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EDITORIAL

The Practice of Emergency Medicine

Beware the counsel of the oracle

Pythia, the high priestess at the Temple of Apollo at Delphi, served as the Oracle of Delphi. In response to questions posed, the Delphic Oracle would give messages of advice, presumably from Apollo, that were often obscure in nature. Similarly, in modern Delphi analyses, questions are posed to a group of experts in a serial manner after which the experts are asked to reconsider their opinions and come to a joint recommendation through convergence or divergence of opinions.[1] Although there is more to the method, basically the Delphi method is an improved way for experts to come to a consensus opinion (recommendation). In this issue of *JACEP Open*, Fermann et al, used the Delphi method to conclude that physicians should consider administering reversal therapy for factor Xa (FXa) inhibitor (FXaI)–related life-threatening gastrointestinal (GI) bleeding.[2] Although it is not clear what makes the authors experts in this field and it is an industry-sponsored analysis in which AstraZeneca funded an independent nonprofit research organization to perform the study, the conclusions are not unreasonable. But, did we need a Delphic Oracle to tell us this? And, although we appreciate the Oracle's counsel, in our opinion, this question remains unanswered based on the following line of thought.

There are 3 important questions that we, as clinicians, need to ask related to any new pharmacologic agent, which in this case is a novel product used to reverse FXaI-associated GI bleeding. Does the reversal agent work to reverse the anticoagulant (AC)? Relatedly, does it specifically reverse the AC or does it have broad effects? The second question is does it improve outcome(s) (which might include death, instability, or need for transfusion)? Finally, is it worth it (cost)?

Direct oral ACs (DOACs) started with dabigatran, a direct thrombin inhibitor approved by the US Food and Drug Administration (FDA) in October 2010 followed by approval of the FXaIs rivaroxaban, apixaban, and edoxaban in 2011, 2012, and 2015, respectively. Initially, lacking specific reversal agents, hemorrhage while on one of these drugs was treated with non-specific interventions such as fresh frozen plasma (FFP) or prothrombin complex concentrate (PCC). FFP, having coagulation factor concentrations about 25 times lower than those found in PCC, is not recommended for the reversal of coagulopathy in patients who are taking a DOAC. PCC contains factors II (prothrombin), VII (depending on whether 3- or 4-factor PCC is used), IX, and X (FX). Although there is not enough FX in PCC to overcome the antagonizing effect of an inhibitor, PCC administration does partially normalize thrombin generation, with a dose-dependent effect.[3–7]

TABLE 1 Reduction in anti-FXa level after bolus of andexanet alfa

FXa inhibitor	Hours after bolus	Median reduction in anti-FXa level (%)
Rivaroxaban	4	43
	8	49
	12	61
Apixaban	4	35
	8	35
	12	38

Andexanet alfa received FDA approval in 2018 for the reversal of coagulopathy attributed to rivaroxaban and apixaban if their effects are contributing to life-threatening or uncontrolled bleeding.[8] It is a recombinant, inactive form of FXa that binds and sequesters FXaI molecules, reducing their AC effect. It is given as a bolus for a period of 15 minutes followed by an infusion for a period of 2 hours. Dosing of the bolus and infusion depends on the specific FXaI taken, the dose, and the time interval since the patient's last dose.

The physiologic efficacy of andexanet alfa can be measured through the reduction in the drug-specific anti-Xa level and is time related. Although there was an immediate drop of 92% in anti-X activity for apixaban and rivaroxaban, this level of reversal was not maintained over time. Table 1 contains data from the final report of the ANNEXA-4 trial regarding the median reduction in anti-Xa level after receiving a bolus of andexanet alfa.[9]

Abbreviation: FXa, factor Xa.

It is questionable whether this measure of physiologic efficacy is related to clinical outcomes; the authors found no correlation between mortality and anti-FXa activity level at nadir. This leads to the following second question: how well do reversal agents work clinically? Here too, proof of concept is also not compelling. Only 109 patients (23% of the total) in the ANNEXA-4 trial suffered from GI hemorrhage, the subgroup on which our Oracle intends to advise us. In this smaller group, 82% of patients had good or excellent hemostatic efficacy at 12 hours (Table 2) using a decrease in hemoglobin as a surrogate marker for their definition of efficacy. Also using this surrogate marker of instability, the authors found a correlation between hemostatic efficacy and mortality.

Importantly, there is no comparator group and no discussion of interventions (endoscopic or otherwise). With no comparator group,

TABLE 2 Definitions of hemostatic efficacy

Hemostatic efficacy	Gastrointestinal hemorrhage
Excellent	<10% decrease in hemoglobin[a] at 12 hours compared with baseline
Good	≤20% decrease in hemoglobin[a] at 12 hours compared with baseline

[a]Corrected for transfusion by subtracting 1 g/dl for each unit of packed red cells given.

the relative risk of harms cannot be determined, although 10% of patients suffered a thrombotic complication within 30 days of receiving andexanet alfa, all of which happened before restarting an oral AC.

