Direct Oral Anticoagulant Reversal in the Pediatric Emergency Department

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Abstract: Direct oral anticoagulants have been used in the adult population for years and are being used more frequently in pediatrics. Direct oral anticoagulants are chosen preferentially because they do not require close outpatient monitoring, have an equal or better safety profile, and are easy for patients to take. Warfarin is the previous, more commonly used oral anticoagulant and acts as a vitamin K antagonist. Direct oral anticoagulants mechanism of action is different in that they directly inhibit part of the coagulation cascade accomplishing the same end goal. Given their differing mechanisms, they require alternate medications for proper reversal when concerned about overdose of life-threatening bleeds. This review will outline the most commonly used direct oral anticoagulants in pediatric populations and the supporting (mainly adult) data available for proper reversal of these medications in times of need.

Key Words: direct oral anticoagulants, reversal, prothrombin complex concentrate, idarucizumab, andexanet alfa

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TARGET AUDIENCE

Emergency medicine, critical care and hematology providers, nurses, and pharmacists.

LEARNING OBJECTIVES

1. Describe the pharmacokinetics of direct oral anticoagulants and their reversal agents.
2. Identify agents available for reversal of anticoagulant agents, dosing and limitations.
3. Explain when to use targeted reversal agents for direct oral anticoagulants in addition to standard supportive care in the emergency department.

Use of direct oral anticoagulants (DOACs) in the pediatric population is increasing because more clinical data becomes available for use in younger patients. The appeal of DOACs is the reduced need for laboratory monitoring, ease of administration, predictable dosing, and safety profile. Because more pediatric patients are prescribed DOACs, providers need to know reversal techniques to use when faced with urgent, emergent, or life-threatening bleeding or overdose. There are 2 strategies: reversal, the targeted neutralization of anticoagulant; and replacement, provision of clotting factors to overcome the anticoagulants effects on the clotting cascade.

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There are 2 categories of DOACs; the anti-Xa inhibitors and the direct thrombin inhibitors (DTIs). Direct oral anticoagulants have been on the market since 2010 with the introduction of dabigatran and rivaroxaban, followed by apixaban in 2012, edoxaban in 2015, and betrixaban in 2017. Dabigatran is a DTI, similar to the intravenous agents, argatroban and bivalirudin. The other 4 medications are anti-Xa inhibitors, similar to enoxaparin and fondaparinux.

In July 2021, dabigatran became the first DOAC Food and Drug Administration approved for use in the pediatric population.[1] Other DOACs under evaluation have several phase I to IV trials in the enrollment process.[2,3]

TARGETED REVERSAL

The introduction of drug specific reversal agents for DOACs has increased the appeal of these agents in both adult and pediatric practice. Reversal agents have limited specific data for pediatric patients; however, the process differs little from adult management. There are 2 agents currently on the market that are agent specific.

Andexanet Alfa

Andexanet alfa was approved in 2018 and targets the reversal of DOACs. Currently, andexanet alfa is only approved for the reversal of apixaban and rivaroxaban; however, it is used off-label for edoxaban and betrixaban reversal. Andexanet alfa competitively binds to the Xa inhibitors, has a quick onset and short duration, and is given as an intravenous bolus and continuous infusion. The specific dose depends on the anticoagulant used and time since last administration. Concerns for the routine use of andexanet include cost and risk of thrombosis. Andexanet alfa is expensive; cost estimates note that a single dose can cost $25,000 to $50,000. In addition, there is thrombotic risk with andexanet alfa.[4–6] Currently, no pediatric data are available. The ANNEXA-4 trial was a prospective, open-label study that looked at the reversal of major bleeding for patients on rivaroxaban, apixaban, edoxaban, and enoxaparin. Hemostasis was evaluated to be good or excellent in 83% of the apixaban arm and 80% in the rivaroxaban arm. There were thrombotic events in 10% of the study patients within 30 days of reversal, even with the restart of anticoagulation, for which there is a black box warning in the prescribing information.[7,8]

