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Ceftriaxone Pharmacokinetics during Iatrogenic Hydroxyethyl Starch-induced Hypoalbuminemia

A Model to Explore the Effects of Decreased Protein Binding Capacity on Highly Bound Drugs

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Background: **Although various drugs used by anesthesiologists highly bind to plasma proteins, the impact of iatrogenically induced hypoproteinemia on their pharmacologic effects has never been investigated. The authors determined the pharmacokinetics of ceftriaxone, a cephalosporin that binds strongly to albumin in postsurgical patients with hydroxyethyl starch-induced hypoalbuminemia.**

Methods: **Eleven hypoalbuminemic (serum albumin < 25 g/l) patients and age (± 5 yr)–, sex-, and body surface area (± 10%)–matched healthy volunteers received a 2-g ceftriaxone dose infused over a 15-min period. Fourteen venous blood samples were collected during the 24-h study period. Free ceftriaxone concentrations were determined by ultrafiltration. Antibiotic concentrations in plasma and ultrafiltrate were measured by ion-paired reversed-phase chromatography. The pharmacokinetic parameters derived from total and free antibiotic concentrations were determined using a noncompartmental method. Data are expressed as median and range.**

Results: **The pharmacokinetic parameters derived from total ceftriaxone concentrations were similar for the two groups except for the median corrected volume of distribution at steady state, which was increased ($P = 0.05$) to 0.18 l/kg (range, 0.11–0.29 l/kg) in patients, compared with 0.15 l/kg (range, 0.13–0.22 l/kg) in volunteers. The area under the free ceftriaxone concentration–time curve was twice as high in patients as in volunteers (median 192, range 114–301 *vs.* median 122, range 84–169 $h \cdot mg^{-1} \cdot l^{-1}$; $P = 0.03$). Moreover, the free ceftriaxone concentration remained more than 4 mg/l during more time in patients (median, 16.7; range, 12.6–21.4 *vs.* median, 11.1; range, 6.0–19.0 h; $P = 0.03$).**

Conclusions: **Compared with healthy volunteers, patients with iatrogenic hypoalbuminemia have higher free ceftriaxone concentrations during the 24 h after antibiotic administration. This modification increases drug distribution into extravascular space and may enhance effectiveness. (Key words: Drug effectiveness; hypovolemia; volume expander.)**

VARIOUS drugs used by anesthesiologists are highly bound to plasma proteins. For example, more than 90% of alfentanil, sufentanil, midazolam, or bupivacaine in the bloodstream is rendered inactive through binding to circulating plasma proteins in healthy subjects.[1–3] Albumin is the leading plasma protein responsible for binding of acidic drugs, whereas α_1-acid glycoprotein binds mainly basic drugs.[3] During the perioperative period, various situations may lead to iatrogenic hypoproteinemia, such as the infusion of high volumes of crystalloid or hydroxyethyl starch solutions. Administration of highly bound drugs in these situations may alter drug disposition and effectiveness. Although a number of pharmacokinetic studies have been conducted on hypoalbuminemic patients, mainly with cirrhosis, no study has evaluated the impact of the diluting effect of solutions infused as plasma substitutes on the pharmacologic effects of highly protein-bound drugs administered during the perioperative period. Moreover, because the concentration of binding proteins in extravascular fluids is approximately one third that in plasma,[4] hypoalbumin-

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emia may result in saturation of binding of highly bound drugs both in plasma and in extracellular fluids and, finally, in modifications of the pharmacologic effects of these drugs.[4]

Ceftriaxone is a β-lactam with concentration-dependent albumin binding[5]: its free fraction ranges from 4% to 17% when its concentration varies from 0.5 to 300 mg/l. Hypoalbuminemia is thus expected to result in a higher free fraction of ceftriaxone, with possible consequences on its clearance and distribution. Moreover, ceftriaxone protein binding is known to be partly restrictive,[6] *i.e.*, this binding may hinder or prevent drug distribution or elimination, so that its bactericidal effect is mostly attributed to the unbound concentration rather than the total concentration. Hence, a modification of free concentration kinetics could have an impact on drug effectiveness.

The current study was therefore designed to determine the pharmacokinetics and pharmacodynamics of ceftriaxone after administration to previously healthy postsurgical patients with iatrogenic hydroxyethyl starch-induced hypoalbuminemia. Ceftriaxone was used as a model to explore the effects of decreased protein binding capacity on highly bound drugs.

Patients and Methods

The study was conducted in the surgical intensive care unit of Bicêtre Hospital, a 1,000-bed teaching hospital in France. Approval was obtained from the Ethical Committee of Ambroise Paré Hospital, Boulogne Billancourt, and informed consent was obtained from each subject or the subject's closest relative.

