be regarded as easily vs. less easily perfused parts of the body. The results are sensitive to analytical errors; however, the choice of mathematical approach is crucial for the stability of the estimates. The best estimates of model parameters have conventionally been made by non-linear least-squares regression programs in the MatLab versions [2,8,9]. Early volume kinetic models often struggled with covariance between the central and peripheral compartments [2]. The models were unable to compute the central fluid space with accuracy, which sometimes gave unrealistically large peripheral fluid spaces. This was partly solved by introducing a fixed elimination rate constant determined by urinary excretion [10].

The aim of this study was to use data from volunteer subjects to simultaneously model plasma dilution together with urinary output to continuously monitor the peripheral fluid accumulation after a crystalloid bolus. Furthermore, the aim is to compute parameters with regard to the distribution, peripheral accumulation and elimination.

Materials and methods

This is a prospective and descriptive study. The study was approved by the Institutional Review Board in the Stockholm County. It was funded by departmental sources. The experiments were performed at the Clinical Research Centre at Karolinska Institutet/Södersjukhuset, Section of Anaesthesiology and Intensive Care. Ten healthy female non-pregnant volunteers, aged 21–39 years (mean 29), with a bodyweight of 58–67 kg (mean 62.5) participated. No oral fluid or food was allowed between midnight and completion of the experiment. The experiments were performed in the morning between 8 am and 10 am. The volunteers were subjected to a period of 20 min in the supine position for equilibration of body fluids before the infusion was started. The volunteers remained in bed during the whole observation, which lasted 4 h. Intravenous cannulas were placed in antecubital veins on each side. One cannula was used for blood sampling, and the other was used for fluid infusion. After meticulous sterile preparation, a urinary catheter was inserted. A standard bladder catheter (Sherwood Medical, St Louis, MO, USA) connected to a drip counter to monitor urine excretion was used. Furthermore, haemodynamic supervision was maintained by electrocardiography, pulsoximetry and non-invasive blood pressure measurements (Propaq 104, Systems Inc., Beaverton, OR, USA). The protocol included an infusion of acetated Ringer's solution, 25 ml/kg (Baxter Healthcare Ltd; Deerfield, IL, USA; ionic content: Na^+ 130 mM, Cl^- 109 mM, calcium

3 mM, K⁺4 mM, acetate 28 mM, pH 6.5, osmolality 273 mOsm/l) over 30 min. However, three subjects differed in infusion rate (23, 20 and 18 ml/min), which was adjusted in the following analyses.

Blood samples (4 ml) were taken every 5 min during the first 120 min, and thereafter the sampling rate was every 10 min until the end of the experiment at 240 min. Haemoglobin (B-Hb) and the red cell count concentrations were analysed using a Coulter Counter STKS device (Coulter Electronics, Hialeah, FL, USA). A trash sample was drawn before each blood sampling to avoid a diluted sample. The discarded sample was reinjected to minimize the blood loss, while each sample blood loss was then replaced by an equivalent volume of 0.9% saline solution to prevent clotting of the cannula and to replace the lost blood volume.

Mathematical modelling

Empirical computation

An empirical approach to peripheral fluid accumulation can be computed by analysis of the initial plasma and blood volumes, set as $V_{P,0}$ (ml) and $V_{B,0}$ (ml), respectively. We used the empirical formula by Nadler for women [11], where BW is bodyweight in kilogram and L is length in metres, as follows:

$$V_{B,0} = (0.6041 + 0.03219 \times BW + 0.3669 \times L^3) \times 1000.$$

To study perturbations caused by the infusion, we computed the actual excess volume of the plasma within the range of individual variations. Previous investigations [11] show that differences in blood volume can vary considerably. For modelling purposes, we have set upper and lower limits for blood volumes to $\pm 15\%$. The maximum and minimum plasma volume expansion was computed for each time point t_i (min) from the measured haematocrit Hct_i and corresponding haemoglobin Hb_i . The following equations, adapted by Hahn [12], are considered:

$$MHb_0 = V_{B,0} \cdot Hb_0,$$

$$V_{P,0} = V_{B,0} \cdot (1 - Hct_0),$$

for each i :

$$MHb_{i+1} = MHb_i - V_{bs} \times Hb_i,$$

$$V_{B,i+1} = \frac{MHb_{i+1}}{Hb_{i+1}},$$

$$V_{P,i+1} = V_{B,i+1} \times (1 - Hct_{i+1}).$$

where MHb_i is the amount of haemoglobin at time t_i and V_{bs} is the blood sampling volume. The perturbation resulted into two plasma volumes (maximum and minimum, see Figure 1) for each time step, $V_{P,i+}$ and $V_{P,i-}$. For each subject, we were able to compute the fluid that resided in the central and peripheral spaces V_E .

$$V_{E,i} = V_{I,i} - a_{p,i} - V_{U,i},$$

where $V_{I,i}$ is the infused volume at t_i , $a_{p,i}$ is the residual plasma volume ($V_{P,i} - V_{P,0}$) and $V_{U,i}$ is the measured urine output at t_i .