Idarucizumab

Idarucizumab is approved for reversal of dabigatran, the only oral DTI. Idarucizumab is a monoclonal antibody fragment that binds to dabigatran and neutralizes its anticoagulant effects. Idarucizumab is administered as 2 short infusions of 2.5 g each, given approximately 15 minutes apart. Idarucizumab has immediate onset and can last for up to 24 hours from administration. The affinity for the binding of idarucizumab to dabigatran is 350 times that for the binding of dabigatran to thrombin.[9] Thrombotic risk is approximately 7% with idarucizumab, including the occurrence of deep venous thromboses, pulmonary emboli, ischemic strokes, atrial thrombi, and myocardial infarction. In one study, these events were not all related to the underlying disease for which patients

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were receiving dabigatran.[10] Currently, a phase III pediatric trial is recruiting and evaluating dosing ranges.[4–6]

Ciraparantag

Ciraparantag (PER977) is the most recently available reversal agent. The appeal of ciraparantag is that it will work by targeting reversal of a variety of anticoagulant products, including the DTIs (argatroban, bivalirudin, and dabigatran), together with unfractionated heparin, enoxaparin, and the factor Xa inhibitors. Trials are currently being conducted in adults only.[4–6]

Factor Replacement

Another strategy for reversing DOACs is the use of factor replacement. Factor replacement therapy is not specific to reversal of DOACS but works by replacing depleted or blocked factors in the clotting cascade (Figs. 1–3).

Four-factor PCC (4PCC or K-centra) is approved for warfarin reversal in adults. Four-factor PCC has also been used for life-threatening hemorrhage due to non–vitamin K anticoagulation, including DOACs, heparin, and DTIs. Four-factor PCC provides vitamin K–dependent clotting factors II, VII, IX, and X together with proteins C and S and is often coadministered with vitamin K to enhance its effects. Unlike vitamin K, 4PCC has a rapid onset of action; international normalized ratios can be reduced within 15 minutes of administration. Four-factor PCC should not be used in patients with a history of heparin-induced thrombocytopenia because it contains heparin. In adult studies looking at the use of 4PCC for nonspecific DOAC reversal, there was good hemostatic efficacy with low incidence of subsequent thrombotic events, although all-cause mortality was still fairly high.[16–18] There are no pediatric studies using 4PCC for DOAC-related bleeding; however, there are data for use of prothrombin concentrates in pediatric patients with major bleeding events.[19,20] There are no comparative studies directly between targeted antidotes and 4PCC in either the adult or pediatric populations.

Activated PCC (aPCC; Feiba) is an activated prothrombin complex concentrate of factors II, IX, X, and activated VII. Dose finding studies for reversal of DOACs ranged from 26 to 100 U/kg.[21,22] Thrombotic events and disseminated intravascular coagulation increased with doses higher than 50 U/kg.[23] A prospective study using aPCC in patients with intracranial hemorrhage (ICH) in adults on DOACs showed no expansion of the ICH or thrombotic events when aPCC was received with 48 hours of incident and median of 13 hours (10–29 hours) of last dose of their DOAC.[24]

BLOOD PRODUCTS

Blood products are also used in reversal, not necessarily to counter the medication directly but to replenish factors and volume that may be lost during a bleeding episode or by the mechanism of action of the anticoagulant medication(s). Whole blood products can be separated out into packed red blood cells, fresh frozen plasma, platelets, and cryoprecipitate. By transfusing packed red blood cells, the patient's volume status can be improved, thereby countering any alterations in hemodynamic instability. Common transfusion parameters are 10 to 20 mL/kg depending on severity of bleed and anemia.[25] Fresh frozen plasma can also provide volume, but more importantly, it provides all coagulation factors. Fresh frozen plasma is more readily available and is relatively inexpensive compared with other factor replacement products, such as antithrombin, factor VIIa, and anti-inhibitor coagulant complex. Each unit of plasma can increase factor levels by 10% to 20%[26] and should be transfused at 10 to 15 mL/kg.[25] Platelet transfusions can dilute the concentration of inhibited platelets due to aspirin or other antiplatelet agents, allowing hemostasis to normalize. Platelets are

