

Bound to bleed: How altered albumin binding may dictate warfarin treatment outcome

Anke C. Fender ^{*,1}, Dobromir Dobrev ¹

Institute of Pharmacology, West German Heart and Vascular Center, University Duisburg-Essen, Germany



ARTICLE INFO

Article history:

Received 8 February 2019

Received in revised form 12 February 2019

Accepted 14 February 2019

Keywords:

Warfarin

Pharmacokinetics

Albumin

Bleeding

ABSTRACT

Although non-vitamin-K anticoagulants are now the preferred option for stroke prevention in atrial fibrillation (AF), warfarin is still used in a significant number of patients. Warfarin dosing requirements are susceptible to drug interactions and genetic polymorphisms in metabolising enzymes. Human serum albumin (HSA) is a candidate modifier of warfarin pharmacokinetics, with hypoalbuminemia now shown to correlate with supratherapeutic INR levels and annual bleeding risk. Warfarin is highly bound to HSA, and a relatively small shift, resulting from displacement by other xenobiotics, hypoalbuminemia or reduced binding capacity, can potentially lead to marked alterations in the free warfarin fraction. Precisely how this relates to the actual concentration of free, pharmacodynamically active, warfarin, is not clear, since measurement of this critical moiety remains an unsolved caveat. Yet awareness how disease, nutrition and polypharmacy affect warfarin binding to HSA and how this may impact (or not) on bioavailability and outcome, is essential for optimal treatment.

© 2019 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Atrial fibrillation (AF), the common arrhythmia, is associated with increased stroke risk. Antiarrhythmic drug therapy remains suboptimal, and stroke prevention with anticoagulants is challenging in many patients [1,2]. Warfarin is still used in a significant number of patients, despite the direct oral anticoagulants now being the preferred option. Warfarin's narrow therapeutic window of adequate thromboprophylaxis without adverse bleeding require awareness of its complex pharmacology. Warfarin pharmacokinetics are highly susceptible to drug-drug and dietary interactions, which together with age contribute to the large variability in warfarin dosing requirement. Pharmacokinetic shifts are largely attributed to genetic polymorphisms in metabolising cytochrome P450 isoenzymes (Fig. 1) and genotype-guided warfarin dosing is recommended to deal with inter-subject variability. Pharmacogenetic testing alone does however not improve health outcomes, and residual variation in dose requirements remains unexplained.

In this issue of the *International Journal of Cardiology Heart & Vasculature*, human serum albumin (HSA) is highlighted as a culprit modifier of warfarin kinetics [3]. Low HSA levels are shown to predict major bleeding in AF patients anticoagulated with warfarin. Conversely, hyperalbuminemia (e.g. in the context of a high-protein diet) increases warfarin dosing requirements [4]. HSA levels might constitute a modifiable control knob to be considered for tailored

anticoagulation in AF, particularly since low HSA and paroxysmal AF are mutually predictive [5].

HSA is the major plasma carrier protein for endogenous and xenobiotic ligands, but binding capacity is finite, so mutual ligand displacement is a key source for drug interactions (Fig. 1). For warfarin, with near complete protein binding, minor displacement can dramatically increase in the free (unbound) fraction f_u . The list of foods and nutritional supplements with warfarin interaction potential is growing. Recently added were alkaloidal compounds such as piperine in peppers, which displace warfarin from HSA in plasma, and promote warfarin uptake into brain endothelial cells [6], also facilitating tissue disposition.

Pharmacokinetic principles tell us that competition and/or altered binding capacity should increase f_u , the ligand fraction that can be transported across biological membranes, bind to target effectors and undergo biotransformation and elimination, while the albumin-bound fraction is essentially inert and unable to disperse, serving as a backup for f_u . For substances exhibiting linear metabolism and elimination kinetics, an increase in f_u will actually increase drug clearance, leading to a net decrease in drug bioavailability in plasma and presumably lower efficacy and toxicity. Displacement of calcium from HSA immediately increases the free moiety, leading to accelerated clearance and ultimately reduced plasma levels of drugs. Low serum calcium has been linked with increased bleeding tendency, though it is unclear if and how this relates to the extent of plasma protein binding, and there is no evidence that physiological changes in calcium affect warfarin-HAS binding. For warfarin itself, which does not follow linear Michaelis-Menten kinetics, the net impact of displacement from protein binding on its plasma levels is not predictable, and augmented responses (e.g.

