Clin Pharmacokinet (2013) 52:1–8
DOI 10.1007/s40262-012-0018-5

CURRENT OPINION

The Clinical Relevance of Plasma Protein Binding Changes

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Published online: 13 November 2012

Abstract Controversy reigns as to how protein binding changes alter the time course of unbound drug concentrations in patients. Given that the unbound concentration is responsible for drug efficacy and potential drug toxicity, this area is of significant interest to clinicians and academics worldwide. The present uncertainty means that many questions relating to this area exist, including "How important is protein binding?", "Is protein binding always constant?", "Do pH and temperature changes alter binding?" and "How do protein binding changes affect dosing requirements?". In this paper, we seek to address these questions and consider the data associated with altered pharmacokinetics in the presence of changes in protein binding and the clinical consequences that these may have on therapy, using examples from the critical care area. The published literature consistently indicates that a change in the protein binding and unbound concentrations of some drugs are common in certain specific patient groups such as the critically ill. Changes in pharmacokinetic parameters, including clearance and apparent volume of distribution (V_d), may be dramatic. Drugs with high protein binding, high intrinsic clearance (e.g. clearance by glomerular filtration) and where dosing is not titrated to effect are most likely to be affected in a clinical context. Drugs such as highly protein bound antibacterials with multiple half-lives within a dosing interval and that have some level of renal clearance, such as ertapenem, teicoplanin, ceftriaxone and flucloxacillin, are commonly affected. In response to these challenges, clinicians need to adapt dosing regimens rationally based on the pharmacokinetic/pharmacodynamic characteristics of the drug. We propose that further pharmacokinetic modelling-based research is required to enable the design of robust dosing regimens for drugs affected by altered protein binding.

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1 Introduction

Protein binding of drugs in humans is a well described phenomenon. Current regulatory processes in most countries make it compulsory for pharmaceutical companies to perform various studies for new drugs, including a detailed in vivo pharmacokinetic characterization. Data on parameters such as drug clearance, apparent volume of distribution (V_d) and protein binding are then used to develop dosing regimens which aim to ensure consistent achievement of target drug concentrations in the patient. The goal of this process is to ensure optimal clinical efficacy and minimal toxicity for the patient.

Clinicians and academics generally have a good understanding of the contribution of these pharmacokinetic parameters to drug dosing. However, a high-level

understanding of how to adjust drug doses when there are changes to one or more of these parameters is less common. For drugs titrated to effect, e.g. vasopressor agents, dosing can be adjusted based on the observed pharmacodynamics. For other drugs where efficacy is not observable in a timely fashion, e.g. antibacterials, a 'one dose fits all' approach is more commonly used because of the difficulties in determining whether drug failure is occurring. Clearly, though, changes in pharmacokinetic parameters will cause a change in drug exposure during a dosing interval, thereby potentially compromising the desired drug effects.

To this end, it remains controversial as to how protein binding changes alter the time course of unbound drug concentration in plasma, and other body compartments, throughout a dosing interval. Critically, the unbound concentration is of paramount interest as it determines drug efficacy and potential drug toxicity. However, rational dose adjustment in the presence of altered protein binding is poorly understood and conflicting views exist in the literature as to the impact of changes in protein binding on drug efficacy. For this reason, clinicians often ask the following questions: (1) How important is protein binding?; (2) What proteins are involved in protein binding?; (3) Is protein binding always constant?; (4) Do pH and temperature changes alter binding?; (5) What are the clinical (practical) effects of the above?; and (6) Are protein displacement drug interactions of significance?

With this background, the purpose of this paper is to consider the data associated with altered pharmacokinetics in the presence of changes in protein binding and the clinical consequences that these may have on therapy. We use examples from the area of critical care to discuss this topic as acute changes in protein binding are common in the critically ill patient [1].

2 Unbound Fraction or Unbound Concentration?

For all drugs, it is the fraction that is not bound to plasma proteins (i.e. the unbound, or free, fraction) that is responsible for pharmacological effect. Whilst knowledge of the fraction of unbound drug is academically of interest, it is changing unbound concentrations over a dosing interval that should be described to accurately predict drug effect [2, 3]. The unbound fraction is most commonly reported as a single value to be assigned to any observed concentration for a particular drug whereas, in reality, many drugs have a different unbound fraction depending on drug concentration and various other factors [4]. It follows that data describing unbound fraction as an isolated value are in some ways not useful without a corresponding drug concentration and both should be considered together to interpret likely drug effects.

3 What is the Effect of Altered Protein Binding on Pharmacokinetics?

The unbound fraction of drug will distribute from the vascular space into tissues or be metabolised or excreted from the body. Therefore, as this fraction changes, differential pharmacokinetic effects will occur. Figure 1 schematically presents a two-compartment model for a drug, including protein binding. From this figure, it is evident that the pharmacologically active unbound concentration will be affected by the bound drug and the drug distributed into tissue, with both acting as a reservoir for unbound drug in the blood (central compartment). As drug clearance occurs, a new equilibrium between bound and distributed drug occurs, which acts to maintain the unbound drug concentration. The unbound drug concentration may decrease faster than the new equilibrium can be established if the rate of distribution from the peripheral compartment or the dissociation from protein binding is slower than drug clearance. This would be rare. The cardinal feature of the above equilibrium is that unbound concentrations are most likely to decrease later in the dosing interval where clearance has reduced the unbound drug and the reservoirs that support its concentrations. From a pharmacokinetic perspective, Fig. 1 describes how decreases in protein binding can lead to increased drug clearance as well as V_d. Therefore, for many highly bound drugs, an increased drug clearance as well as V_d is observed in states of reduced protein binding such as that commonly observed in critical illness [5].