Drug	Approved Indications	Administration	Drug Interactions	Half Life (hours)	Clearance Considerations	Pediatric Specific Info/ Pending Studies
Rivaroxaban (Xarelto®)	·NVAF ·Treatment and prevention of DVT/PE	·Indication specific frequency ·Pediatric dosing is more frequent due based on clearance ·Give with large meal if dose ≥ 15 mg ·Ok to give via NG/OG, but not ND ·may be crushed ·Avoid if >120 kg	·P-GP substrate ·CYP3A4/5	5-13 hrs	·66% renally cleared ·Avoid in severe hepatic impairment ·Avoid if CrCl < 30 mL/min; some available dose adjustment for specific indications ·Avoid in moderate to severe hepatic impairment	·EINSTEIN Jr: Phase III RC. S/E in acute VTE. 6 mon-18 yrs ·4 PK/PD studies have been completed
Apixaban (Eliquis®)	·NVAF ·Treatment of DVT/PE ·Prevention of DVT after THA/TKA	·twice daily ·can be given without regards to food ·Ok to give via NG/OG ·may be crushed ·Avoid if >120 kg	·P-GP substrate ·CYP3A4/5	8-15 hrs	·75% hepatically cleared ·Avoid in severe hepatic impairment ·Avoid if CrCl < 25 mL/min	·Phase I PK/PD prevention 37 weeks-18 yo (comp Oct 2017) ·Phase III, S/E to prevent clots in pediatric pts w/ leukemia or lymphoma w/ CVL & asparaginase (May 2020) ·Phase IV, open label, S/E for treatment of VTE (est completion April 2023) ·Phase IV, open label, safety and PK compared to Vit K antagonists or LMWH in pediatric cardiac patients (est completion Oct 2021)
Edoxaban (Savaysa®)	·Treatment of DVT/PE ·NVAF	·once daily ·can be given without regards to food ·Ok to give via gastric tubes ·may be crushed ·Avoid if >120 kg	·P-GP substrate	10-14 hrs	·50% renally & 50% hepatically cleared ·Renal dosing for CrCl 15-50 mL/min ·Black Box warning for CrCl >95 mL/min in NVAF ·Avoid in moderate to severe hepatic impairment	·Phase I: PK/PD and S/E vs SOC in treatment of VTE (comp Sept 2021) ·Phase III: PK/PD and S/E vs SOC in treatment of VTE (est completion December 2021)
Dabigatran (Pradaxa®)	·Treatment of DVT/PE ·NVAF	·twice daily ·give w/ food if having dyspepsia ·Needs to be in original container ·Avoid if >120 kg ·can crush/ break/ open (↑ absorption by 75%)	·P-GP substrate	12-17 hrs	·80% renally cleared ·Dose adjust for CrCl 30-50 mL/min ·Avoid if CrCl < 30 mL/min	·First DOAC approved for use in pediatrics (July 2021) ·Phase III: S/E vs SOC, dosing finding, birth-18 yo (comp Nov 2019) ·Phase III: S/E in secondary prevention of VTE (comp Nov 2019) ·Phase II: liquid formulation PK/PD

FIGURE 1. Direct oral anticoagulants and pediatric data (see end of the article).

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normally transfused at 10 to 15 mL/kg.[25] Cryoprecipitate replenishes fibrinogen and other clotting factors; 1 U (15–20 mL) can increase fibrinogen by 5 to 10 mg/dL. Pediatric dosing of cryoprecipitate ranges from 2 to 5 mL/kg and increases to adult dosing of up to 10 U per transfusion.[27]