Participants

Postsurgical patients between 18 and 60 yr of age were enrolled when they were hemodynamically stable, were within 20% of their ideal body weight, had severe hypoalbuminemia (serum albumin level < 25 g/l, normal value ≥ 40 g/l), and had received at least 1,000 ml hydroxyethyl starch (Elohes 6%; Fresenius France Pharma, Sèvres, France) during the 24 h preceding inclusion. Patients were not included when they had known hypersensitivity to β-lactam antibiotics, renal failure with estimated creatinine clearance less than 60 ml/min, hepatic failure with prothrombin time less than 70% or bilirubin level more than 2 times normal, leukopenia with granulocyte count less than 0.5×10^9/l, or were receiving vasopressors or drugs able to interfere with ceftriaxone binding to albumin (*e.g.*, warfarin, sulfamethoxazole, salicylate, ibuprofen, furosemide). Patients with preexisting severe disease and women of childbearing age with a positive urine pregnancy test were also excluded.

For each patient, body surface area was determined using a standard formula based on height and weight.[7] Creatinine concentration in plasma was measured before starting antibiotic infusion to determine creatinine clearance according to the Cockcroft and Gault formula without adjustment for ideal body weight.[8] Serum total proteins, albumin, and immunoglobulin G (IgG) levels (normal values, 68–80, 35–50, and 6–12 g/l, respectively) were determined at the beginning of the pharmacokinetic study. Serum albumin was measured again at the end of the protocol to rule out significant variations during the 24-h study.

Healthy volunteers matched to patients according to age (± 5 yr), sex, and body surface area (± 10%) were also enrolled. None of the volunteers had any remarkable history of organ dysfunction, and none took any medication during at least the month preceding study entry. The subjects were nonsmokers, and alcohol consumption was prohibited for at least 24 h before the study period. The subjects fasted for at least 8 h before and for the first 4 h after the start of their antibiotic infusion. After dosing, 300 ml of water was drunk at 4-h intervals.

Drug Formulation, Sampling, and Assay

Ceftriaxone was purchased from Roche Pharma (Produits Roche, Neuilly-sur-Seine, France) as a dry powder. Each vial contained 2 g of ceftriaxone and was reconstituted with 30 ml of sterile water just before administration, according to the manufacturer's recommendations. Two grams of ceftriaxone was infused intravenously over a 15-min period with a perfusion pump. Venous blood samples were drawn from the arm contralateral to the antibiotic infusion before drug administration and 0.25, 0.33, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 16, 20, and 24 h after the start of the antibiotic infusion and were collected in heparin-coated tubes. After mixing, samples were centrifuged for 10 min at approximately 1,000*g* and 4°C to separate the plasma, which was stored at −70°C pending ceftriaxone assay. Measurements of total and free antibiotic levels were recorded within 15 days after sampling.

Free ceftriaxone concentrations were determined by ultrafiltration using the Microsep 3 K Micropartition System (Filtron Technology Corporation, PolyLabo, Stras-

bourg, France). After warming, plasma samples (500 μl) were equilibrated for 1 h at 37°C and then centrifuged at 1,500*g* for 1 h at 37°C. The free concentration was determined from the ultrafiltrate. Although preliminary experiments indicated that nonspecific binding of ceftriaxone to the filter membrane was low (< 4%), adjustments were made to take this adsorption into account for the estimation of the free fraction.

The ceftriaxone concentrations in plasma and ultrafiltrate were determined using a validated, ion-paired, reversed-phase chromatography assay described elsewhere.[9] The calibration was linear, in the range of 2.5–500 mg/l in plasma and in the range of 0.5–50 mg/l in the ultrafiltrate. The quantification limit of the assay was 2.5 mg/l in plasma and 0.5 mg/l in the ultrafiltrate. The overall interassay coefficient of variation was less than 10%, and the overall intraassay coefficient of variation was less than 6% over the entire calibration range.

Pharmacokinetic–Pharmacodynamic Analyses

Total (bound and unbound) and free (unbound) ceftriaxone concentration-*versus*-time data were fitted individually by noncompartmental analysis using the Siphar software version 4.0 (Simed, Créteil, France). The maximum ceftriaxone concentration was obtained from direct observation of the plasma concentration-*versus*-time curves. The minimum ceftriaxone concentration was defined as the lowest observed plasma concentration and was reached 24 h after the infusion started. The area under the plasma ceftriaxone concentration-*versus*-time curve (AUC) was calculated from the time of ceftriaxone administration to the last measurable plasma concentration using log-linear interpolation. Extrapolation of the AUC from the time of the last measurable ceftriaxone concentration to infinity was calculated by dividing the last plasma concentration by the first-order rate constant of the terminal phase of the profile. The first-order rate constant was determined by linear regression of the terminal phase of the log-transformed plasma ceftriaxone concentration data after visually identifying the terminal portion. The sum of these two components was the estimated total AUC ($AUC_{0\text{-}\infty}$). The terminal elimination half-life of ceftriaxone was calculated from the first-order rate constant of the terminal phase of the plasma concentration-*versus*-time profile. The total body clearance for total ceftriaxone was defined as the ratio of the ceftriaxone dose to $AUC_{0\text{-}\infty}$. The free fraction of ceftriaxone was defined as the ratio of the adjusted free to the total antibiotic concentrations. The area-weighted average free fraction of ceftriaxone in plasma (f_u) was calculated as the ratio of free ceftriaxone $AUC_{0\text{-}\infty}$ to total ceftriaxone $AUC_{0\text{-}\infty}$.[10] The volume of distribution at steady state for unbound ceftriaxone (Vd_{ssu}) was calculated according to the noncompartmental method, based on AUMC (area under the first moment of the plasma concentration-*versus*-time curve from 0 to infinity, calculated using the log-linear trapezoidal rule) and the $AUC_{0\text{-}\infty}$. The corrected volume of distribution of total ceftriaxone at steady state (Vd_{ss}) was calculated as