If we further explore these concepts using pharmacokinetic equations, we can see confirmation that plasma protein binding directly affects both V_d and drug clearance [6]. V_d can be calculated using Eq. 1:

$$V_d = \left(\frac{f_u}{f_{uT}}\right) V_T + V_p \quad (1)$$

where f_u is the fraction unbound in plasma, f_{uT} is the fraction unbound in tissues, V_T is the volume of tissue and V_P is the volume of plasma. From this equation it is evident that the larger the f_u, the larger the V_d, meaning that acute or chronic changes in protein binding will lead to increases in V_d. This is especially relevant for hydrophilic antibacterial agents, namely β-lactams, glycopeptides, aminoglycosides and lipopeptides, whose distribution is limited to the extracellular space, so that the amount of plasma protein binding is the major factor influencing their V_d, which is linearly correlated with the unbound fraction [7].

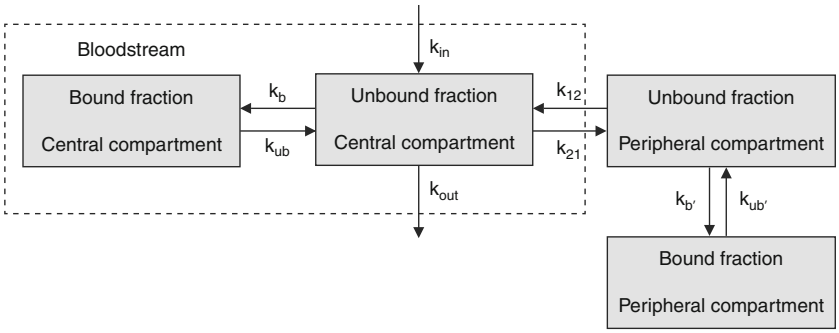

Fig. 1 The equilibrium between unbound, bound and distributed drug in the body in a two-compartment model. The bloodstream is the central compartment and the peripheral compartment represents the extravascular tissues where the drug distributes from the central compartment. k_{in} corresponds to the absorption constant (in oral administration) or the infusion rate (in intravenous infusion), k_{12} corresponds to the constant that describes the movement of drug from the central compartment (1) to the peripheral compartment (2). k_{21} describes the movement from the peripheral compartment(s) back to the central compartment. k_b and k_{ub} describe the equilibrium between bound and unbound drug, respectively, and albumin in the bloodstream. k_b and k_{ub} will depend on the binding affinity. $k_{b'}$ and $k_{ub'}$ describe the equilibrium between bound and unbound drug and albumin in the peripheral compartment where binding can occur to extravasated albumin or to cell membranes (including intracellular distribution). The albumin binding equilibrium will displace depending on the plasma albumin concentration and the plasma drug concentration. k_{out} corresponds to the elimination constant from the central compartment. Adapted from Ulldemolins et al [5], with permission from Springer International Publishing AG (© 2011. All rights reserved)

For clearance, drug removal is governed by blood flow of the eliminating organ (Q), f_u and intrinsic clearance (CL_{int}), which may vary in the presence of enzyme or renal tubular secretory activity. Clearance (CL) can be calculated using Eq. 2:

$$CL = \frac{Q(f_u \cdot CL_{int})}{Q + (f_u \cdot CL_{int})} \quad (2)$$

For a drug cleared predominantly by glomerular filtration, clearance will increase significantly with an increase in renal blood flow because of a typically high CL_{int} and/or with an increase in the unbound fraction. The influence of unbound concentration on clearance was well demonstrated in a group of critically ill patients treated with the highly protein bound antibacterial teicoplanin, with a significant inverse relationship between drug clearance and albumin concentrations observed [8].

From Eqs. 1 and 2, it is evident that a decrease in protein binding will lead to an increased V_d and increased clearance for drugs with high CL_{int}. Data on individual drugs may be required to determine the magnitude of any changes in pharmacokinetic parameters and whether these translate to the need for altered dosing regimens.

