Bleeding news

Anticoagulation reversal (vitamin K, prothrombin complex concentrates, idarucizumab, andexanet-α, protamine)

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In this **bleeding news** we will discuss this **review article** on the available drugs to revert anticoagulation in patients suffering from critical hemorrhage.

Pharmacokinetics and pharmacodynamics of frequently used anticoagulants

ANTICOAGULANTS	Inhibited factors	Time maximum concentration	Metabolism	Half life	Monitoring
ANTI-VITAMIN K	II, VII, IX, X		Hepatic		INR
Warfarin		72-96 h		31-51 h	
Acenocumarol		1-3 h		3-11 h	
HEPARINS			Hepatic + RES		
UHF	Xa, IIa (AT III)	minutes		0.5-2 h	APTTr
LMWH	Mainly Xa (AT III)	3-6 h		2-7 h	Not necessary Possible, Anti-Xa
DOACs					Not necessary Possible, Anti-Xa
Dabigatran	IIa	0.5-2 h	Unaltered renal clearance	12-17 h	
Xabans (Rivaroxaban, Apixaban, Edoxaban)	Xa	1-4 h	Hepatic	5-15 h	

Viscoelastic tests are being used by some authors to monitor anticoagulation, although always together with the tests described in the table above, with no clear evidence.

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Anticoagulants and their antidotes

ANTIDOTES	ANTICOAGULANTS	Dose in case of critical hemorrhage	Adverse reactions
VITAMIN K	Anti-Vitamin K	10 mg iv	✓ Low risk of anaphylaxis ✓ INR correction excess with ↑ dose
4-CCP	Anti-Vitamin K	INR 2-4: 25 UI/Kg iv INR 4-6: 35 UI/Kg iv INR > 6: 50 UI/Kg iv	3-8 % thrombotic events
	DOACs	25-50 UI/Kg iv	
IDARUCIZUMAB	Dabigatran	2 perfusions, 2.5 mg each, iv in 10 min	4-5 % thrombotic events
ANDEXANET-α	Rivaroxaban, Apixaban	✓ Low dose: 400 mg (bolus), 480 mg (in 2 h) iv ✓ High dose: 800 mg (bolus), 960 mg (in 2 h) iv	10-14% thrombotic events
PROTAMINE	Heparins	✓ It should be administered in at least 10 min ✓ Not more than 50 mg at once	✓ Immunoallergic reactions ✓ Paradoxal increase of anticoagulation with excessive dose
	UHF	✓ Usually not necessary after STOP 3 h ✓ 1 mg of protamine neutralizes 1 mg UHF	
	LMWH	✓ 1 mg protamine neutralizes 1 mg enoxaparin (within 8 hours of administration) ✓ 1 mg protamine neutralizes 100 UI dalteparin or nadroparin	

To revert anticoagulation of **anti-vitamin K** drugs, we must never forget jointly administering vitamin K together with 4F-PCC.

In case of intoxication with **rat poison** (which contains anti-vitamin K drugs), high doses of vitamin K (25-600 mg/day iv) should be administered. It could even be necessary to extend the treatment for months, since the toxin can accumulate in the fatty tissue.

To revert anticoagulation caused by **dabigatran**, idarucizumab is the first-choice treatment. If it is not available, 4F-PCC administration may be considered.

As for thrombotic events evidenced when using 4F-PCC, they look like the ones expected from the baseline disease that led to the indication of anticoagulants.

To revert anticoagulation induced by **rivaroxaban and apixaban** against a critical cerebral hemorrhage, andexanet-à would be the preferred treatment rather than 4F-PCC. When the commented article was published, there had been no communication yet of the ANNEXA-I clinical trial results [Connolly SJ, et al; ANNEXA-I Investigators. Andexanet for Factor Xa Inhibitor-Associated Acute Intracerebral Hemorrhage. N Engl J Med. 2024 May 16;390(19):1745-1755. doi: 10.1056/NEJMoa2313040. PMID: 38749032], which proved the efficacy

of andexanet-α to revert hemostasis in anticoagulated patients on rivaroxaban or apixaban with cerebral hemorrhage.

In order to revert the anticoagulation induced by **rivaroxaban and apixaban** against a critical non-cerebral hemorrhage, the use of andexanet-à may be considered, based on observational studies on real-world evidence, since there is no clinical trial in those clinical settings.

As for thrombotic events evidenced when using andexanet-α, they look higher than those expected from the baseline disease that led to the indication of anticoagulants. Thus, the ANNEXA-I clinical trial reported up to 10.3% of thrombotic events, compared to 5.6% in the usual treatment group, with mortality not increasing but a higher incidence of ischemic stroke.

In **conclusion**, in case of a critical hemorrhage in an anticoagulated patient, we have antidotes available. We must bear in mind that in case of an overdose without critical bleeding, they must not be used, given their thrombotic risk. Antidotes with sound scientific evidence are vitamin **K + 4F-PCC** to revert anticoagulation induced by **anti-vitamin K; idarucizumab** to revert anticoagulation induced by **dabigatran, protamine** to revert anticoagulation induced by **HNF,** and **andexanet-α** to revert anticoagulation induced by **rivaroxaban or apixaban** in case of critical cerebral hemorrhage.

Abbreviations. 4F-PCC: Four-factor prothrombin complex concentrate. UHF: Unfractionated heparin LMWH: Low molecular weight heparin RES: Reticuloendothelial system DOACs: Direct oral anticoagulants