$$Vd_{ss} = f_u \times Vd_{ssu}.^{10}$$

According to Øie *et al.*,[4] Vd_{ssu} is expected to be linearly related to $1/f_u$:

$$Vd_{ssu} = V_p \times (1 + R_{ei}) \times 1/f_u + (V_e - V_p \times R_{ei})$$

where V_p and V_e are the physiologic volumes of the vascular and extravascular spaces, respectively, and R_{ei} is the ratio of the total amount of interstitial to intravascular albumin. Because Vd_{ssu} and f_u are both subject to uncertainty, the parameters (slope and intercept) of their relation could not be determined by ordinary regression without bias and were determined by orthogonal regression (*i.e.*, the residuals were minimized along two orthogonal directions).[11]

The French breakpoint determining ceftriaxone effectiveness is 4 mg/l, *i.e.*, strains with higher minimal inhibitory concentrations are not considered sensitive. For each patient, we calculated the time that free ceftriaxone concentration in plasma remained more than 4 mg/l.[12]

Ceftriaxone Binding to Hydroxyethyl Starch

The potential binding of ceftriaxone to hydroxyethyl starch was assessed by exposing the antibiotic to different hydroxyethyl starch concentrations. To obtain conditions comparable to those observed in our patients, pooled human plasma was diluted 50% with phosphate-buffered saline to obtain a final albumin concentration of 20–25 g/l; hydroxyethyl starch solutions were added to obtain final concentrations of 0, 6, and 12 mg/l, and the pH was adjusted to 7.4 before adding ceftriaxone. The free ceftriaxone fraction was then determined in triplicate in these preparations and in a commercial solution of 6 mg/l hydroxyethyl starch (Elohes 6%) without plasma.

Three ceftriaxone concentrations were tested (10, 50, and 250 mg/l), corresponding to the range of concentrations usually observed in plasma after administration of a 2-g ceftriaxone dose. Total and free ceftriaxone levels were determined after equilibration of the antibi-

otic in the solution tested for 30 min at 37°C. The absence of hydroxyethyl starch in the ultrafiltrate was verified using the iodine test.[13]

Statistical Analyses

Results are reported as median values and range. Two-way analysis of variance for repeated measures was used to compare the patients' serum albumin levels at the beginning and the end of the study. The Mann–Whitney U test was used to compare data between hypoalbuminemic patients and healthy volunteers, and the Kruskal-Wallis H test was used to compare the free ceftriaxone fractions in diluted plasma. Correlation between serum albumin level and total ceftriaxone clearance or Vd_{ss} were sought by linear regression. Statistical analyses were performed using the Stat View software version 4.5 for PowerPC (Abacus Concepts, Berkley, CA). For two-tailed tests, $P \leq 0.05$ was considered significant. Orthogonal regression analyses were performed using Winbugs.[14]

Results

Eleven patients (six men and five women) and 11 volunteers were studied. All completed the study without any adverse effect. Patients and volunteers were correctly matched except for their total protein and albumin concentrations in serum, which were halved in patients (median [range]: 41 [32–48] *vs.* 72 [66–82] g/l and 20.0 [12.5–24.9] *vs.* 46.1 [40.9–52.0] g/l, respectively; $P < 0.001$ for both parameters). Patients received a median of 2,000 ml (range, 1,000–4,000 ml) of hydroxyethyl starch during the 24 h preceding study entry. The median serum IgG level was 4.2 g/l (range, 3.1–6.8 g/l) at study entry. Patients and volunteers received comparable amounts of fluids during the 24-h study (median [range]: 2,000 [1,500–2,500] *vs.* 1,800 [1,600–2,100] ml, respectively; $P = 0.25$). Finally, patients' serum albumin levels did not vary significantly during the study period (median [range]: 20.0 [12.5–24.9] g/l at the beginning *vs.* 21.0 [12.5–27.6] g/l at the end of the study; $P = 0.15$).