4 Does the Unbound Fraction Change in the Same Dosing Interval at Different Antibacterial Concentrations?

It is unlikely for a drug to have the same unbound fraction (or unbound concentration) at all times because after

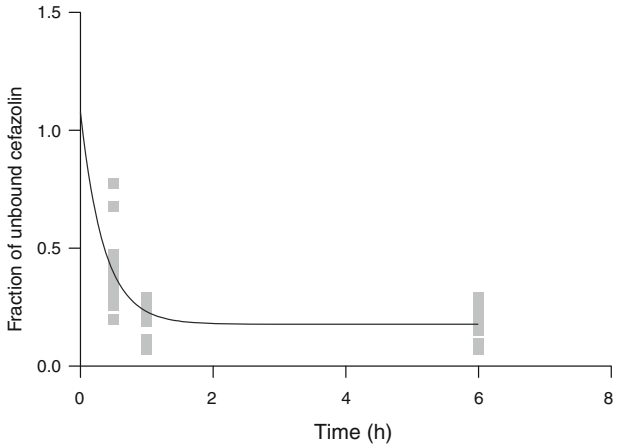

Fig. 2 Change in the fraction of unbound cefazolin in plasma during a single dosing interval (1,000 mg 30-min intravenous infusion) in critically ill patients ($n = 11$) with traumatic soft tissue injuries [9]. The figure shows that a higher unbound fraction is present in the first phase following drug administration. The *grey squares* are the observed unbound fraction of cefazolin for each patient at each timepoint and the *solid line* is the line of best fit for the two-phase decay in unbound fraction

administration, particularly bolus parenteral administration, the very high concentrations in plasma in this initial phase will result in disproportionately higher unbound concentrations until binding to plasma proteins can occur. This is illustrated in Fig. 2, where the unbound fraction of cefazolin is shown throughout a dosing interval [9]. In this example, the unbound fraction is highest early in the dosing interval and then as the process of drug–protein binding equilibration occurs (as well as other pharmacokinetic processes such as distribution), the unbound fraction and

unbound concentration stabilizes. The clinical consequences of this may be negligible depending on the distribution and clearance of the drug as well as the changes to the unbound concentration relative to the concentrations required for therapeutic effect. Similar data have previously been shown for ceftriaxone [10] and carbamazepine [11] amongst other drugs.

5 What Causes Changes in Protein Binding?

There are many patient presentations that will affect protein binding (Fig. 3). The likelihood of altered protein binding is more common in some patient populations such as burn injury patients, cancer, diabetes mellitus, liver and renal disease. Whether a drug will be affected in these cases depends on whether it is acidic or basic and whether it binds to albumin (typically acidic drugs) or an acute-phase reactant protein such as α_1-acid glycoprotein (typically basic drugs). Some patient populations have been less well studied, although a similar prevalence of altered albumin concentrations is apparent. For instance, the SAFE (Saline versus Albumin Fluid Evaluation) study defined hypoalbuminaemia as an albumin concentration less than 25 g/L and reported that this was present in 40–50 % of critically ill patients in this study [12]. Likewise, a very high incidence of hypoalbuminaemia was observed in 200 critically ill patients with cancer, 45 % of whom had plasma albumin concentrations less than 20 g/L [1]. This suggests that altered protein binding is likely to be common for highly protein bound drugs in these acutely ill patients. Data from the antibacterials ceftriaxone, teicoplanin, cefazolin and flucloxacillin confirm these problems [5, 13–18] and we provide some example data in Fig. 4. Suffice to say, altered protein binding may occur in any of the patient groups described in Fig. 3, although the extent and clinical consequences of this may not necessarily be significant.

Temperature and pH are also reported to affect protein binding. It is important to note that changes mediated by either of these environmental conditions are unlikely to be sufficient in clinical treatment to cause a change in the unbound concentration that is likely to affect the success of therapy. Some variation is expected to be seen in protein binding, but it would not significantly exceed typical inter-subject variability [19–21]. This area has been reviewed in detail by Hinderling and Hartmann [20] who hypothesized few likely clinical sequelae from pH changes, with clinically relevant protein binding from pH changes only proposed for fentanyl and lidocaine. The available data do emphasize the importance of replicating in vivo temperature and pH conditions in an in vitro setting if reliable prediction of in vivo effects of changes in protein binding is to be achieved [22].

The clinical relevance of drug displacement interactions has also been the source of controversy. In this context, it is considered that the presence of a newly introduced drug will displace from protein binding sites a drug already present in the system. What is certain is that these drug displacement interactions can occur. The consequence of any changes in unbound concentration should be interpreted as for protein binding changes caused by changes in protein concentration, pH or temperature. It follows that a drug displacement interaction will be far more likely to be problematic for therapy with a high CL_{int} than for a drug with a low CL_{int}. That is, clinical relevance will be determined by the pharmacokinetics/pharmacodynamics of the drug as described in Sect. 6 and 7.