So, andexanet alfa has hemostatic efficacy, but we do not know its clinical efficacy compared with usual care. Is this drug worth the price? Interestingly, the wholesale price was cut by more than half in April 2022. Yet andexanet alfa is not inexpensive. The cost of the low-dose protocol of andexanet alfa (83% of patients with intracranial hemorrhage [ICH] in ANNEXA-4 received the low-dose protocol) is $12,500; the cost for the high-dose protocol is $22,500.[10]

Based on clinical studies to date, the "worth it" question is not so easily answered. At least 2 economic model analyses (both by authors who have directly or indirectly worked with and received funding from the pharmaceutical company) have demonstrated the cost-effectiveness of andexanet alfa compared with PCC in patients with ICH.[11,12] We note that the ANNEXA-I trial, a randomized controlled trial comparing andexanet alfa with usual care in patients with ICH, was stopped early because of the superior efficacy of andexanet alfa, but there is no such data, economic or clinical, for GI bleeds, which are more amenable to intervention.[13]

As we move from the use of broad-spectrum ACs to factor-specific ACs, the prospect of specific reversal agents that do not also precipitate thromboses similar to broad-spectrum reversal therapies (factor VII, maybe PCC) presents clinicians an opportunity to do good without doing harm. However, based on the cost of these new drugs, hard outcomes must be demonstrated. We appreciate the Oracle's counsel, but this question remains unanswered. In the face of ongoing equipoise, clinicians will have to decide for themselves what is reasonable.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to report.

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REFERENCES

1. Beiderbeck D, Frevel N, von der Gracht HA, et al. Preparing, conducting, and analyzing Delphi surveys: cross-disciplinary practices, new directions, and advancements. *MethodsX*. 2021;8:101401. doi:10.1016/j.mex.2021.101401
2. Fermann G, Coehlo-Prabhu N, Maegele M, et al. Definition of factor Xa inhibitor-related life-threatening gastrointestinal bleeding and guidance on when to use reversal therapy: a Delphi panel. *JACEP Open*. 2023;4(5). doi:10.1002/emp2.13043
3. Nagalla S, Thomson L, Oppong Y, et al. Reversibility of apixaban anticoagulation with a four-factor prothrombin complex concentrate in healthy volunteers. *Clin Transl Sci*. 2016;9(3):176-180. doi:10.1111/cts.12398
4. Levi M, Moore KT, Castillejos CF, et al. Comparison of three-factor and four-factor prothrombin complex concentrates regarding reversal of the anticoagulant effects of rivaroxaban in healthy volunteers. *J Thromb Haemost*. 2014;12(9):1428-1436. doi:10.1111/jth.12599
5. Zahir H, Brown KS, Vandell AG, et al. Edoxaban effects on bleeding following punch biopsy and reversal by a 4-factor prothrombin complex concentrate. *Circulation*. 2015;131(1):82-90. doi:10.1161/CIRCULATIONAHA.114.013445
6. Cheung YW, Barco S, Hutten BA, et al. In vivo increase in thrombin generation by four-factor prothrombin complex concentrate in apixaban-treated healthy volunteers. *J Thromb Haemost*. 2015;13(10):1799-1805. doi:10.1111/jth.13115
7. Song Y, Wang Z, Perlstein I, et al. Reversal of apixaban anticoagulation by four-factor prothrombin complex concentrates in healthy subjects: a randomized three-period crossover study. *J Thromb Haemost*. 2017;15(11):2125-2137. doi:10.1111/jth.13815
8. FDA approval for andexanet alfa. https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/andexxa
9. Milling TJ, Middeldorp S, Xu L, et al. Final study report of andexanet alfa for major bleeding with factor xa inhibitors. *Circulation*. 2023;147(13):1026-1038. doi:10.1161/CIRCULATIONAHA.121.057844
10. Product Ordering Fact Sheet for Andexxa. Published April 1, 2022. https://www.andexxa.com/content/dam/open-digital/andexxa-hcp/en/pdf/ANDEXXA-Pricing-Leave-Behind-Email-Website-Resource.pdf
11. Fanikos J, Goldstein JN, Lovelace B, et al. Cost-effectiveness of andexanet alfa versus four-factor prothrombin complex concentrate for the treatment of oral factor Xa inhibitor-related intracranial hemorrhage

in the US. *J Med Econ*. 2022;25(1):309-320. doi:10.1080/13696998.2022.2042106

12. Micieli A, Demchuk AM, Wijeysundera HC. Economic evaluation of andexanet versus prothrombin complex concentrate for reversal of factor xa-associated intracranial hemorrhage. *Stroke*. 2021;52(4):1390-1397. doi:10.1161/STROKEAHA.120.031108
13. Andexxa phase IV trial stopped early after achieving pre-specified criteria on haemostatic efficacy versus usual care. Published June 5, 2023. https://www.astrazeneca.com/media-centre/press-releases/2023/andexxa-phase-iv-trial-stopped-early-after-achieving-pre-specified-criteria-on-haemostatic-efficacy-versus-usual-care.html