The pharmacokinetic parameters derived from total ceftriaxone concentrations are shown in table 1. Estimates of Vd_{ss} for pair no. 5 had to be excluded from the comparison between patients and volunteers because the extrapolated AUMC for volunteer no. 5 was greater than 40% of the total area. For most pharmacokinetic parameters, no difference was observed between the two groups of subjects. However, the patients' free ceftriaxone fraction observed at maximum ceftriaxone concentration and minimum ceftriaxone concentration and the patients' median corrected Vd_{ss} were significantly higher than those of volunteers. No correlation ($P = 0.65$) was observed between total ceftriaxone clearance and serum albumin level. By contrast, a correlation ($r^2 = 0.25$, $P = 0.02$) was found between Vd_{ss} and serum albumin level, indicating that the Vd_{ss} value was higher at low albumin concentration. Finally, the interindividual variability for all pharmacokinetic parameters were similar for the two groups of subjects.

Table 1. Median (Range) Kinetic Parameters Derived from Total Concentrations of Ceftriaxone after a 15-min Intravenous Infusion of 2 g into Hypoalbuminemic Patients and Their Matched Healthy Volunteers

Parameter	Patients	Volunteers
C_{max} (mg/l)	247 (196–363)	246 (166–323)
Free fraction at C_{max} (%)	46*	18
C_{24h} (mg/l)	8 (4–21)	10 (4–23)
Free fraction at C_{24h} (%)	14†	10
Vd_{ss}‡ (l/kg)	0.18§ (0.11–0.29)	0.15 (0.13–0.22)
Cl (ml/min)	34.8 (22.8–53.7)	25.8 (19.0–59.3)
$t_{1/2\beta}$ (h)	5.9 (4.5–12.9)	6.4 (4.8–8.0)
$AUC_{0-\infty}$ ($h \cdot mg^{-1} \cdot l^{-1}$)	950 (621–1,460)	1337 (562–1,757)

* $P \leq 0.01$ *versus* volunteers.

† $P \leq 0.05$ *versus* volunteers.

‡ Pair No. 5 was excluded from the comparison (see text).

C_{max} = highest observed concentration in plasma; C_{24h} = concentration in plasma observed 24 h after the start of the antibiotic infusion; Vd_{ss} = corrected volume of distribution at steady state for total ceftriaxone; Cl = total body clearance for total ceftriaxone; $t_{1/2\beta}$ = elimination half-life; $AUC_{0-\infty}$ = area under plasma concentration–time curve from 0 to ∞.

The pharmacokinetic parameters derived from free ceftriaxone concentrations are given in table 2. Here too, estimates of Vd_{ssu} for pair no. 5 had to be excluded from the comparison between patients and volunteers for the same reasons. Compared with volunteers, patients had higher maximum ceftriaxone concentration, minimum ceftriaxone concentration, $AUC_{0-\infty}$, and f_u, and lower Vd_{ssu} and total body clearance for free ceftriaxone. Moreover, terminal elimination half-life was also lower in patients, but the difference did not reach significance ($P = 0.10$).

Total and free ceftriaxone concentration–time curves in plasma after intravenous infusion of 2 g ceftriaxone in patients and volunteers are shown in figures 1 and 2, respectively. Total antibiotic concentrations in plasma as a function of time were higher in volunteers, whereas free antibiotic levels were higher in patients throughout the study period. The free ceftriaxone concentration

Table 2. Median (Range) Kinetic Parameters Derived from Free Concentrations of Ceftriaxone after a 15-min Intravenous Infusion of 2 g into Hypoalbuminemic Patients and Their Matched Healthy Volunteers

Parameter	Patients	Volunteers
C_{max} (mg/l)	107* (74–187)	51 (31–88)
C_{24h} (mg/l)	1.5† (0.7–3.0)	0.8 (0.5–1.6)
f_u (%)	18* (14–25)	10 (6–26)
Vd_{ssu}‡ (l/kg)	1.1† (0.7–1.9)	1.5 (1.1–2.4)
Cl_u (ml/min)	175† (111–292)	272 (197–394)
$t_{1/2\beta}$ (h)	4.6 (3.5–6.2)	5.5 (3.5–6.1)
$AUC_{0-\infty}$ ($h \cdot mg^{-1} \cdot l^{-1}$)	192† (114–301)	122 (84–169)
Time > 4 mg/l (h)	16.7† (12.6–21.4)	11.1 (6.0–19.0)

* $P \leq 0.01$ *versus* volunteers.

† $P \leq 0.05$ *versus* volunteers.

‡ Pair No. 5 was excluded from the comparison (see text).