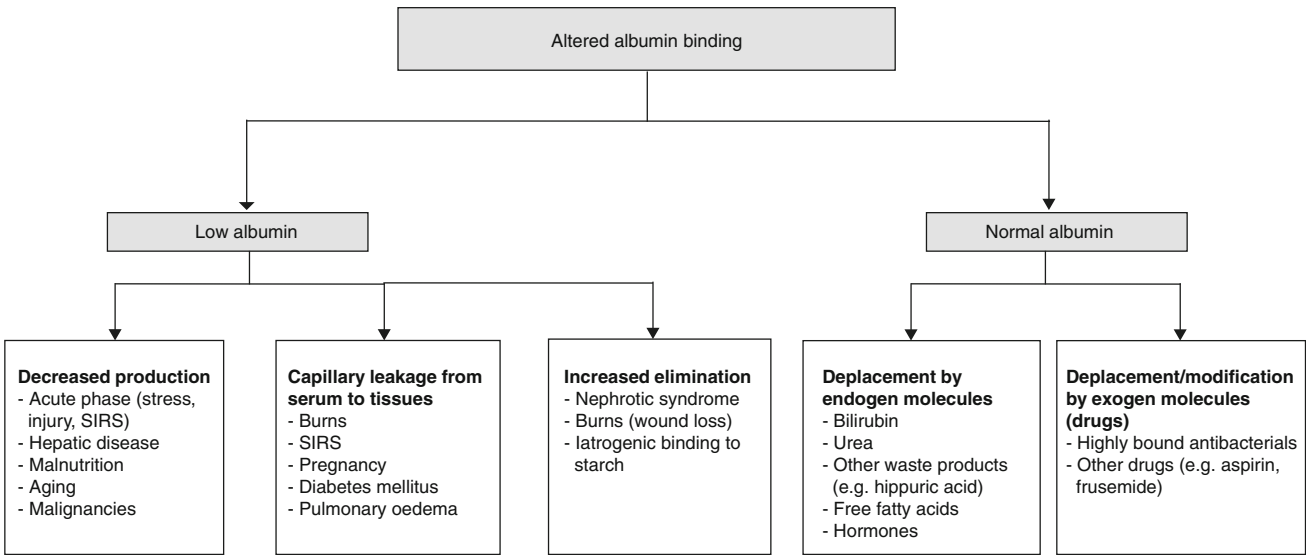

Fig. 3 Main factors responsible for alterations in drug–albumin binding [52]. *SIRS* systemic inflammatory response syndrome

6 When are Changes in Protein Binding Likely to be Therapeutically Relevant?

In the authors' opinion, the three clinical presentations that should all be present in a patient to cause changes in the protein binding of a drug and lead to adverse clinical consequences are:

a) highly protein bound drugs (e.g. ceftriaxone, phenytoin);
b) high clearance drugs, particularly drugs predominantly cleared by glomerular filtration; and
c) drugs where dosing is not titrated to effect (e.g. antibacterials).

The number of examples of drugs where pharmacokinetic changes mediated by altered protein binding are of clinical relevance is small in the context of clinical practice [23–25]. However, examples exist, particularly in acute settings, where each of the criteria discussed in Sect. 6.1–6.3 are satisfied.

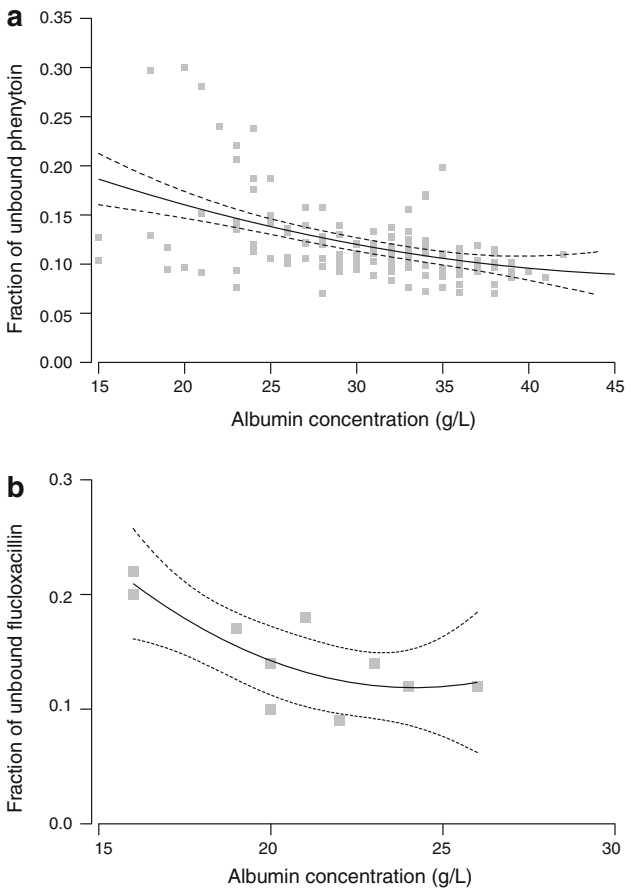

Fig. 4 The effect of biological variability of the fraction unbound in plasma in critically ill patients for phenytoin [$n = 53$] (**a**) and flucloxacillin [$n = 10$] (**b**). The *grey squares* are the observed values, the *solid line* represents the line of non-linear regression and the *dashed lines* represent the 95 % confidence interval of the non-linear regression. For both drugs, the unbound fraction increases with reducing plasma albumin concentrations

6.1 Highly Protein Bound Drugs

For highly protein bound drugs, changes in the fraction bound will have a much larger overall effect on the unbound concentration. For instance, if Drug A experiences a protein binding change from 99 to 98 %, the free concentration will double, enabling more rapid clearance and extensive distribution. If Drug A changes from 99 to 95 %, then the free concentration would be assumed to increase fivefold (although the distributive processes may make this difficult to measure). However, for a drug with minimal protein binding, Drug B, a change from 5 to 4 % protein binding or even 5 to 1 % will barely affect the unbound concentration, let alone clearance and distribution pharmacokinetics. For this reason, changes in the unbound fraction of highly protein bound drugs appear to result in more significant changes in pharmacokinetics [5, 13–16].