Reversal Agent	Target	Dosing	Additional Information
4-factor PCC (K-centra®)	Off-label use for life-threatening hemorrhage associated with non-vitamin-K anticoagulation	aFXI: 25-50 units/kg (up to 2000 units) DTI: 50 units/kg	Provides coagulation factors II, VII, IX, & X plus Protein C & S IV bolus Quick onset ~ 10 minutes Duration ~ 7 hours Contains heparin—avoid in patients with active HIT Quick preparation time
aPCC (Feiba®)	Off-label use for life-threatening hemorrhage associated with non-vitamin-K anticoagulation	aFXI or DTI: 50 units/kg	Provides factors II, IX and X and activated VII IV bolus Onset ~15-30 minutes Duration 8-12 hrs
Andexanent alfa (Andexxa®)	FDA approved: apixaban and rivaroxaban Off label: edoxaban and betrixaban	**Low Dose: 400 mg bolus(30 mg/minute) then 4 mg/min infusion up to 120 minutes** Rivaroxaban ≤10 mg (<8 hrs or unknown since last dose) Apixaban ≤5 mg (<8 hrs or unknown since last dose) Any dose/any agent >8 hrs since last dose **High Dose: 800 mg bolus(30 mg/minute) then 8 mg/min infusion up to 120 minutes** Rivaroxaban >10 mg or unknown dose (<8 hrs or unknown since last dose) Apixaban >5 mg or unknown dose (<8 hrs or unknown since last dose)	Competitive binding to direct FXa inhibitors IV bolus +/- infusion Quick onset ~5 minutes Short Duration ~2 hours Expensive Thrombotic risk Prep time can be 30-60 minutes to reconstitute all 5-9 vials needed per dose
Idarucizumab (Praxbind®)	dabigatran	Fixed dosing: 2.5 g x 2 within 15 minutes of each other No pediatric data/dosing available	Non-competitive with high binding affinity for dabigatran Short infusion Immediate onset of action Duration 12-24 hours
Ciraparantag	UFH, LMWH, Xa inhibitors, DTIs		Currently under investigation in adult population only

FIGURE 2. Reversal agents.[11–14]

Society	When to Use	First Line	Second Line Alternative	Supportive
NCS/SCCM 2016	ICH	**Dabigatran**: Idarucizumab **aFXI:** 4PCC or aPCC	**Dabigatran**:4PCC or aPCC	Activated charcoal if recent ingestion (<2 hrs) and low risk of aspiration
ESO 2019	ICH	**Dabigatran**: Idarucizumab **Apixaban/Rivaroxaban:** andexanet alfa[a] **Edoxaban:** 4PCC	**Apixaban/Rivaroxaban:** 4PCC (37.5-50 units/kg) **Edoxaban:** 4PCC 50 units/kg	Recommend against FFP and antifibrinolytics
Anticoagulation Forum 2019	Life-threatening, critical site or unresponsive major bleeding	**Dabigatran**: Idarucizumab **Apixaban/Rivaroxaban:** andexanet alfa[a] **Edoxaban:** high dose andexanet alfa	**Dabigatran**: aPCC **aFXI:** 4PCC	Fluid resuscitation, transfusion, compression/surgery/IR, and charcoal if recent ingestion, antifibrinolytics if mucosal bleeding (epistaxis, uterine)
ACC 2020	Major bleeding	**Dabigatran**: Idarucizumab **Apixaban/Rivaroxaban:** andexanet alfa[a] **Edoxaban:** high dose andexanet alfa	**Dabigatran**:4PCC or aPCC **aFXI:** 4PCC or aPCC	Fluid resuscitation, transfusion, compression/surgery/IR, and charcoal if recent ingestion (<4 hrs)
ACEP 2020	Life-threatening or critical site bleed, emergent procedure	**Dabigatran**: Idarucizumab **Apixaban/Rivaroxaban:** andexanet alfa[a] **Edoxaban:** high dose andexanet alfa	**Dabigatran**:4PCC (preferred) or aPCC or dialysis **aFXI:** 4PCC(preferred) or aPCC	Fluid resuscitation, transfusion, compression/surgery/IR, and charcoal if recent ingestion (<2 hrs), antifibrinolytics if mucosal bleeding (epistaxis, uterine)

FIGURE 3. Summary of DOAC reversal from various societies.[11–15].