C_{max} = highest observed concentration in plasma; C_{24h} = concentration in plasma observed 24 h after the start of the antibiotic infusion; f_u = area–weight average free fraction of ceftriaxone in plasma; Vd_{ssu} = corrected volume of distribution at steady state for free ceftriaxone; Cl_u = total body clearance for free ceftriaxone; $t_{1/2\beta}$ = elimination half-life; $AUC_{0-\infty}$ = area under plasma concentration–time curve from 0 to ∞; Time > 4 mg/l = duration of time during which ceftriaxone concentration in plasma remained more than 4 mg/l.

(table 2) remained more than 4 mg/l longer ($P = 0.03$) in patients.

The point estimates (SE) of the slope and intercept of the Vd_{ssu} *versus* $1/f_u$ relations were 9.2 (3.3) and 13.8 (36.0) for healthy volunteers ($r^2 = 0.50$, $P = 0.02$) and 8.9 (2.8) and 25.6 (16.2) for hypoalbuminemic patients ($r^2 = 0.53$, $P = 0.01$), respectively (fig. 3). These values are not significantly different, although the intercept tended to be higher in patients.

The free ceftriaxone fractions in simulated hypoalbuminemic plasma did not differ significantly as a function of the hydroxyethyl starch concentrations (table 3). Moreover, the free ceftriaxone fraction added to the commercial solution of hydroxyethyl starch at concentrations of 10, 50, and 250 mg/l were 103% (range, 102–103%), 105% (range, 105–108%), and 99 (range, 98–103%), respectively; these three values were not significantly different ($P > 0.5$). These results clearly indicate that ceftriaxone does not bind to hydroxyethyl starch and that the presence of hydroxyethyl starch in plasma does not modify its free fraction.

Discussion

Pharmacokinetic studies are often conducted in healthy volunteers or patients with stable organ dysfunction, *e.g.*, renal impairment. However, during anesthesia and the postoperative period, pharmacokinetic parameters may differ markedly from those of healthy subjects, thereby resulting in altered drug distribution or clearance, leading to larger-than-expected variations of plasma concentrations. For example, variations of serum albumin levels caused by vascular expansion with plasma substitutes in response to hypovolemia may alter drug disposition. Indeed, total drug concentrations in plasma exist in two forms: that which is bound to plasma proteins, the most important of which are albumin, α_1-acid glycoprotein, and, to a lesser extent, globulins; and that which is unbound (or free).[3] Because only free drug is considered to be pharmacologically active, alterations of plasma protein binding may alter a patient's response to pharmaceutical agents if protein binding is restrictive for receptor binding.[3] Such changes appeared to be greater with highly bound agents.[3] Traditionally, most drug assays monitor total drug concentrations and do not quantitate free drug. When binding modifications occur, total drug concentrations may mislead the clinicians' evaluation of the patient's response.

We studied the pharmacokinetic modifications of ceftriaxone, a cephalosporin that normally binds highly (> 90%) to albumin in patients with hydroxyethyl starch–induced hypoalbuminemia during the immediate postoperative period. Hypoalbuminemic patients were compared with matched healthy volunteers to avoid possible analytical discrepancies between studies (especially when determining the free antibiotic concentration) and variability caused by physical characteristics of the patients studied. Because the erythrocyte penetration of ceftriaxone is insignificant,[15] drug measurements were assayed in plasma rather than whole blood. Free drug concentration was estimated by ultrafiltration because, compared with equilibrium dialysis, this method is rapid and relatively simple.[16] The major difficulty associated with ultrafiltration involves drug binding to the ultrafilters.[16] However, the use of new filters with low binding affinity and the determination of the fraction of the drug assayed bound to the filter has solved this problem.[17]

Although the binding of ceftriaxone to each specific plasma protein has not been well characterized, its binding behavior to plasma proteins, in general, was carefully evaluated.[18] Close agreement among the binding parameters in pooled human plasma and serum albumin has been reported, indicating that albumin is the major ceftriaxone protein binding in normal human plasma.[18] Previous studies showed that ceftriaxone does not bind avidly to α_1-acid glycoprotein, the second leading bind-