* Corresponding author at: Institute of Pharmacology, West German Heart and Vascular Center, University Duisburg-Essen, Hufelandstr. 55, 45122 Essen, Germany.

E-mail address: anke.fender@uk-essen.de (A.C. Fender).

¹ This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

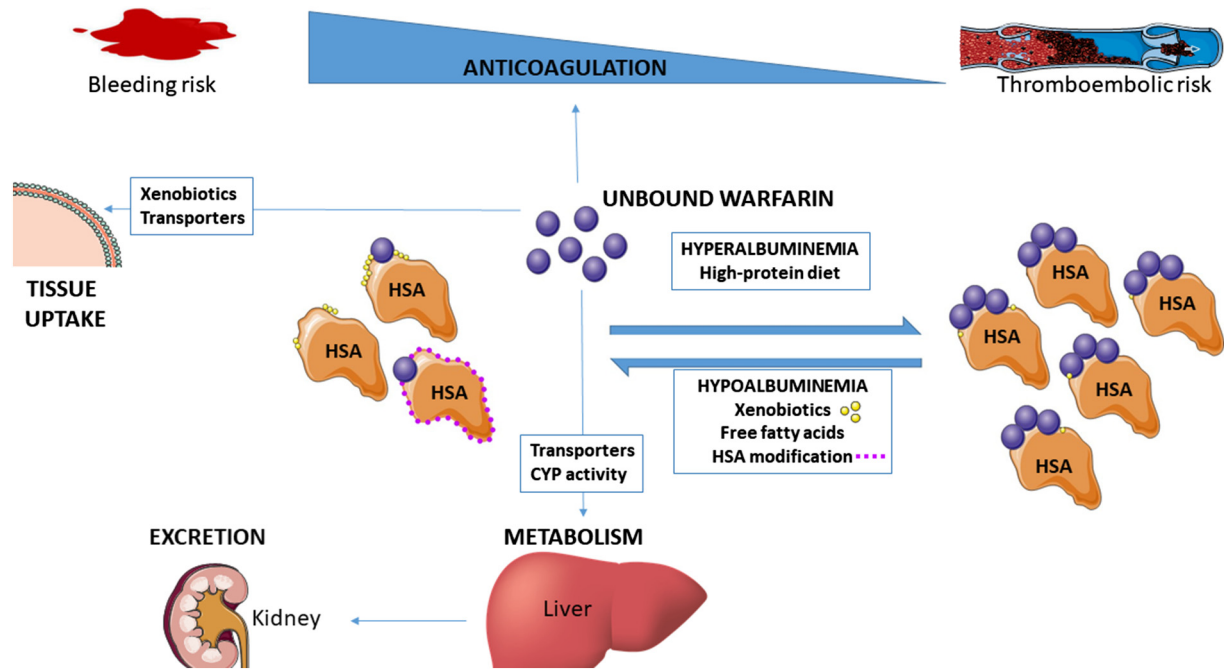


Fig. 1. Putative factors modulating warfarin pharmacokinetics and anticoagulant outcome. CYP, cytochrome P450 isoenzymes.

bleeding) are the likely consequence. One point to emphasize here is how rapidly dynamic changes in active warfarin levels may occur. Warfarin dosing is based on INR, so slow changes in active free warfarin can be compensated for with dose adjustment. Rapid fluctuations may however result in supratherapeutic INR levels that cause bleeding before dose correction is undertaken at the next follow-up visit. Rapid changes in HSA-warfarin binding could therefore be an important concern.

Kawai and colleagues [3] show reduced HSA correlates inversely with time in INR > 3.0, and predicts the annual risk of major bleeds, with a cut-off value of 3.6 g/dl. Based on this, the authors suggest that close monitoring for hypoalbuminemia may help to prevent excessive warfarin levels and hence adverse bleeding. Interestingly hypoalbuminuria is common in high-risk patients and appears to predict bleeding [7] even in the absence of warfarin. HSA modification by glycation or oxidation further impairs ligand binding capacity (Fig. 1) and accelerates HSA clearance [8], and moreover generates a potent platelet agonist (referred to in [9]), suggesting a novel link between oxidative stress conditions and bleeding risk.

