Kidney Medicine

Apixaban Dosing in Patients With Kidney Failure Treated With Peritoneal Dialysis

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As randomized controlled studies in the general population have continued to demonstrate the greater safety of direct oral anticoagulants over warfarin, a growing number of patients with kidney failure have been initiated on direct oral anticoagulants for treatment of nonvalvular atrial fibrillation. However, patients with kidney failure have an increased risk of both bleeding and clotting, making the risk–benefit calculation of anticoagulant use more complicated than it is for patients with normal kidney function. Despite this uncertainty, few studies have been conducted to explore the pharmacokinetics of direct oral anticoagulants in patients treated with maintenance hemodialysis (HD), and less still is known regarding patients treated with peritoneal dialysis (PD).

Related article, p ● ● ●

In this issue, Fung et al[1] describe the results of an open-label pharmacokinetics study of apixaban in 10 patients treated with PD. The authors recruited patients treated with PD with nonvalvular atrial fibrillation and no significant residual kidney function from a single center in the Hong Kong area, excluding those with increased risk of bleeding or contraindications to anticoagulation. Participants were given a total of 14 doses of apixaban, dosed 2.5 mg twice daily for 1 week, and venous blood was collected at multiple time points. The 12-hour steady-state area under the curve (AUC_{0-12}) for these participants was 2,574 ng·h/mL, which the authors noted was markedly higher than AUC_{0-12} values found in previous studies of apixaban, both in patients receiving HD and in patients without kidney disease.

To understand these findings, we must first consider the basic pharmacokinetics, distribution, and elimination of apixaban. Absolute oral bioavailability of apixaban is roughly 50%.[2,3] Apixaban has a volume of distribution of roughly 21 L, which is modified by body mass.[3,4] Multiple studies have noted that the AUC of apixaban is increased in patients with low body weight (<60 kg) and decreased in those with higher body weight.[5,6] Apixaban is extensively (roughly 87%) protein-bound, with albumin accounting for most of this protein binding.[7] The majority of apixaban is eliminated in stool, with renal elimination accounting for only around 27% of the total elimination.[4] Age is also significantly associated with apixaban AUC, irrespective of kidney function. A population pharmacokinetics study pooling data from phase 1-3 studies found that older patients (age greater than or equal to 65 years) had higher AUC than younger populations (age 18-40 years).[6] In accordance with these findings, the recommended dose for apixaban in nonvalvular atrial fibrillation in the United States is 5 mg by mouth twice daily, with a reduction to 2.5 mg twice daily in patients with 2 or more of the following: age greater than or equal to 80 years, weight ≤60 kg, and serum creatinine ≥1.5 mg/dL.[8] By contrast, in Europe, the reduced 2.5 mg twice daily dose is recommended for patients with creatinine clearance 15-29 mL/min, regardless of age or weight, and apixaban is not recommended for those with creatinine clearance <15 mL/min or undergoing dialysis.[9]

The recommended dose in the United States of apixaban for individuals receiving dialysis was based on a pharmacokinetic study of 8 patients treated with maintenance HD who were given a single dose of 5 mg of apixaban; these individuals had a 36% higher AUC compared with participants without kidney disease (Table 1).[10] Since then, more studies have been conducted examining the pharmacokinetics of the drug at steady state, when drug levels would be expected to be higher than after a single dose. Mavrakanas et al[11] recruited 7 maintenance HD patients and administered a reduced dose of 2.5 mg of apixaban twice daily for 8 days. In this group, with an average age of 62 years and mean body mass index of 32.9 kg/m^2, the AUC_{0-12} was 1,010 ng·h/mL, comparable to the AUC_{0-12} of healthy individuals who had received multiple doses of 5 mg twice daily.[12]

The recently-published Renal Hemodialysis Patients Allocated Apixaban Versus Warfarin in Atrial Fibrillation trial was a prospective, randomized, open-label, blinded outcome evaluation of apixaban versus warfarin in patients receiving HD with atrial fibrillation and a CHA_2DS_2-VASc score ≥2.[13] Participants were randomly assigned to 5 mg of apixaban twice daily, with this dose reduced to 2.5 mg twice daily for those participants who were greater than or equal to 80 years of age or weighed ≤60 kg. Patents were on average 68 years old, and the mean weight was 86 kg. Among participants taking apixaban 5 mg twice daily, the median steady-state AUC_{0-12} was 2,475 ng·h/mL, whereas among participants taking 2.5 mg twice daily, the median steady-state AUC_{0-12} was 1,269 ng·h/mL. These studies suggest that steady-state concentrations of apixaban are significantly higher in those treated with HD than in those with normal kidney function. Of note, the apixaban levels in patients treated with HD in the Renal Hemodialysis Patients Allocated Apixaban Versus Warfarin in Atrial Fibrillation study are still lower than those in patients treated with PD reported by Fung et al[1] (Table 1).