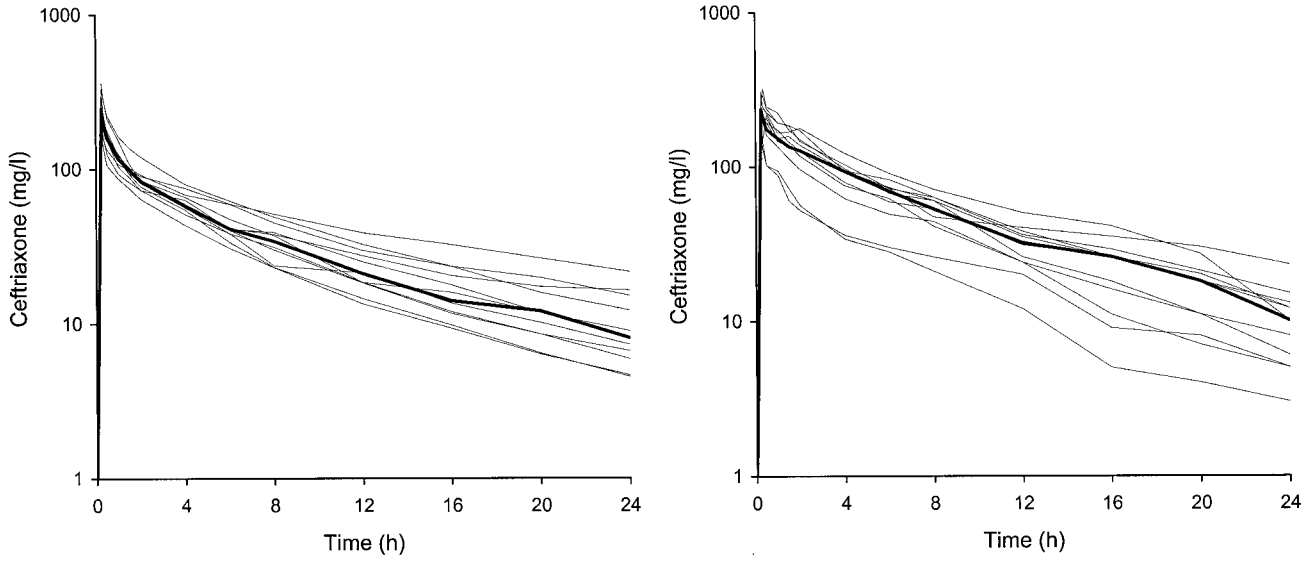

Fig. 1. Total antibiotic concentration–time curves in plasma after the administration of the 15-min intravenous infusion of 2 g ceftriaxone in 11 hypoalbuminemic patients (*left*) and 11 matched healthy volunteers (*right*). The thick line indicates the median values.

ing protein, at human concentrations in serum[19] but can bind to IgG at two binding sites.[18] IgG can have an effect on the free ceftriaxone concentration only when it reaches very high levels (*e.g.*, after intravenous immune globulin therapy or in patients with hypergammaglobulinemia) or in cases of severe hypoalbuminemia.[18] The parallel decrease of both the albumin and IgG serum concentrations indicated that the pattern of ceftriaxone protein binding was probably not modified by the hypoalbuminemia of our patients.

The model describing the pharmacokinetics of a drug with saturable binding is far from simple, because clearance and volume of distribution may both vary with time.[4] In the case of ceftriaxone, the model is simplified because ceftriaxone does not penetrate into cells. Hence, ceftriaxone distribution is restricted to plasma

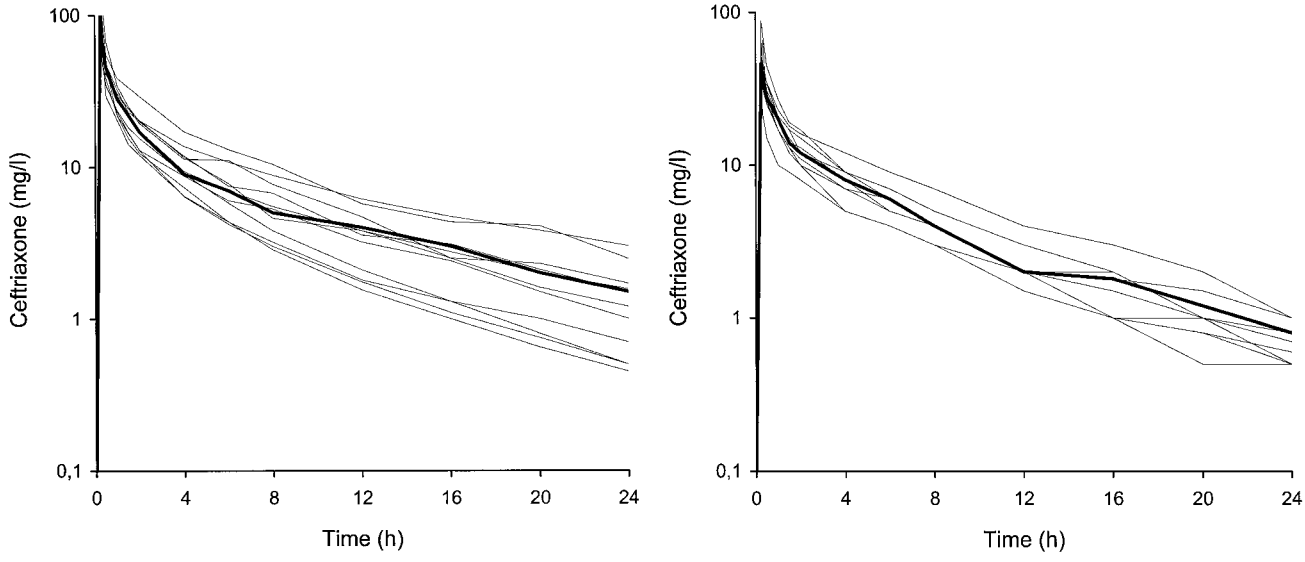

Fig. 2. Free antibiotic concentration–time curves in plasma after the administration the 15-min intravenous infusion of 2 g ceftriaxone in 11 hypoalbuminemic patients (*left*) and 11 matched healthy volunteers (*right*). The thick line indicates the median values.