A significant limitation in this discussion is the rarely considered question if changes in the unbound fraction f_u always translate into alterations in the free plasma concentration C_{free} . C_{free} is mathematically extrapolated from a supposedly known f_u , but the classical assumption that altered drug binding resulting in a shift in f_u also produces a corresponding shift in C_{free} and hence biological effect, may not hold true. C_{free} transiently increases only until redistribution and elimination of the realistically very small amount of displaced drug occurs. This makes the in vivo situation very different from an in vitro detection system, where the total drug concentration is experimentally fixed. In real life, displacement can alter the total concentration of a drug without affecting C_{free} . A full discussion of this pharmacokinetic dilemma is beyond the scope of this editorial, but is excellently provided elsewhere [10].

We are reminded of the adage attributed sometimes to Albert Einstein, sometimes to William Bruce Cameron, that “not everything that can be counted counts, and not everything that counts can be counted.” The estimation of the real-time concentration of a free drug, able to exert biological effects and to be distributed, metabolised and cleared, remains an unsolved caveat. Yet awareness of how disease, nutrition and polypharmacy lead to relative shifts in f_u and C_{free} , and how this

relates (or not) to detectable total concentrations in plasma, is essential for optimal treatment.

Funding

The authors are supported by NIH (R01-HL131517 and R01-136389) and German Research Foundation (DFG, Do 769/4-1).

Disclosures

None.

References

- [1] T.Y. Chang, J.N. Liao, T.F. Chao, J.J. Vicera, C.Y. Lin, T.C. Tuan, et al., Oral anticoagulant use for stroke prevention in atrial fibrillation patients with difficult scenarios, *Int. J. Cardiol. Heart Vasc.* 20 (2018) 56–62.
- [2] G.A. Dan, D. Dobrev, Antiarrhythmic drugs for atrial fibrillation: imminent impulses are emerging, *Int. J. Cardiol. Heart Vasc.* 21 (2018) 11–15.
- [3] M. Kawai, M. Harada, Y. Motoike, M. Koshikawa, T. Ichikawa, E. Watanabe, et al., Impact of serum albumin levels on supratherapeutic PT-INR control and bleeding risk in atrial fibrillation patients on warfarin: a prospective cohort study, *Int. J. Cardiol. Heart Vasc.* 22 (2019) 111–116.
- [4] L.B. Hornsby, E.K. Hester, A.R. Donaldson, Potential interaction between warfarin and high dietary protein intake, *Pharmacotherapy.* 28 (4) (2008) 536–539.
- [5] Y.M. He, X.J. Yang, J. Hui, T.B. Jiang, J.P. Song, Z.H. Liu, et al., Low serum albumin levels in patients with paroxysmal atrial fibrillation: what does it mean? *Acta Cardiol.* 61 (3) (2006) 333–337.
- [6] R.K. Dubey, B. Leeners, B. Imthurn, G.S. Merki-Feld, M. Rosselli, Piperine decreases binding of drugs to human plasma and increases uptake by brain microvascular endothelial cells, *Phytother. Res.* 31 (12) (2017) 1868–1874.
- [7] A.H. Abdelhafiz, M.P. Myint, J.A. Tayek, N.M. Wheeldon, Anemia, hypoalbuminemia, and renal impairment as predictors of bleeding complications in patients receiving anticoagulation therapy for nonvalvular atrial fibrillation: a secondary analysis, *Clin. Ther.* 31 (7) (2009) 1534–1539.
- [8] M. Maciazek-Jurczyk, A. Szkuclarek, M. Chudzik, J. Pozycka, A. Sulkowska, Alteration of human serum albumin binding properties induced by modifications: a review, *Spectrochim. Acta A Mol. Biomol. Spectrosc.* 2018 (188) (2018) 675–683.
- [9] S. Niemann, A. Bertling, M.F. Brodde, A.C. Fender, H. Van de Vyver, M. Hussain, et al., Panton-Valentine Leukocidin associated with *S. aureus* osteomyelitis activates platelets via neutrophil secretion products, *Sci. Rep.* 8 (1) (2018) 2185.
- [10] P.L. Toutain, A. Bousquet-Melou, Free drug fraction vs free drug concentration: a matter of frequent confusion, *J. Vet. Pharmacol. Ther.* 25 (6) (2002) 460–463.