6.2 High Clearance Drugs

It is widely agreed that changes in protein binding are unlikely to be important for drugs with low extraction ratios, i.e. those drugs where changes in organ perfusion do not significantly affect drug clearance or metabolism (e.g. carbamazepine, diazepam, warfarin). This was shown in Eq. 2, where drugs with low CL_{int} are less likely to be affected by changes in f_u. Other drugs with high CL_{int} may result in clinically relevant increases in clearance; this is likely to be particularly problematic for drugs significantly cleared renally. Using the critically ill as an example population, Table 1 summarizes the studies that report antibacterial clearance in critically ill or healthy subjects for various highly protein bound antibacterials [8, 10, 13, 14, 16, 26–35]. Antibacterials appear to be at particular risk of significant pharmacokinetic changes. This is probably because they often have multiple half-lives within a single dosing interval and therefore clearance changes in this setting will amplify changes in pharmacokinetic exposure. Evidently, drug clearance and V_d can be particularly elevated in these patients receiving drugs with a high CL_{int}, suggesting that the time to re-dose would be expected to be shorter.

6.3 Drugs where Dosing is Not Titrated to Effect

For drugs where dosing is titrated to effect, altered exposures from protein binding changes are unlikely to be problematic, unless there is a low therapeutic window

Table 1 Changes in drug clearance for moderate to highly bound antibacterials in critically ill patients with hypoalbuminaemia compared with healthy volunteer data

Drug	% Protein binding in healthy volunteers	ICU/healthy subjects (*n*)	Change in clearance in ICU patients[a]	Change in V_d in ICU patients[a]
Aztreonam [26, 27]	60	48/7	15 % increase	Nil change
Ceftriaxone [10, 16]	85–95	6/11	99 % increase	32 % increase
Daptomycin [28, 29]	90–93	9/24	151 % increase	10 % increase
Ertapenem [30, 31]	85–95	17/10	113 % increase	200 % increase
Ertapenem [14]	85–95	8/16	462 % increase	624 % increase
Flucloxacillin [13, 32]	95	10/10	10 % increase	57 % increase
Fusidic acid [33, 34]	95–97	6/8	94 % increase	NA
Teicoplanin [8, 35]	90–95	12/6	36 % increase	NA

ICU intensive care unit (critically ill), *NA* not available, V_d apparent volume of distribution

[a] Calculated as (observed value − reference value/reference value) × 100

whereby small concentration increases may result in undesired supra-therapeutic effects as seen with warfarin [36]. In the case of vasopressor therapy, a change in the pharmacokinetics of an agent will be catered for by using dosing based on blood pressure, which can be measured in real time. Whilst initial dosing may be standardized for these patients, hour-to-hour dosing is based on observed blood pressure with doses adjusted to meet desired targets. For other drugs such as antibacterials and anticonvulsants where pharmacological effect is less measurable, changes in pharmacokinetics may not be identifiable unless drug concentrations are measured using therapeutic drug monitoring (TDM). For many of these drugs, of course, TDM may not be widely available, so failures of therapy may be due to decreased exposure that was not measured, resulting in a decreased effect.

To illustrate this challenge we use a recent case from our hospital in which a critically ill adult was administered ertapenem (protein binding ~90 %) 1 g intravenously daily for a ventilator-associated pneumonia caused by *Enterobacter cloacae* (minimum inhibitory concentration [MIC] 0.5–1.0 mg/L). The patient had a plasma albumin concentration <15 g/L and a measured urinary creatinine clearance of 220 mL/min. Using the β-lactam TDM assay available through our laboratory [37], the initial unbound trough concentration was <0.1 mg/L (our target unbound concentration was 1.0 mg/L). Eventually with incremental dosing, it was found that a dose of 1 g 8-hourly as a 4-h infusion was required to achieve an unbound concentration of 1.1 mg/L. The reason this patient had such low ertapenem concentrations was the presence of severe hypoalbuminaemia resulting in an increased unbound concentration that was rapidly cleared by supranormal renal function, otherwise known as augmented renal clearance [38–41]. The patient did not sufficiently improve with ertapenem therapy and did not demonstrate an adequate resolution of infection signs and symptoms. An alternative antibacterial was subsequently prescribed, but without having measured the concentrations we would not have known that the pharmacokinetics were so profoundly affected as no clinical symptom for infection changes sufficiently dynamically to allow appropriate dosing based on response [42]. A similar case was observed a couple of years ago in a hypoalbuminaemic transplant patient treated with teicoplanin and undergoing continuous venovenous haemofiltration [17]. While these are merely two case studies, they summarize the potential problems caused by changes in drug clearance associated with highly protein bound drugs in patients with hypoproteinaemia.

