Relationship between kinetics of albumin-bound bilirubin and water-soluble urea in extracorporeal blood purification

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Abstract

Background. The purpose of the study was to examine the relationship between urea and conjugated bilirubin kinetics during extracorporeal liver support (ELS) therapy and to determine the dose of therapy for urea and conjugated bilirubin as markers for water-soluble and protein-bound solutes, respectively.

Methods. Kinetics of urea and bilirubin were described by standard two-compartment models with central clearance, constant intercompartment clearance, constant generation rate and constant volume. While the concentration of urea was assumed as equilibrated between compartments at the beginning of ELS therapy, the concentration of conjugated bilirubin between compartments was assumed to follow the partition of albumin between plasma and interstitial spaces. Treatment dose was calculated as removed solute mass and fractional solute removal.

Results. Seven patients were studied during 15 treatments lasting at least 6 h. Bilirubin distribution volume of 14.8 ± 5.4 L was not different from urea extracellular water volume of 15.0 ± 2.8 L. The correspondence between models was used to predict the mass of bilirubin removed based on urea kinetic analysis, average data from bilirubin kinetics, as well as selected treatment and patient information. The prediction of bilirubin mass removed based on this reduced information was not different from the mass of solute removed based on complete bilirubin kinetic analysis.

Conclusions. The correspondence between kinetics of urea and conjugated bilirubin can be used to identify the bilirubin distribution volume from urea kinetic analysis. This information is then useful to estimate and predict the solute removal of conjugated bilirubin in ELS.

Keywords: bilirubin kinetics; distribution volume; extracorporeal liver support therapy; treatment dose; urea kinetics

Introduction

In haemodialysis, urea kinetic analysis is widely used to prescribe and to control the efficiency and the dose of dialysis therapy [1, 2]. Urea is easily dialysed and measured by standard laboratory equipment, it is removed in considerable amounts during dialysis and it is one of the major end products of protein catabolism, all of which make it a prime candidate to measure and to control the process of dialysis. However, it is not a uraemic toxin, and the exclusive focus on urea to prescribe an adequate dose of dialysis has been questioned [3, 4]. In fact, owing to selective urea transporters found throughout the body [5, 6], urea is a rather unique solute and the question arises whether this molecule is a good surrogate for other solutes with limited membrane permeability such as creatinine and other guanidino compounds and, most importantly, well-known uraemic toxins such as p-cresyl sulphate and indoxyl sulphate. The latter are largely protein bound [7–10] but the free fraction of these solutes may be removed during haemodialysis and haemodiafiltration [8].

Conjugated bilirubin is for extracorporeal liver support (ELS) what urea is for haemodialysis. Conjugated bilirubin is of little toxicity and easily measured by routine tests, but in the presence of albumin, conjugated bilirubin is protein bound [11] and therefore only poorly cleared from blood by haemodialysis and haemodiafiltration [12–14]. Its removal, however, is enhanced by adsorptive techniques such as fractional plasma separation and adsorption [15–17]. Significant amounts of conjugated bilirubin are removed during ELS of acute-on-chronic liver failure. In these techniques, urea is also removed by concomitant haemodialysis. The treatment of acute liver failure by such techniques usually supervised by nephrologists and dialysis staff therefore provides a unique setting to analyse and to compare the kinetics of water soluble solutes such as urea and protein-bound solutes such as conjugated bilirubin within the same treatment.
The purpose of this study was to compare previously validated two-compartment kinetic models of urea and bilirubin, to demonstrate the relationship between models and model parameters for both solutes and to predict the removal of one solute based on kinetic information available from the other solute. This approach could be of more general interest as it has the potential to be extended to other protein-bound solutes studied in extracorporeal blood purification.

Materials and methods

The study was done in patients with acute-on-chronic liver failure and approved by the Ethics Committee of the Medical University of Graz. Informed consent was obtained in accordance with the Declaration of Helsinki. ELS was provided by the Prometheus system (Fresenius Medical Care, Bad Homburg, Germany). This system combines high efficiency dialysis done in a primary circuit with fractionated plasma and albumin separation into a secondary circuit from which albumin-bound solutes are removed by adsorption [15–17].

Treatments were initiated after failure to respond to standard medical treatment and were performed for 6, 8 or 10 h at identical blood flows (Qb) and dialysate flows in all patients (200 and 300 mL/min, respectively). The same dialysis machine (4008H; Fresenius Medical Care) was used during the entire study. The flow in the secondary circuit was set to 300 mL/min.