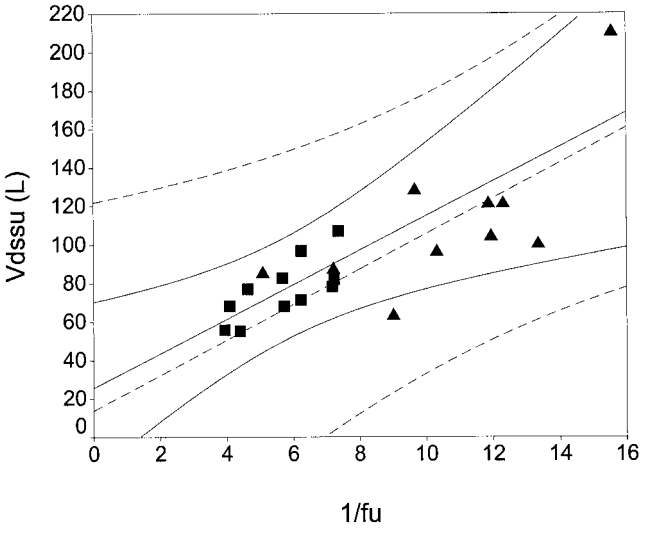

Fig. 3. Relation between free ceftriaxone corrected volume of distribution at steady state (Vd_{ssu}) and inverse area-weighted free fraction in plasma ($1/f_u$). Continuous lines and squares = hypoalbuminemic patients. Dashed lines and triangles = healthy volunteers. The straight lines are the regression lines. The curves delineate the 95% confidence interval of the regression lines.

water and interstitial fluid.[10,20] Concerning ceftriaxone clearance (which is eliminated by means of renal and biliary mechanisms), total body clearance for free ceftriaxone decreases at high concentration because the biliary elimination of free ceftriaxone is saturable.[21] To describe the distribution of drugs with saturable binding, the relevant pharmacokinetic parameters have been shown to be f_u, which accounts for the influence of dose and time on the free fraction in plasma, and the corrected Vd_{ss}, which variation reflects a shift in drug mass between intravascular and extravascular space fluid.[10] Conversely, the Vd_{ssu} carries no information about the spaces in which free drug distributes, but relates the free concentration at steady state to the total amount of drug in the body.[10]

Table 3. Free Ceftriaxone Concentrations*† in Simulated Hypoalbuminemic (20–25 g/l) Pooled Human Plasma Containing Different Hydroxyethyl Starch Concentrations

Ceftriaxone Concentration (mg/l)	Diluted, Hypoalbuminemic Plasma		
	Alone	+ 6 mg/l HES	+ 12 mg/l HES
10	5 (5–5)	6 (5–6)	7 (6–7)
50	8 (7–8)	8 (8–8)	10 (9–10)
250	50 (50–53)	50 (48–50)	48 (46–50)

* Three concentrations of ceftriaxone were added to pooled human plasma, diluted 50% in phosphate-buffered saline to simulate perioperative hypoalbuminemia, and incubated with hydroxyethyl starch (HES) concentrations close to those observed in the surgical patients.

† Expressed as percentages (range).

The pharmacokinetic data derived from the total ceftriaxone concentrations of our hypoalbuminemic patients were similar to those observed for their matched healthy volunteers and those previously reported when a 2-g dose had been given over a 20- or 30-min period to healthy patients or volunteers.[22–24] However, free ceftriaxone concentrations were higher in patients throughout the entire study period. Our results may be interpreted as follows: The decreased albumin level secondary to the administration of hydroxyethyl starch solutions is responsible for a 70% increase of the ceftriaxone f_u in plasma, resulting in the saturation of its biliary elimination and a 36% decreased total body clearance for free ceftriaxone. Since the increase in f_u is higher than the decrease in total body clearance for free ceftriaxone, total ceftriaxone clearance is increased in hypoalbuminemic patients. The 20% increased corrected Vd_{ss} in hypoalbuminemic patients indicates that, compared with healthy volunteers, there is a shift of ceftriaxone from plasma to extravascular space. The correlation between ceftriaxone Vd_{ss} and serum albumin level supports the idea that binding modifications are involved. Part of this Vd_{ss} shift may be explained by the higher level of saturation of binding to extravascular albumin than to plasma albumin, owing to the three times lower concentration of this protein in the interstitial fluid.[25] Part of this shift may also be related to variations of the physiological volumes into which ceftriaxone distributes (V_p, V_e) and/or to the ratio or binding sites between extravascular and intravascular compartments (R_{ei}). The theoretical value of these quantities, in healthy subjects, are $V_p = 3$ l, $V_e = 12$ l, and $R_{ei} = 1.3$.[26] The slope of the Vd_{ssu} *versus* $1/f_u$ line, which is equal to $V_p \times (1 + R_{ei})$, was similar in both groups and approaches the theoretical value of 7 l. Hence, either V_p and R_{ei} did not significantly vary or they varied in the opposite direction. The point estimate of the intercept of the Vd_{ssu} *versus* $1/f_u$ line, which is equal to $V_e - (V_p \times R_{ei})$, was doubled in the group of hypoalbuminemic patients, although the difference did not reach significance because of the large SEs. Both values were (not significantly) higher than the theoretical value of 8 l. Hence, the increased intercept, if any, would be related to an increased V_e in hypoalbuminemic patients. Similar findings were obtained when other high albumin binding drugs where given to hypoalbuminemic subjects. Slight increased volume of distribution and clearance of total concentration of midazolam were observed in crit-