Several factors may explain the difference in pharmacokinetics between this study of patients treated with PD and the previous studies focused on patients treated with HD. First, participants in this study had a mean weight of

Table 1. Summary of AUC of apixaban obtained in studies of patients treated by using dialysis

Study	Fung et al[1]	Peyro-Saint-Paul et al[15]	Wang et al[10]	Mavrakanas et al[11]	Mavrakanas et al[11]	RENAL-AF[13]	RENAL-AF[13]
Dialysis modality	PD	PD	HD	HD	HD	HD	HD
N	10	12	8	7	7	20	43
Mean age (y)	70	63	47	62	62	68[a]	68[a]
Mean weight (kg)	61	74	96	Mean BMI, 33 kg/m^2	Mean BMI, 33 kg/m^2	86[a]	86[a]
Apixaban dose	2.5 mg 2×/d	Single 5 mg dose	Single 5 mg post-HD	2.5 mg 2×/d	5 mg 2×/d	2.5 mg 2×/d	5 mg 2×/d
$AUC_{0\text{-}12}$	2,574	NA	NA	1,010	3,027	1,269	2,475
AUC_{inf} (ng·h/mL)	NA	3,115	1,717	NA	NA	NA	NA

Abbreviations: AUC, area under the curve; BMI, body mass index; HD, hemodialysis; inf, infinity; PD, peritoneal dialysis; NA, not assessed; RENAL-AF, Renal Hemodialysis Patients Allocated Apixaban Versus Warfarin in Atrial Fibrillation.
[a]Reported mean age and weight for RENAL-AF is for the entire study population and not limited to participants in the pharmacokinetic substudy.

60.5 kg, barely above the 60 kg threshold for dose reduction to 2.5 mg twice daily and 20 kg lighter than the mean weight of patients in Renal Hemodialysis Patients Allocated Apixaban Versus Warfarin in Atrial Fibrillation (Table 1). Second, the mean age of participants in this study was 70 years, older than those in the HD studies (who were on average 62 and 68 years old), which may have also been associated with increased AUC. Third, participants had very low residual kidney function by 24-hour urine output collection (mean, 1.26 mL/min/1.73 m^2), which may have eliminated any potential renal clearance of apixaban, thereby increasing the observed AUC. Finally, participants in this study were recruited exclusively from a single clinic affiliated with the University of Hong Kong. It has been hypothesized that polymorphisms in CYP3A5 and P-glycoprotein might be associated with decreased elimination and increased AUC in Asian populations as compared with primarily White populations; however, population-based pharmacokinetic studies have suggested that this results in only modest decreases in clearance (roughly 12%), which are not thought to be clinically-significant.[6] These characteristics may in part explain the findings.

An additional possibility is that the dialysis procedure itself may clear apixaban differently in PD versus in HD. Despite being extensively protein-bound, a small amount of apixaban (roughly 4% of a dose given immediately before dialysis) is removed by the HD procedure,[11] although shorter times between apixaban administration and dialysis may augment HD clearance of apixaban.[14] By contrast, PD is associated with very low clearance of apixaban (0.67 ± 0.16% of an administered dose).[15] These dialysis effects would tend to increase the apixaban AUC in PD compared with HD, although the overall difference in clearance may be small.

This hypothesis is corroborated by a recent single-dose study of 5 mg of apixaban conducted in 12 patients treated with PD.[15] The average age was 63 years, and mean weight was 74 kg. Patients had a mean residual kidney clearance of 2.27 mL/min. The mean AUC in patients treated with PD was 73% higher than the mean AUC of healthy controls matched by age, weight, and sex. This was about twice as high as the 36% increase seen in the single-dose HD study. As opposed to the study by Fung et al[1], the difference in AUC cannot be explained by older age or lower weight, suggesting that PD may indeed clear apixaban less well than HD, independent of patient characteristics.

An important consideration in interpreting these findings, though, is whether the higher AUC described in this study of PD patients is concerning or not. Data from the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation trial, which established the use of apixaban in nonvalvular atrial fibrillation, noted median (IQR) steady-state AUC of 3,566 (2,926-4,286) ng·h/mL in participants with weight >60-120 kg.[16] It is important to note that rates of major bleeding were much lower in the apixaban arm of

Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation trial than the warfarin arm.[17] Similarly, in the Renal Hemodialysis Patients Allocated Apixaban Versus Warfarin in Atrial Fibrillation trial, despite a median AUC of 2,475 ng·h/mL, there were only 9 major bleeding events observed in 82 participants allocated apixaban over a median follow-up time of 330 days, which was not significantly greater than the bleeding events observed in the warfarin arm. Although we typically do not follow AUC as a clinical marker for apixaban dosing and there are no suggested AUC goals, it is unclear based on these data whether the median AUC reported in present analyses are concerning given that these AUC ranges do not seem to be associated with increased bleeding risk when compared with warfarin.