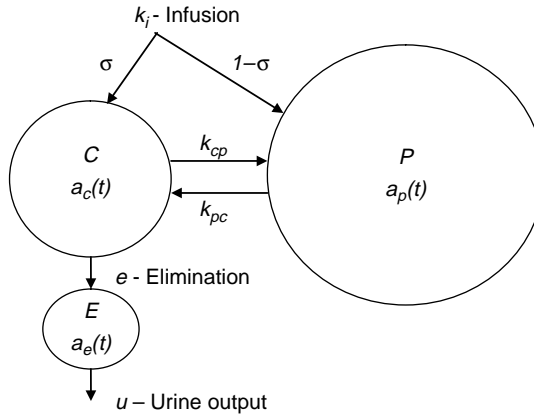


Figure 1. Overview of kinetic model. See text for definitions of symbols.

Kinetic calculations

To analyse, quantify and categorize each subject in their response to the fluid bolus, a three-compartment model was used (Figure 2). A central compartment V_1 , with a volume $v_1(t)$ (ml) at time t (min) communicates with a peripheral compartment V_2 with a volume $v_2(t)$ (ml).

A fluid infusion k_i (ml/min) is administrated into the central compartment V_1 . Since we anticipated that this compartment has variable compliance, and therefore cannot initially be expanded more than to a certain limit, we defined a factor σ that allows the administrated fluid to bypass V_1 during infusion.

V_1 also communicates by the rate constants k_{12} and k_{21} (ml/min) with V_2 .

The system eliminates fluid from V_1 by a flow e (ml/min) to an intermediate compartment V_E . The flow e is considered to mainly depend on the expansion of the central space V_1 by an exponential function [6].

Since elimination does not occur immediately, we coped with this problem by defining pertinent delay factors. Initially, we defined T_1 (min), which reflects the delay from when V_1 expands before elimination starts to V_E . Furthermore, we defined a parameter T_e , which is a turnover time of the fluid through V_E . Finally, we defined a time delay T_u between V_E and the sampling point, where urinary output flow u_{output} (ml/min) is measured.

If we define the initial volumes as $v_1(0) = v_{1,0}$, the amounts a (ml) as $a = v(t) - v(0)$, and rewrite the rate constants k_{12} and k_{21} as $\mu = k_{12}/k_{21}$, $k_t = k_{21} \cdot v_{1,0}$, we may formulate the following differential equations:

$$\begin{aligned}\frac{da_1}{dt} &= k_i \cdot \sigma - \frac{k_t}{v_{1,0}} \cdot (a_1 - \mu \cdot a_2) - e(t), \\ \frac{da_2}{dt} &= k_i \cdot (1 - \sigma) + \frac{k_t}{v_{1,0}} \cdot (a_1 - \mu \cdot a_2), \\ \frac{da_E}{dt} &= e(t) - u(t),\end{aligned}$$