ically ill patients.[26] Elevated plasma unbound fraction, apparent volume of distribution, and total plasma clearance of piroxicam were noted in animals rendered hypoalbuminemic by the administration of Ficol-70, another plasma expander, to replace blood.[27]

It has long been thought that only the free drug in plasma was available for diffusion into tissues.[1] Although this hypothesis has been confirmed in most cases, recent studies have shown opposite consequences of plasma binding in terms of drug transfer into tissues.[3] With restrictive binding, the drug is almost totally retained in the albumin-distribution compartment, *i.e.*, 0.1 l/kg for a drug with $f_u = 0$ or 0.2 l/kg for a drug with $f_u = 1$. Drugs with permissive binding, in contrast, have correspondingly higher volumes of distribution. Moreover, for most drugs, the percentage of protein binding remains relatively constant throughout the dosing range, whereas some drugs, such as ceftriaxone, can saturate plasma protein-binding sites within their usual dosing ranges, resulting in nonlinearity of various pharmacokinetic parameters.[5] Increasing drug concentrations in plasma or decreasing the number of plasma protein-binding sites may enhance the free fraction of the drug. Although the effects of drug–protein binding on pharmacokinetics have been previously investigated,[5] whether changes of such drug binding result in altered pharmacodynamic effect(s) is a relatively unexplored area, mainly because it is so difficult to design and conduct meaningful studies.[1,3] A few relevant clinical studies have suggested that the concentration of free drug may correlate with the clinical effect better than the total drug concentration does,[28] but there are too few definitive studies in the area of free drug concentration–effect relations.

For β-lactams, the time that plasma concentrations remain above the minimal inhibitory concentration of the pathogen is the pharmacodynamic parameter most closely linked with outcome.[12] It has been shown that this time need be only 60–70% of a dose interval to obtain the maximum bactericidal effect, providing unbound drug levels are used for assessing effectiveness of highly protein-bound cephalosporins such as ceftriaxone.[6,12] Based on surrogate markers for effectiveness of β-lactams, and because the time that the free ceftriaxone concentration in plasma (and thus in extravascular fluid) remained more than 4 mg/l was 1.5-fold higher in patients, we can hypothesize better effectiveness when ceftriaxone is given to hypoalbuminemic patients. No conclusion can be drawn regarding toxicity, because it was not evaluated.

However, the increase free drug concentration in plasma of hypoproteinemic patients may enhance the potential drug toxicity, especially when low therapeutic index drugs are used. Recently, seizures were reported in a hypoalbuminemic patient receiving phenytoin.[29] Despite a therapeutic serum phenytoin concentration, the free concentration was more than doubled. After lowering the daily phenytoin dose, the patient improved. This report clearly indicates better phenytoin distribution in hypoalbuminemic patients with toxic drug concentrations in tissues. Many drugs used by anesthesiologists are highly plasma bound, such as midazolam, thiopental, lidocaine, bupivacaine, mupivacaine, alfentanil, sufentanil, fentanyl, propranolol, warfarin, digitoxin, and so on.[2,3] Because some of these highly bound drugs have a low therapeutic index, administration of a standard dose in a patient with hypoproteinemia may lead to higher-than-expected free drug levels with a theoretical risk of toxicity. Further studies exploring the pharmacologic and possible toxic effects of decreased protein binding capacity on other highly bound drugs frequently used by anesthesiologists are warranted.

In conclusion, this study indicates that in plasma, iatrogenic hypoalbuminemia induces greater free ceftriaxone concentration, a cephalosporin that binds strong to serum albumin. The higher free drug concentration observed in these hypoproteinemic patients increases drug distribution and may have greater effectiveness.

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