Each study consisted of up to four treatments done on consecutive days. Details of the analytical methods are described elsewhere [16, 19]. Urea concentrations, whereas pre-treatment urea concentrations in intracellular compartment of urea kinetics. The total distribution volume of bilirubin kinetics is assumed to coincide with the extracellular compartment of urea kinetics. The arrows indicate flows into, between and out of compartments. Intercompartment clearance for urea (Ku) and intercompartment clearance for bilirubin (Kb).

\[
V_{ct} \frac{db}{dt} = -K_b b_b + K_u \left( \frac{b_i}{C_0} - b_b \right) + G_b,
\]

where \( f_h \) refers to the central fraction of extracellular water and where the two compartments refer to plasma (\( V_e \), \( f_p \)) and interstitial [\( V_i \), (1\( - f_p \))] volumes, respectively. Subscripts p and interstitial refer to plasma and interstitial compartments and to bilirubin, respectively. \( K_u \) refers to extracorporeal bilirubin clearance and \( G_b \) refers to bilirubin generation rate.

In this previous study [19], it was noted that the value identified for \( V_e \) (1\( - f_p \)) [equation (5)] relating to interstitial volume was much smaller than expected. It was speculated that this could be due to the low albumin concentration in interstitial fluid. Since conjugated bilirubin is close to 100% bound to albumin [11], the distribution of conjugated bilirubin throughout the extracellular space can be assumed to correspond to the distribution of albumin and to the different levels of albumin in plasma and interstitial fluid [21, 22]. The variable \( f \) introduced in equation (4) and equation (5) therefore refers to the ratio of interstitial to plasma albumin concentration in the steady state. Unlike previously, the contribution of residual clearance was not taken into account in the current description.

Parameter identification

The extracorporeal clearance (\( K_u \), \( K_b \)) determined experimentally was used as an input to the models described above. The model output was obtained by numerical integration (fourth order Runge-Kutta algorithm with variable step size) to provide the time course of urea and bilirubin concentrations. In these calculations, the extracellular fraction \( f_e \) of total body water was set as 1/3 following standard assumptions [1]. The central fraction \( f_i \) was assumed as 1/3 of extracellular water volume as determined in the preceding study [19]. Interstitial albumin concentration was assumed as 1/3 of the plasma albumin concentration as determined elsewhere [23]. Therefore, the same relationship was used to describe pre-treatment bilirubin concentrations, whereas pre-treatment urea concentrations in intracellular and extracellular compartments were assumed as fully equilibrated.

Three parameters were identified for each solute: total distribution volumes (\( V_e \), \( V_i \)), intercompartment clearances (\( K_u \), \( K_b \)) and solute generation rates (\( G_u \), \( G_b \)) so that six parameters were modelled for both solutes. To identify these parameters, the time course of urea in the extracorporeal compartment and of bilirubin in the plasma compartment was fit to experimental data using a least square minimization simplex method (MathLab 7.0; The MathWorks Inc., Natick, MA).

Treatment quantification

Solute reduction ratio (SRR) for urea (index u) or bilirubin (index b) was quantified as:

\[
SRR_{ub} = \left( 1 - \frac{c_5}{c_0} \right) \times 100\%,
\]

where \( c_0 \) and \( c_5 \) refer to plasma concentrations at the beginning and at the end of treatment, excluding the effect of the post-treatment solute rebound.

The post-treatment rebound (Reb) for urea (index u) or bilirubin (index b) was measured as:

\[
Reb = \frac{c_5 - c_0}{c_0} \times 100\%.
\]
Rebu,b = \frac{c_{60}}{c_1} - 1, \quad (7)

where \( c_1 \) and \( c_{60} \) refer to plasma concentrations at the end of treatment and 60 min later, respectively.

Treatment dose for urea was calculated as the solute removed (\( M \)) relative to the total solute mass present at the beginning of the treatment:

\[ F_u = \frac{M}{c_0 V_t}, \quad (8) \]

where \( c_0 \) (in mg/mL) is the initial solute concentration, \( V_t \) (in mL) is the total distribution volume obtained from parameter identification, and where the mass of solute removed was calculated as:

\[ M = \int_{t=0}^{t} K c_o dt, \quad (9) \]

where \( K_t \) and \( c_t \) refer to extracorporeal clearance and concentration in the extracellular compartment as functions of time.

The fraction of bilirubin removed (\( F_b \)) was calculated in analogy to equation (8) and equation (9) accounting for fractions of compartment volumes (\( c_t, f \)) and for the relationship \( f \) between equilibrated plasma and interstitial concentrations:

\[ F_b = \frac{M}{c_0 V_t (f_p + f (1 - f_p))}, \quad (10) \]

**Prediction**

When the kinetics of urea and bilirubin are examined in the same subject, \( V_e \) is defined by two solutes, either as the total distribution volume of bilirubin kinetics [equation (4) and equation (5)] or as the extracellular volume of classic urea kinetics [equation (3); Figure 1]. This correspondence can be used to substitute information obtained in one kinetic model for information required in the other model. This was done to predict the mass of bilirubin removed based on urea distribution volume identified from urea kinetic modelling, bilirubin intercompartment clearance (\( K_{ib} \)), bilirubin generation rate, bilirubin concentration at treatment start (\( c_0 \)) as well as bilirubin clearance (\( K_b \)) measured 2 h after treatment start.