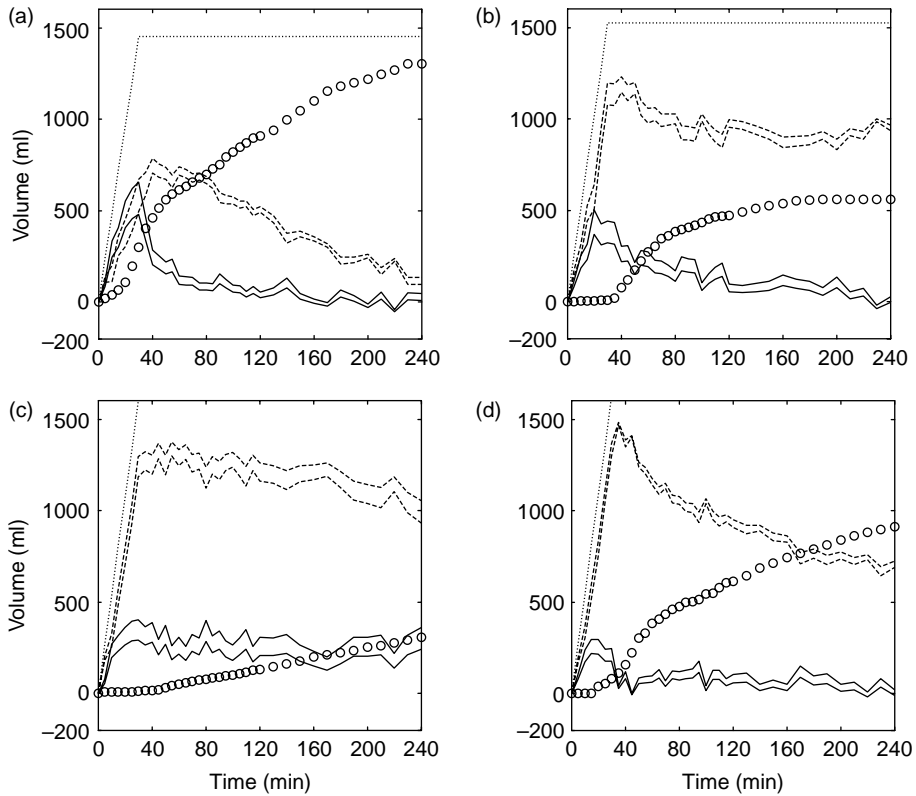


Figure 2. Empirical computation. Double bar lines show perturbed volumes of central (lower) and peripheral (upper) volumes, respectively. Circle lines reflect urinary output. Small dotted lines represent infusion which ends at 30 min.

where

$$\begin{aligned}
 e(t) &= k_b \cdot e^{\frac{k_{el} \cdot a_1^*}{V_{1,0}}} \quad a_1^* = a_1(t - T_1), \\
 u(t) &= \frac{a_e}{T_e}, \\
 u_{\text{output}} &= u(t - T_u).
 \end{aligned}$$

T_1 reflects the response time of elimination from the central compartment V_1 . The intermediate compartment V_E together with the turnover time T_e and the delay time T_u reflects the pathway of urine from the renal filtration in the kidney through the urinary bladder to the sampling point outside the patient. Input values for the model analyses were gender, bodyweight, haemoglobin, haematocrit, infusion rate, infusion time and urinary output. The parameters estimated were k_b , k_{el} , k_b , σ , μ , T_u , T_1 and T_e (Table 1). Estimates of the unknown parameters in the fluid space models were obtained by using the MatLab function *fminsearch*, which uses a simplex search method [13]. The differential equations were solved by the MatLab function *dde23* suitable for delay differential equations [14].

Table 1. Definition of model parameters.

	Unit	Description
k_t	ml/min	Intercompartment rate constant
k_{el}	–	Dilution-dependent elimination parameter
k_b	ml/min	Basal elimination constant
σ	–	Bypass factor
μ	–	Distribution factor v_c/v_p
T_u	min	Delay time of elimination response
T_b	min	Turnover time of intermediate compartment
T_d	min	Delay from intermediate compartment to u_{output}

The minimizing function computes the residuals of plasma volume expansion (a_1) and urine output (u_{output}).

The elimination has conventionally been modelled as proportional to the expansion of the central volume (dilution) [2,10,15]. A problem in earlier volume kinetics [2] arose when the excess volume became negative, but the subject still eliminated fluid. We therefore modelled the elimination by an exponential expression.

At a normal hydration state, the renal filtration together with fluid losses through breathing and sweating is at a basal level of 1.0–1.5 ml/min [16].

By considering the Taylor expansion of $e(t)$ near $a_1^* = 0$, an expression for a elimination efficacy may be derived as follows:

$$e(t) \approx k_b + \frac{E_{eff}}{v_{1,0}} \cdot a_1^* + \dots,$$

where $E_{eff} = k_b \cdot k_{el}$.

This parameter quantifies the renal response to a fluid challenge and corresponds to the parameter k_r in fluid kinetics.

Subsequently, the total bypass fluid amount could be expressed as follows:

$$V_\sigma = (1 - \sigma) \cdot T_1 \cdot k_1.$$

Modelling plots are shown for four individuals in the Results section.

Statistics and data presentation

Data are presented as medians and ranges for the 25th and 75th percentiles.

Results

All experiments were analysed according to the kinetic model chosen.

It was also possible to compute the infusion amount, plasma dilution and simultaneous urinary output for each consecutive time point. Examples of these progressive plots are shown in Figure 3(a)–(d) (for subjects no. 3, 5, 7 and 8).