7 Relevance of Altered Protein Binding to Dosing Regimens

From the discussion thus far, it is our contention that changes in protein binding may be significant, particularly for highly protein bound and high clearance drugs where dosing is not titrated to effect. In this circumstance, it is more likely that changes in protein binding will be problematic for patients where drug concentrations are close to the efficacy or toxicity borderline.

To rationally adjust drug doses taking into account pharmacokinetic changes mediated by altered protein binding, knowledge of the pharmacokinetics/pharmacodynamics of the drug is important. To describe this concept further, we use antibacterial dosing in critically ill patients as an example. The pharmacokinetics/pharmacodynamics of antibacterials has been reviewed in detail previously [43–47] and these data emphasize that antibacterials may have concentration-dependent bacterial killing, time-dependent bacterial killing or a combination of both described with the ratio of the area under the concentration–time curve to MIC of the pathogen ratio. For all antibacterials where a larger V_d is likely because of changes

in protein binding (e.g. see Table 1), larger initial doses are suggested, particularly for the first 24–48 h [48]. Such higher doses are considered especially necessary in the critically ill given the other pathophysiological changes that occur in these patients and the associated iatrogenic interventions [48, 49]. After this initial phase, dosing should be guided by the likely antibacterial clearance. For high-clearance antibacterials more frequent dosing is suggested, particularly for time-dependent antibacterials where maintaining antibacterial concentrations above the MIC for extended periods within a dosing interval is important [50].

For all antibacterials, reduced protein binding will result in higher unbound antibacterial concentrations early in the dosing interval, which should maximize bacterial killing at that time [51]. However, the increased clearance appears to result in low unbound concentrations at the end of the dosing interval. Increased clearance will again be problematic for drugs where the goal is to maintain concentrations above a certain threshold (e.g. the MIC), for instance for time-dependent antibacterials such as β-lactams. For concentration-dependent antibacterials such as daptomycin, higher dosing, rather than more frequent dosing, would be appropriate.

8 Conclusion

A change in the protein binding of drugs appears to be common in some specific patient groups and may result in variable unbound concentrations, thereby potentially affecting pharmacological activity. However, the circumstances, drugs and patients in which this is likely to be problematic may be limited to specific patient groups such as the critically ill. Specifically, drugs with high protein binding, high CL_{int} and where dosing is not titrated to effect are most likely to be affected. The response from clinicians regarding how to adjust dosing in the presence of the associated increased V_d and drug clearance is governed by the pharmacokinetic/pharmacodynamic characteristics of drug action. We propose that further pharmacokinetic modelling-based research is required to enable the design of robust dosing regimens for drugs affected by altered protein binding.

Acknowledgments Dr. Roberts is supported by a Fellowship from the National Health and Medical Research Council of Australia (Australian Based Health Professional Research Fellowship 569917). The authors have no conflicts of interest that are directly relevant to the content of this article.

References

1. Namendys-Silva SA, Gonzalez-Herrera MO, Texcocano-Becerra J, Herrera-Gomez A. Hypoalbuminemia in critically ill patients with cancer: incidence and mortality. Am J Hosp Palliat Care. 2011;28(4):253–7.
2. Ensom MH. Comment: unbound drug concentration versus unbound drug fraction. Ann Pharmacother. 2002;36(4):731–2. (author reply 732).
3. Toutain PL, Bousquet-Melou A. Free drug fraction vs. free drug concentration: a matter of frequent confusion. J Vet Pharmacol Ther. 2002;25(6):460–3.
4. Smith DA, Di L, Kerns EH. The effect of plasma protein binding on in vivo efficacy: misconceptions in drug discovery. Nat Rev Drug Discov. 2010;9(12):929–39.
5. Ulldemolins M, Roberts JA, Rello J, Paterson DL, Lipman J. The effects of hypoalbuminaemia on optimizing antibacterial dosing in critically ill patients. Clin Pharmacokinet. 2011;50(2):99–110.
6. Burton ME, Shaw LM, Schentag JJ, Evans WE. Applied pharmacokinetics and pharmacodynamics: principles of therapeutic drug monitoring. 4th ed. Baltimore: Lippincott Williams and Wilkins; 2006.
7. Nix DE, Goodwin SD, Peloquin CA, Rotella DL, Schentag JJ. Antibiotic tissue penetration and its relevance: impact of tissue penetration on infection response. Antimicrob Agents Chemother. 1991;35(10):1953–9.
8. Barbot A, Venisse N, Rayeh F, Bouquet S, Debaene B, Mimoz O. Pharmacokinetics and pharmacodynamics of sequential intravenous and subcutaneous teicoplanin in critically ill patients without vasopressors. Intensive Care Med. 2003;29(9):1528–34.
9. Roberts JA, Roberts MS, Semark A, Udy AA, Kirkpatrick CM, Paterson DL, et al. Antibiotic dosing in the 'at risk' critically ill patient: linking pathophysiology with pharmacokinetics/pharmacodynamics in sepsis and trauma patients. BMC Anesthesiol. 2011;11:3.
10. Stoeckel K, McNamara PJ, Brandt R, Plozza-Nottebrock H, Ziegler WH. Effects of concentration-dependent plasma protein binding on ceftriaxone kinetics. Clin Pharmacol Ther. 1981; 29(5):650–7.
11. MacKichan JJ, Zola EM. Determinants of carbamazepine and carbamazepine 10,11-epoxide binding to serum protein, albumin and alpha 1-acid glycoprotein. Br J Clin Pharmacol. 1984; 18(4):487–93.
12. Finfer S, Bellomo R, McEvoy S, Lo SK, Myburgh J, Neal B, et al. Effect of baseline serum albumin concentration on outcome of resuscitation with albumin or saline in patients in intensive care units: analysis of data from the saline versus albumin fluid evaluation (SAFE) study. BMJ. 2006;333(7577):1044.
13. Ulldemolins M, Roberts JA, Wallis SC, Rello J, Lipman J. Flucloxacillin dosing in critically ill patients with hypoalbuminaemia: special emphasis on unbound pharmacokinetics. J Antimicrob Chemother. 2010;65(8):1771–8.
14. Brink AJ, Richards GA, Schillack V, Kiem S, Schentag J. Pharmacokinetics of once-daily dosing of ertapenem in critically ill patients with severe sepsis. Int J Antimicrob Agents. 2009; 33(5):432–6.
15. Douglas A, Altukroni M, Udy AA, Roberts MS, Taraporewalla K, Jenkins J, et al. The pharmacokinetics of cefazolin in patients undergoing elective & semi-elective abdominal aortic aneurysm open repair surgery. BMC Anesthesiol. 2011;11:5.
16. Joynt GM, Lipman J, Gomersall CD, Young RJ, Wong EL, Gin T. The pharmacokinetics of once-daily dosing of ceftriaxone in critically ill patients. J Antimicrob Chemother. 2001;47(4):421–9.
17. Pea F, Brollo L, Lugano M. Dal Pos L, Furlanut M. Therapeutic drug monitoring-guided high teicoplanin dosage regimen required to treat a hypoalbuminemic renal transplant patient undergoing continuous venovenous hemofiltration. Ther Drug Monit. 2001;23(5):587–8.
18. Pea F, Viale P, Candoni A, Pavan F, Pagani L, Damiani D, et al. Teicoplanin in patients with acute leukaemia and febrile