**Statistics**

Changes in urea and conjugated bilirubin blood levels and clearances over time were assessed by Friedman test. The Gaussian distribution was verified by Kolmogorov–Smirnov test and the correspondence of volumes as well as treatment dose measures were compared by paired \( t \)-test. Correlations between parameters were calculated using Pearson’s test. A probability \( P < 0.05 \) was considered significant to reject the null hypothesis.

**Results**

Only studies providing a complete set of intra- and post-treatment urea and bilirubin concentrations were considered for kinetic modelling so that 15 treatments done in seven patients entered final analysis (Table 1).

Extracorporeal blood treatment provided a significant decrease of urea and bilirubin concentrations and SRRs in the range of 68 and 55%, respectively, as well as significant 1-h post-treatment rebounds in the range of 12% for both urea and bilirubin, indicating two-compartment kinetics (Figure 2, Table 2).

Bilirubin clearance was 23.9 ± 4.5 mL/min at \( t = 0.5 \) h and continuously decreased during the treatment, while urea clearance remained stable at 145 ± 12 mL/min (Figure 3). Therefore, a variable clearance was assumed for bilirubin, while a constant clearance was assumed for urea kinetic modelling, respectively (Table 2). Parameter identification provided a total bilirubin distribution volume of 14.8 ± 5.4 L (Table 3). This volume was not different from extracellular water volume of 15.0 ± 2.8 L assumed as one-third (\( f_e = 1/3 \)) of total urea distribution volume and identified from urea kinetic modelling (\( P = 0.90 \), paired \( t \)-test). Most model parameters showed considerable variability with confidence intervals in the range of 50% between treatments (Table 3) and also between patients (Table 4). An example of urea and bilirubin concentrations

![Graph](https://example.com/graph.png)

*Fig. 2. Urea and bilirubin concentrations. Urea (top panel) and bilirubin concentrations (bottom panel) relative to initial concentrations for intra- and post-treatment phases (average ± SD, \( n = 17 \)) for treatments lasting 6 circles, 8 squares and 10 h diamonds.*
In this study, the kinetics of urea and conjugated bilirubin, two metabolites largely different especially with regard to albumin binding, were analysed during 15 extracorporeal blood purification treatments done in seven acute-on-chronic liver failure patients.

Both urea and bilirubin kinetics were described by separate two-compartment models using different model parameters. It was observed that the total distribution volume of bilirubin (14.8 ± 5.4 L) was not different from the extracellular volume identified from urea kinetics (15.0 ± 2.8 L). Based on this correspondence and using average bilirubin kinetic parameters as well as selected information from individual treatments, the total removal of bilirubin identified from complete kinetic analysis (M_p; r = 0.97, F_p; r = 0.66; Figure 5).

Discussion

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The correspondence between kinetic models in \( V_u \) and \( V_b(t) \) was used to predict the total mass (\( M_p \)) as well as the fraction (\( F_p \)) of bilirubin removed from urea kinetic volume \( V_u \), average bilirubin generation rate (\( G_b = 0.45 \text{ mg/min} \)) and average bilirubin intercompartment clearance (\( K_{ib} = 40.7 \text{ mL/min} \)) as well as individual bilirubin concentration at treatment start (\( c_{ib0} \)) and individual bilirubin clearance (\( K_{ib} \)) 2 h after treatment start (Tables 5 and 6). \( M_p \) as well as \( F_p \) were not different (\( P = 0.27 \) and 0.66, respectively, paired \( t \)-test) and highly correlated to the mass as well as to the fraction of bilirubin removed determined from complete bilirubin kinetic analysis (\( M_p, r = 0.97, F_p, r = 0.66; \) Figure 5).

**Table 2.** Treatment characteristics (n = 15)

<table>
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<th>#</th>
<th>ID</th>
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<th>( V_u(t) ) (L)</th>
<th>( V_b(t) ) (L)</th>
<th>( K_{iu} ) (mL/min)</th>
<th>( K_{ib} ) (mL/min)</th>
<th>( G_u ) (mg/min)</th>
<th>( G_b ) (mg/min)</th>
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<td>0.24</td>
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*a*, treatment number; ID, patient ID; \( V_u \), urea distribution volume; \( V_u(t) \) and \( V_b(t) \), extracellular urea and bilirubin distribution volumes; \( K_{iu} \) and \( K_{ib} \), intercompartment urea and bilirubin clearances; \( G_u \) and \( G_b \), urea and bilirubin generation rates; RMSE_u and RMSE_b, root mean square errors of urea and bilirubin kinetic models.