As for the kinetic calculations, it was possible to use the model and solve all subjects.

Subject no. 3 (Figure 3(a)) had a small excess volume and large urinary output, while subject no. 5 (Figure 3(b)) showed a large peripheral accumulation with no significant elimination. Subject no. 7 (Figure 3(c)) had a very small accumulation centrally, no elimination and huge peripheral accumulation. Finally, subject no. 8 showed a large peripheral accumulation with some elimination (Figure 3(d)).

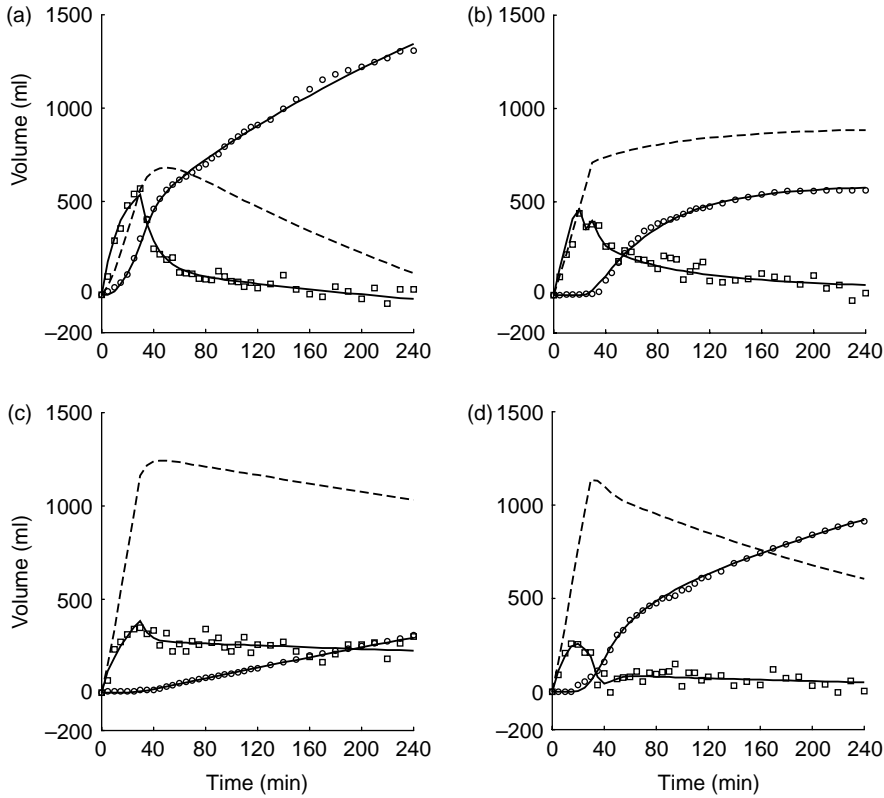


Figure 3. Kinetic computations. Squared box line reflects central volume. Circle dotted line reflects urinary volume. Dashed line reflects peripheral accumulation of fluid.

Table 2 shows median and ranges (25th and 75th percentiles) for parameters related to peripheral fluid accumulation and elimination for all 10 subjects. Parameters k_i is 114 (45–209) ml/min, and distribution factor $1/\mu$ is 2.7 (2.0–5.7). The bypass factor σ is 0.69 (0.56–0.87), which resulted in the computed bypass volume of $V_\sigma = 372$ (184–694) ml. The table further shows the median elimination rate constants k_{el} , k_b and E_{eff} . Constant k_{el} was found to be 21.4 (9.3–34.3), k_b 1.11 (0.28–2.90) ml/min and E_{eff} 24 (5–35) ml/min. Time delay constants are T_e 10.6 (4.9–20.9), T_1 1.4 (0.8–3.4) and T_u 4.2 (2.3–7.2) min. Individual values are shown in Table 3.

Table 2. Parameter estimates.

k_i	116	(46–161)
$1/\mu$	2.8	(1.8–5.6)
σ	0.71	(0.57–0.85)
V_σ	372	(184–694)
k_{el}	21.7	(9.6–29.1)
k_b	1.20	(0.29–2.92)
E_{eff}	26	(5–35)
T_e	8.5	(4.9–17.2)
T_1	1.4	(0.8–3.5)
T_u	4.2	(2.2–6.8)

Discussion

The aim of this study was to use data from volunteer subjects to *simultaneously* model plasma dilution together with urinary output to continuously monitor the peripheral fluid accumulation after a crystalloid bolus.