EXPERT OPINION AND RECOMMENDATIONS FOR APPROACHING DOAC REVERSAL

In the clinical setting, there is much debate over which strategy to use in various clinical scenarios. The first step in treating a bleeding patient is always supportive measures: airway, breathing, and circulation.

The most recent guidelines for DOAC reversal comes from a collaboration between the Neurocritical Care Society and the Society of Critical Care Medicine (NSC/SCCM) published in 2016, which was just before the Food and Drug Administration approval of andexanet alfa. The committee's joint recommendation for patients taking factor Xa inhibitors with a suspected or confirmed ICH or a major bleed is to use 4PCC if the event occurred within 3 to 5 terminal half-lives of the anticoagulant or in the context of liver failure. They recommend this over other factor replacement with rFVIIa because of the lower risk of thrombotic complications. If the exposure is less than 2 hours and the patient is intubated with enteral access or at a low risk of aspiration, activated charcoal should also be used. They do acknowledge that these recommendations are conditional and have low-quality evidence.[11]

For patients exposed to dabigatran, the committee recommends using idarucizumab if the event occurred within 3 to 5 terminal half-lives of the exposure. If the setting of renal insufficiency, one can administer idarucizumab beyond normal 3 to 5 half-lives because of delayed clearance and should consider emergent dialysis. In the event that idarucizumab is not available, the recommendation is to use 4PCC.[11] Although there is debate about redosing of reversal agents, the NSC/SCCM recommendations do suggest the consideration of repeating a dose of idarucizumab if there is ongoing, clinically significant bleeding after the initial treatment. Based on the lack of efficacy, the committee did recommend against use of rFVIIa for reversal of dabigatran.[11,21,28,29]

The European Stroke Organization guidelines for DOAC reversal in the presence of ICH differ from the NSC/SCCM

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guidelines. In adult patients taking apixaban or rivaroxaban with ICH, the European Stroke Organization recommends the first-line use of andexanet alfa based on the data from the ANNEXA-4 study.[7,15] For anti-Xa inhibitors, they recommend use of 4PCC at doses of 37.5 to 50 U/kg. This is based on data in healthy patients that showed complete reversal for edoxaban and rivaroxaban at 50 U/kg and partial reversal of all agents at 25 U/kg. There have been no safety data for the use of 4PCC in DOAC-associated ICH. Four-factor PCC was not successful in the reversal of dabigatran.[15,30–34] For patients on dabigatran, they strongly recommend the utilization of idarucizumab for reversal of ICH in adult patients based on data presented in RE-VERSE AD trial.[10,15]

The North American Anticoagulation Forum published their guidelines on the reversal of DOACs in 2019. Their recommendations are to use reversal agents only in the event of life-threatening bleeding, bleeding that involves a critical organ, or if bleeding is not controlled by initial supportive measures. The Anticoagulation Forum recommends idarucizumab as first-line for dabigatran reversal, but if not available to use aPCC. For factor Xa inhibitors, they recommend andexanet alfa for apixaban- and rivaroxaban-related bleeding if available otherwise 4PCC. For patient with edoxaban- or betrixaban-related bleeding, they recommend the off-label use of high-dose andexanet alfa or 4-factor PCC. These are the same agent-specific recommendations if an emergent invasive procedure. In the event of an overdose or trauma without bleeding, the Anticoagulation Forum recommends against the use of reversal agents but rather to focus on standard supportive measurements.[12]

The American College of Cardiology (ACC) released their expert consensus in 2020 for the management of bleeding in patients on oral anticoagulants. For nonmajor bleeding, the committee does not support the routine use of reversal agents, rather the temporary discontinuation of the agent. For major bleeding, the committee recommends the utilization of reversal agents if available. First line for dabigatran would be idarucizumab; if not available, then the ACC recommends 4PCC or aPCC. For apixaban or rivaroxaban, the ACC recommends andexanet alfa if available, otherwise 4PCC or aPCC. For bleeding related to betrixaban or edoxaban, they recommend high-dose andexanet alfa first- or second-line therapy with PCC or aPCC. Their recommendations are based on product availability and acknowledge that there are currently no randomized trials comparing targeted therapy to factor replacement.[13]