In conclusion, Fung et al[1] described the pharmacokinetics of apixaban 2.5 mg twice daily in a Chinese population of PD patients; the reported AUC_{0-12} was much higher than has been reported in patients on maintenance HD, which may be due, in part, to the older age and lower weight of the study participants, but also signals decreased clearance of apixaban in PD versus HD. It is unclear if these findings translate into an increased risk of bleeding. However, these results underscore the importance of dose reduction for apixaban in elderly patients with low body weight. Moreover, they suggest that it would be prudent to also reduce the dose of apixaban to 2.5 mg twice daily for stroke prevention in atrial fibrillation in patients treated with PD, no matter their age or weight. Notably, although this may be lower than what the United States has approved for patients with advanced kidney failure who are younger than 80 years of age and weigh at least 60 kg, it is already the recommended dose in Europe for all patients with stage 4 chronic kidney disease. Future studies in more diverse populations are clearly indicated to further assess the safety and effectiveness of apixaban among patients with kidney failure treated with PD.

ARTICLE INFORMATION

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REFERENCES

1. Fung WW, Cheng PM, Ng JK, et al. Pharmacokinetics of apixaban among peritoneal dialysis patients. *Kidney Med*. Published online May 1, 2023. https://doi.org/10.1016/j.xkme.2023.100646
2. Frost C, Wang J, Nepal S, et al. Apixaban, an oral, direct factor Xa inhibitor: single dose safety, pharmacokinetics, pharmacodynamics and food effect in healthy subjects. *Br J Clin Pharmacol*. 2013;75(2):476-487.
3. Vakkalagadda B, Frost C, Byon W, et al. Effect of rifampin on the pharmacokinetics of apixaban, an oral direct inhibitor of factor Xa. *Am J Cardiovasc Drugs*. 2016;16(2):119-127.
4. Frost C, Yu Z, Nepal S, et al. Apixahan, a direct factor Xa inhibitor: single-dose pharmacokinetics and pharmacodynamics of an intravenous formulation. *J Clin Pharmacol*. 2008;48(9):1132.
5. Upreti VV, Wang J, Barrett YC, et al. Effect of extremes of body weight on the pharmacokinetics, pharmacodynamics, safety and tolerability of apixaban in healthy subjects. *Br J Clin Pharmacol*. 2013;76(6):908-916.
6. Cirincione B, Kowalski K, Nielsen J, et al. Population pharmacokinetics of apixaban in subjects with nonvalvular atrial fibrillation. *CPT Pharmacometrics Syst Pharmacol*. 2018;7(11):728-738.
7. He K, Luettgen JM, Zhang D, et al. Preclinical pharmacokinetics and pharmacodynamics of apixaban, a potent and selective factor Xa inhibitor. *Eur J Drug Metab Pharmacokinet*. 2011;36(3):129-139.
8. Package insert. Bristol Myers Squibb. Eliquis (apixaban) prescribing information. 2018.
9. Eliquis, apixaban - European Medicines Agency. Accessed June 26, 2023. https://www.ema.europa.eu/en/documents/product-information/eliquis-epar-product-information_en.pdf
10. Wang X, Tirucherai G, Marbury TC, et al. Pharmacokinetics, pharmacodynamics, and safety of apixaban in subjects with end-stage renal disease on hemodialysis. *J Clin Pharmacol*. 2016;56(5):628-636.
11. Mavrakanas TA, Samer CF, Nessim SJ, Frisch G, Lipman ML. Apixaban pharmacokinetics at steady state in hemodialysis patients. *J Am Soc Nephrol*. 2017;28(7):2241-2248.
12. Frost C, Nepal S, Wang J, et al. Safety, pharmacokinetics and pharmacodynamics of multiple oral doses of apixaban, a factor Xa inhibitor, in healthy subjects. *Br J Clin Pharmacol*. 2013;76(5):776-786.
13. Pokorney SD, Chertow GM, Al-Khalidi HR, et al. Apixaban for patients with atrial fibrillation on hemodialysis: a multicenter randomized controlled trial. *Circulation*. 2022;146(23):1735-1745.
14. Van den Bosch I, Bouillon T, Verhamme P, et al. Apixaban in patients on haemodialysis: a single-dose pharmacokinetics study. *Nephrol Dial Transplant*. 2021;36(5):884-889.
15. Peyro-Saint-Paul L, Bechade C, Cesbron A, et al. Effect of peritoneal dialysis in end stage renal disease on apixaban pharmacokinetics. *Nephrol Dial Transplant*. Published online May 11, 2023. https://doi.org/10.1093/ndt/gfad087
16. Harrington J, Giczewska A, Wojdyla D, et al. Abstract 9290: Relationship between body weight and pharmacokinetics of apixaban in patients with atrial fibrillation: insights from the ARISTOTLE trial. *Circulation*. 2021;144(suppl 1):A9290.
17. Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365(11):981-992.