neutropenia: a special population benefiting from higher dosages. Clin Pharmacokinet. 2004;43(6):405–15.
19. Burney RG, DiFazio CA, Foster JA. Effects of pH on protein binding of lidocaine. Anesth Analg. 1978;57(4):478–80.
20. Hinderling PH, Hartmann D. The pH dependency of the binding of drugs to plasma proteins in man. Ther Drug Monit. 2005;27(1): 71–85.
21. Paxton JW, Calder RL. Propranolol binding in serum: comparison of methods and investigation of effects of drug concentration, pH, and temperature. J Pharmacol Methods. 1983;10(1):1–11.
22. Kochansky CJ, McMasters DR, Lu P, Koeplinger KA, Kerr HH, Shou M, et al. Impact of pH on plasma protein binding in equilibrium dialysis. Mol Pharm. 2008;5(3):438–48.
23. Benet LZ, Hoener BA. Changes in plasma protein binding have little clinical relevance. Clin Pharmacol Ther. 2002;71(3): 115–21.
24. Rolan PE. Plasma protein binding displacement interactions: why are they still regarded as clinically important? Br J Clin Pharmacol. 1994;37(2):125–8.
25. Sansom LN, Evans AM. What is the true clinical significance of plasma protein binding displacement interactions? Drug Saf. 1995;12(4):227–33.
26. Swabb EA, Leitz MA, Pilkiewicz FG, Sugerman AA. Pharmacokinetics of the monobactam SQ 26,776 after single intravenous doses in healthy subjects. J Antimicrob Chemother. 1981;8 Suppl E:131–40.
27. Janicke DM, Cafarell RF, Parker SW, Apicella MA, Jusko WJ. Pharmacokinetics of aztreonam in patients with gram-negative infections. Antimicrob Agents Chemother. 1985;27(1):16–20.
28. Dvorchik B, Sica D, Gehr T. Pharmacokinetics and safety of single-dose daptomycin in subjects with graded renal insufficiency and end-stage renal disease [poster]. Interscience Conference on Antimicrobial Agents and Chemotherapy. San Diego, 2002. pp. 27–31.
29. Mohr JF 3rd, Ostrosky-Zeichner L, Wainright DJ, Parks DH, Hollenbeck TC, Ericsson CD. Pharmacokinetic evaluation of single-dose intravenous daptomycin in patients with thermal burn injury. Antimicrob Agents Chemother. 2008;52(5):1891–3.
30. Pletz MW, Rau M, Bulitta J, De Roux A, Burkhardt O, Kruse G, et al. Ertapenem pharmacokinetics and impact on intestinal microflora, in comparison to those of ceftriaxone, after multiple dosing in male and female volunteers. Antimicrob Agents Chemother. 2004;48(10):3765–72.
31. Burkhardt O, Kumar V, Katterwe D, Majcher-Peszynska J, Drewelow B, Derendorf H, et al. Ertapenem in critically ill patients with early-onset ventilator-associated pneumonia: pharmacokinetics with special consideration of free-drug concentration. J Antimicrob Chemother. 2007;59(2):277–84.
32. Landersdorfer CB, Kirkpatrick CM, Kinzig-Schippers M, Bulitta JB, Holzgrabe U, Drusano GL, et al. Population pharmacokinetics at two dose levels and pharmacodynamic profiling of flucloxacillin. Antimicrob Agents Chemother. 2007;51(9): 3290–7.
33. Taburet AM, Guibert J, Kitzis MD, Sorensen H, Acar JF, Singlas E. Pharmacokinetics of sodium fusidate after single and repeated infusions and oral administration of a new formulation. J Antimicrob Chemother. 1990;25 Suppl B:23–31.
34. Peter JD, Jehl F, Pottecher T, Dupeyron JP, Monteil H. Pharmacokinetics of intravenous fusidic acid in patients with cholestasis. Antimicrob Agents Chemother. 1993;37(3):501–6.
35. Outman WR, Nightingale CH, Sweeney KR, Quintiliani R. Teicoplanin pharmacokinetics in healthy volunteers after administration of intravenous loading and maintenance doses. Antimicrob Agents Chemother. 1990;34(11):2114–7.