The American College of Emergency Physicians assembled a panel to develop a consensus on how to approach patients presenting to the emergency department. Their algorithm does not differentiate adult and pediatric care. The algorithm first asks if bleeding is life-threatening, at a critical site, or if an emergent procedure is indicated. If so, the first steps are to provide emergent treatment and supportive care with appropriate laboratory/radiologic workup and then to initiate treatment if the last dose of DOAC is within a certain time frame. Reversal is then divided into Tier 1 and Tier 2, with Tier 1 being targeted reversal and Tier 2 being factor replacement and other supportive therapies if a Tier 1 product is not available.[14]

LABORATORY MONITORING OF DOACS

The International Council for Standardization in Hematology developed a consensus of recommendations for the laboratory monitoring of DOACs, when clinically necessary. There are both qualitative and quantitative measurements possible but are limited by availability and turnaround time. Based on pharmacokinetic studies of the individual agents, the International Council for Standardization in Hematology presented expected "therapeutic ranges" for specific doses and indications of the four most used DOACs.

The criterion standard quantitative measurement for all DOACs is the use of liquid chromatography-tandem mass spectrometry; however, use in the clinical setting is limited given the wide therapeutic range of these medications and lack of correlation between drug level and bleeding risk.[35]

Qualitative measures to assess the presence or absence of a DOAC are more readily available, especially in the emergency department setting, but these also have limitations. Each of these agents interferes with various standard coagulation studies that are more widely available and less costly than quantitative measurements. Dabigatran can prolong activated partial thromboplastin time and thrombin time, and the anti-Xa inhibitors can be detected by the anti-Xa measurements (unfractionated heparin and low molecular weight heparin) and prolonged PT, although none of these indicate the significance in relation to a level or bleeding risk.[13,35]

DISCUSSION

Anticoagulation reversal may not require the use of targeted antidotes if there is time for the medication to be cleared from the bloodstream while providing other supportive therapies; however, there are times when pediatric patients are experiencing life- or organ-threatening complications from their anticoagulation when the use of a reversal agent may be warranted. It is imperative that the providers know what agents are available in their armamentarium, how to use these products, and in what situations. For any pediatric patient currently taking a DOAC that presents to the emergency department with concerns for bleeding, overdose, or need for emergent surgery, the agent should be discontinued. Providers should determine the last time a patient received a dose. If needed to stabilize the patient, transfusion of blood products should be initiated. If bleeding is unable to be halted with supportive therapy, use of a reversal agent should be considered.[36] There are limited data to indicate that supratherapeutic levels are linear to the bleed risk associated with the DOACs.[37] Furthermore, the therapeutic ranges are extremely wide and not necessarily dose dependent.[38]

Targeted reversal is the preferred choice for an antidote; however, there may be limitations in the pediatric population. Currently, there is no pediatric dosing for andexanet alfa or idarucizumab. The use of DOACs in the pediatric population is most common in older, more adult patients, making the use of these reversal agents more feasible. More research is necessary in younger patients to know what the safest and most effective dose would be. Given available dosing parameters and data for the use of 4PCC and aPCC in the pediatric population, it is more commonly used as a reversal agent. Because of the lack of data and the high cost of acquisition, andexanet alfa and idarucizumab are less likely to be available. Lastly, time to administration of a reversal agent is one of the most important factors in minimizing morbidity and mortality. Adexanent alfa can take up to 60 minutes to prepare, whereas PCC is more readily available.

Pediatric hospitals that are seeing their patients use DOACs should develop reversal strategies for the potential of bleeding events. These strategies should encompass a collaborative, multidisciplinary approach between hematology, pharmacy, cardiology, surgery, critical care, and emergency medicine providers. This cooperative approach will decrease delays in care and help providers choose the most appropriate agent in a timely manner.

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