Fluid shifting out of the vasculature is an apparent problem during anaesthesia and surgery. This occurs intra-operatively as well as postoperatively when it can last for several days. Due to the nature of the capillary endothelial wall, there is an inevitable leak of protein-free fluid to interstitial tissues. Normally, the lymph system should recirculate the extravasated fluid. As long as this is managed by the lymphatic flow, a physiologic shift does not cause interstitial oedema. However, due to changed interstitial compliance, patients can extensively accumulate such fluid and thereby increase their postoperative weight, which has been attributed to increased morbidity and mortality [17]. Fluid shifting is also particularly exaggerated during pathological conditions and if addressed wrongly by giving large amounts of crystalloids, this could be even more detrimental to the patient [1,17]. This condition has commonly been addressed as part of 'third spacing' during anaesthesia and surgery [18–21].

When analysing the computed curves, it is obvious that

- (1) Some subjects immediately distribute fluid to peripheral spaces without any resistance (Figure 3(c),(d)).
- (2) Other subjects may eliminate all infused fluid at a rate equivalent to the infusion rate; with as high a rate as 40 ml/min (Table 3, e_{\max} , subjects 2, 6 and 10).
- (3) Finally, some subjects may receive the infused fluid almost without any sign of elimination response, having only a low basal elimination throughout the whole experiment (Figure 3(c), Table 3, subjects 2, 3 and 6).

In earlier fluid kinetics, the distribution volumes of the central fluid space V_1 and peripheral fluid space V_2 were estimated [2]. If the volume V_1 is estimated to be large, it corresponds to a state where the infusion causes a slow dilution of the endogenous tracer haemoglobin in V_1 . This means that

- (1) The central fluid space V_1 has a low compliance, or V_1 shows a weak and slow response by delayed compliance [22] and cannot initially be expanded, which forces the infused fluid to be located elsewhere.

Table 3. e_{\max} (ml/min) is the maximum empirical measured urinary flow, u_{tot} (ml) is the final measured urine. T_{tot} is computed by $T_e + T_l + T_u$, and reflects the total delay.

Subject	σ	$1/\mu$	k_{el}	k_{b}	E_{eff}	T_{tot}	e_{\max}	u_{tot}
1	0.85	2.0	38	0.13	5.1	3	32	1040
2	0.91	2.2	12	4.41	54.5	11	28	1702
3	0.88	3.5	8	3.40	28.3	6	21	1305
4	0.70	0.9	29	0.09	2.7	11	9	467
5	0.59	21.9	40	0.03	1.1	55	12	562
6	0.93	6.1	28	1.24	35.3	11	40	1340
7	0.55	4.5	7	0.72	4.7	26	2	307
8	0.48	8.3	36	0.98	35.2	33	16	914
9	0.69	2.0	14	1.39	20.0	32	16	1243
10	0.37	1.7	8	4.20	34.3	23	32	1253

- (2) There is an osmotic imbalance that is equalized during infusion, which causes an immediate fluid shift into the cellular space.
- (3) The endothelium is damaged, and fluid leaks more profoundly into V_2 .

Therefore, when we compute the parameters with a fixed central volume, the rate constants k_{12} and k_{21} may not be able to cope with a fast and constant rate of fluid shift from V_1 to V_2 during infusion (Figure 2). We modelled this by dividing the rate of infusion between V_1 and V_2 by a parameter σ , the bypass factor. This parameter is explained by the fact that k_{12} and k_{21} cannot be determined adequately if parts of the infusion do not cause any expansion of V_1 , but goes directly into V_2 .

However, if a pronounced vasodilatation of the vascular bed occurs and fluid accumulates quickly in the central compartment during infusion, we would expect σ to be close to 1 or even higher. Earlier fluid kinetics would then estimate a small volume of distribution. This effect may arise when the subject suffers from hypovolaemia or from other disease states that distribute fluid centrally.

As stated earlier, peripheral fluid accumulation can either be regarded as normal extravasations where recirculation occurs or be regarded a more permanent accumulation due to dehydration or inadequacy by the lymph system. A low σ combined with a low k_t and a low elimination efficacy E_{eff} suggests that the subject initially accumulates fluid peripherally and may not readily dispose of the excess fluid.

The delay time of elimination (T_1) from the central fluid space depends on a complex feedback mechanism that involves neurohumoral systems. T_1 was found to be in the region of 1 min, but for one subject, it was as high as 9 min. As seen in Figure 3 for the four chosen subjects, T_1 was estimated to (a) 1.5 min, (b) 3.8 min, (c) 3.6 min and (d) 8.9 min, respectively.