*\( *P \) = 0.90 compared to \( V_u(t) \).
This was more than the corresponding SRR of 68 and the treatment were removed by combined diffusive and ad-

sorption, such as conjugated bilirubin and dialysis for freely water-soluble solutes, such as urea. On average, 86 and 66% of total urea and bilirubin mass present at the beginning of the treatment were removed by combined diffusive and absorptive elimination within the same treatment (Table 5).

This was more than the corresponding SRR of 68 and 55% (P = 0.001, paired t-test) because of ongoing solute generation during the treatment phase (Table 3). With long treatment times and ongoing solute generation, solute removal is therefore underestimated when focussing on reduction ratio. The concomitant removal of both solutes allowed for a comparison of solute kinetics and an examination of different or shared characteristics under comparable experimental conditions.

A close correspondence between distribution volumes was noted. The total distribution volume of bilirubin is generally assumed to correspond to extracellular space, which includes the plasma compartment. Conjugated bilirubin is largely albumin bound [11], and since albumin and protein concentration in the interstitial space is postulated as 1/3 (con-

stant parameter f in this study) of the plasma concentration.

With this model assumption, the bilirubin distribution volume identified from concomitant urea kinetic modelling.
Table 6. Solute removal in individual patients (n = 7)

<table>
<thead>
<tr>
<th>ID</th>
<th>$M_u$ (g)</th>
<th>$F_u$</th>
<th>$M_b$ (g)</th>
<th>$F_b$</th>
<th>$K_u$ (mL/min)</th>
<th>$E$ (%)</th>
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<td>1.04 ± 0.42</td>
<td>0.72 ± 0.1</td>
<td>18.7 ± 1.2</td>
<td>4.4 ± 1.6</td>
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<td>80.3 ± 4.2</td>
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<td>0.34 ± 0.1</td>
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<td>0.48</td>
<td>0.58</td>
<td>15.7</td>
<td>30.46</td>
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*ID, patient ID; $M_u$, mass of urea or bilirubin removed; $F_u$, fractional solute removal of urea or bilirubin; $K_u$, bilirubin clearance; $E$, relative error of estimated solute removal.

The total urea distribution volume was $56 ± 9\%$ when expressed as a fraction of body mass (Tables 1 and 4), which is rather high when compared to average dialysis patients where this value ranges from 43% [24] through 49% [25] up to 55% [26]. The high volume found in acute liver patients could be explained by vasodilatation and volume expansion common with acute-on-chronic liver failure patients.

With the exception of Patient #4 where post-dialysis urea rebound was unexpectedly small (data not shown) and where intercompartment clearance was exceptionally high, the average urea intercompartment clearance in this study (666 mL/min) was somewhat lower than that identified in renal failure patients (800 mL/min) [1]. These effects are most likely related to altered patient haemodynamics [18,27–29].

Excluding extreme values median urea generation rate (16 mg/min) was comparable to that observed in haemodialysis (~7 mg BUN/min [1], equivalent to 15 mg urea/min) [30].

The intercompartment clearance for bilirubin (40.7 ± 64 mL/min) was much smaller than previously reported in eight patients (103 ± 108 mL/min) [19]. This difference is due to accounting for lower bilirubin concentrations (assumed as 1/3 of plasma concentrations) in the interstitial part of the extracellular volume in the present study. The low value can be explained by slow microvascular exchange during dialysis [31] as the transport of albumin-bound bilirubin is filtration controlled and therefore much smaller than urea transport. Bilirubin generation rate (0.45 ± 0.24 mg/min) was somewhat higher than that reported in the previous study (0.33 ± 15 mg/min) [19]. It was assumed as constant for individual treatments, as its identification from intradialytic changes is almost impossible because several processes are going on at the same time.

Based on the correspondence between structure and parameters of different models, it is not surprising that the information obtained for a specific solute such as urea can be used to compute the output for other solutes such as bilirubin. It is likely that the correspondence between urea and bilirubin models can be improved even further. The comparison presented in this study is akin to a previous comparison between urea and creatinine, where the different kinetics could be traced to a single parameter of membrane permeability [32]. In the end, it is the aim to provide a unified model structure for solutes distinguished from urea by membrane permeability such as with creatinine or by protein binding such as with bilirubin. Finally, such models need to be applied to toxic substances and not just to simple markers of uraemia and liver failure.

In conclusion, the kinetics of urea and conjugated bilirubin, solutes with distinct differences in their solubility in plasma as well as in their distribution volumes, show several parallels. The correspondence between kinetics of urea and bilirubin can be used to substitute information such as the bilirubin distribution volume from urea kinetic analysis. This information is then useful to estimate and predict the solute removal of conjugated bilirubin based on treatment information such as bilirubin clearance and changes in bilirubin concentration during extracorporeal liver therapy.

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