36. Tincani E, Mazzali F, Morini L. Hypoalbuminemia as a risk factor for over-anticoagulation. Am J Med. 2002;112(3):247–8.
37. McWhinney BC, Wallis SC, Hillister T, Roberts JA, Lipman J, Ungerer JP. Analysis of 12 beta-lactam antibiotics in human plasma by HPLC with ultraviolet detection. J Chromatogr B Analyt Technol Biomed Life Sci. 2010;878(22):2039–43.
38. Udy AA, Putt MT, Shanmugathasan S, Roberts JA, Lipman J. Augmented renal clearance in the intensive care unit: an illustrative case series. Int J Antimicrob Agents. 2010;35(6):606–8.
39. Udy AA, Roberts JA, Boots RJ, Paterson DL, Lipman J. Augmented renal clearance: implications for antibacterial dosing in the critically ill. Clin Pharmacokinet. 2010;49(1):1–16.
40. Udy AA, Roberts JA, Dewaele JJ, Paterson DL, Lipman J. What's behind the failure of emerging antibiotics in the critically ill? Understanding the impact of altered pharmacokinetics and augmented renal clearance. Int J Antimicrob Agents. 2012;39(6): 455–7.
41. Udy AA, Varghese JM, Altukroni M, Briscoe S, McWhinney B, Ungerer J, et al. Subtherapeutic initial β-lactam concentrations in select critically ill patients: association between augmented renal clearance and low trough drug concentrations. Chest. 2012; 142(1):30–9.
42. Roberts JA, Ulldemolins M, Roberts MS, McWhinney B, Ungerer J, Paterson DL, et al. Therapeutic drug monitoring of beta-lactams in critically ill patients: proof of concept. Int J Antimicrob Agents. 2010;36(4):332–9.
43. Pea F, Viale P. The antimicrobial therapy puzzle: could pharmacokinetic-pharmacodynamic relationships be helpful in addressing the issue of appropriate pneumonia treatment in critically ill patients? Clin Infect Dis. 2006;42(12):1764–71.
44. Pea F, Viale P, Furlanut M. Antimicrobial therapy in critically ill patients: a review of pathophysiological conditions responsible for altered disposition and pharmacokinetic variability. Clin Pharmacokinet. 2005;44(10):1009–34.
45. Roberts JA. Using PK/PD to optimize antibiotic dosing for critically ill patients. Curr Pharm Biotechnol. 2011;12(12):2070–9.
46. Roberts JA, Lipman J. Antibacterial dosing in intensive care: pharmacokinetics, degree of disease and pharmacodynamics of sepsis. Clin Pharmacokinet. 2006;45(8):755–73.
47. Ulldemolins M, Roberts JA, Lipman J, Rello J. Antibiotic dosing in multiple organ dysfunction syndrome. Chest. 2011;139(5): 1210–20.
48. Taccone FS, Laterre PF, Dugernier T, Spapen H, Delattre I, Wittebole X, et al. Insufficient beta-lactam concentrations in the early phase of severe sepsis and septic shock. Crit Care. 2010;14(4):R126.
49. Pea F, Pavan F, Furlanut M. Clinical relevance of pharmacokinetics and pharmacodynamics in cardiac critical care patients. Clin Pharmacokinet. 2008;47(7):449–62.
50. Sime FB, Roberts MS, Peake SL, Lipman J, Roberts JA. Does beta-lactam pharmacokinetic variability in critically ill patients justify therapeutic drug monitoring? A systematic review. Ann Intensive Care. 2012;2(1):35.
51. Burian A, Wagner C, Stanek J, Manafi M, Bohmdorfer M, Jager W, et al. Plasma protein binding may reduce antimicrobial activity by preventing intra-bacterial uptake of antibiotics, for example clindamycin. J Antimicrob Chemother. 2011;66(1): 134–7.
52. Tillement JP, Lhoste F, Giudicelli JF. Diseases and drug protein binding. Clin Pharmacokinet. 1978;3(2):144–54.