The intermediate compartment V_E together with the turnover time T_e and the delay time T_u reflects the pathway of urine from the renal filtration in the kidney through the urinary bladder to the sampling point outside the patient. This pathway should to some degree be dependent on catheter placement and function. The sum of the delays, T_{tot} , is presented in Table 3.

The results in this study are rather surprising. This was a standardized group of fairly young and healthy volunteers. They were all fasting using the same morning regime with a light breakfast before the experiments. In spite of this, they showed quite different responses to the infused fluid. Figures 2 and 3 together with Table 3, e_{max} and u_{tot} underline those differences empirically.

As for the Nadler calculations, some subjects (example given, Figure 3(a)) show small peripheral accumulation, while other subjects show a more pronounced peripheral accumulation. However, the clearance of fluid from the peripheral space is directly connected to the E_{eff} and is particularly low for subjects 5 and 7. In general, the subjects were likely to accumulate three times as much of the infused fluid peripherally as centrally ($1/\mu = 2.7$, Table 2) in spite of a rather instant ability to start elimination ($T_u = 4.2$ min, Table 2).

At the most extreme, E_{eff} varied from 1 to 54 ml/min (Table 3). This parameter reflects the combined effect of maximum urinary flow e_{max} (ml/min) and total urinary output u_{tot} (ml). Figure 3(a) shows a fast and pronounced response to the fluid administration ($E_{\text{eff}} = 28$ ml/min, $k_{\text{el}} = 8$, $k_b = 3.4$ ml/min). Figure 3(b), on the other hand, shows a normal elimination, but has merely no basal elimination ($E_{\text{eff}} = 1$ ml/min, $k_{\text{el}} = 40$, $k_b = 0.03$ ml/min). The high value of k_{el} is motivated by the steep response of elimination that occurs at $t \approx 40$ min. However, the elimination decays quickly and stops, leaving only a slow equilibration between V_1 and V_2 which motivates the low E_{eff} . Figure 3(c) shows

almost no response at all to the fluid infusion ($E_{\text{eff}} = 5$ ml/min, $k_{\text{el}} = 7$, $k_{\text{b}} = 0.7$ ml/min), but in comparison to Figure 3(b), the subject shows a weak disposal of excess fluid through k_{b} which motivates a higher E_{eff} . The subject in Figure 3(d) dampens the expansion of V_1 quickly through urinary output giving a high elimination efficacy ($E_{\text{eff}} = 35$ ml/min, $k_{\text{el}} = 36$, $k_{\text{b}} = 1.0$ ml/min).

Our study has several limitations. This is a macro model dependent on sampling from venous blood in an antecubital vein. It can only reflect what happens at that actual sampling spot. We have not validated what happens in pertinent tissues nor have sampled for sodium in plasma or urine, calculated plasma osmolality or measured any hormones.

The results are also dependent on the amount and rate of infusion. An infusion rate that is too high may cause non-physiological distribution and correspondingly, a rate that is too low may cause low accuracy and scattered data. Previous studies, however, conducted mainly on sheep, indicate that the kinetic parameters are fairly robust within clinical feasible limits [23,24]. Furthermore, it has been shown that the kinetic parameters may be used for controlling infusion rate, in order to achieve a pre-determined target dilution [25].

The modelling of fluid shifts has also taken into account that fluid distributes through several fluid spaces, which have a wide range of non-linear compliance and perfusion properties [26]. We may only quantify an average result of all these effects.

In this model, the rate of infusion was computed to be proportional to the weight. The question then arises whether it would be more accurate to use the size of the fluid spaces, rather than the weight, when determining the size of bolus. Unfortunately, this requires tracer dilution techniques to determine the size of the body fluids accurately enough, and furthermore these methods that are not practical in clinical use.

However, this is the first attempt to simultaneously model plasma dilution and urinary output which is an improvement compared with conventional volume kinetics.

Today, there is a lack of tools in analysing fluid distribution in means of flows, distribution factors and time delays in order to get comparable results for future research and clinical applications. This model should be able to provide tools to better understand fluid distribution during different pathological states. By using fluid kinetic analysis, we may point out more accurately why subjects handle excess fluid differently.

Conclusion

It was possible to model plasma dilution and urinary output simultaneously. Results were varying in spite of a homogenous volunteer group. This may be explained by differences in tissue and hormonal responses to fluid boluses, which needs to be explored in the future. The model also allows quantification of fluid distribution by a finite set of pertinent parameters, over time.

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