LETTER TO THE EDITOR

Anticoagulation Strategies for the Orthopaedic Surgeon: Reversal and Timelines

Dear Editor

Anticoagulation and antiplatelet therapies present dynamic challenges for orthopaedic surgeons in both urgent and elective settings. While lifesaving for many, these ubiquitous drugs provide an extra variable in maintaining the hemodynamic status of an orthopaedic patient. Due to the rapid proliferation of drugs available and shifting demographics, it is of paramount importance to be able to quickly reference the mechanism of action, half-life of elimination, and potential reversal agent for each commonly available therapy for thromboembolic disease prior to surgical intervention. Here, we have compiled the relevant information in a comprehensive reference chart to guide decision making and orthopaedic surgeon education.

In 2000, the percentage of the male and female population over sixty-five years was eleven and fifteen percent, respectively. This is expected to increase to 22.7 for males and 27.7 percent for females by 2050 (1). This increase in the geriatric population is already impacting the field of orthopaedic surgery—patients sixty-five and older are the fastest growing patient demographic at trauma centers, already accounting for over 25% of trauma patients (2). These geriatric patients are getting ever more complicated to manage. Barnes et al. presents data suggesting that quarterly visits to physicians for oral anticoagulant management raised by roughly 40% from 2009 to 2.83 million visits per quarter in 2014 (3). These demographic shifts represent an increased percentage of orthopaedic patients with both thromboembolic and hemodynamic risk.

Anticoagulation is not only becoming more prevalent; it is becoming more diverse. While 66.8% of Medicare beneficiaries with atrial fibrillation (AF) are currently taking warfarin, direct oral anticoagulants (DOACs) are quickly gaining market share (4). These DOACs provide therapeutic advantages over the traditional anticoagulants, however, they also present new operative variables and with them, risks. Interestingly, AF patients treated with warfarin are significantly more comorbid than their counterparts taking dabigatran extexilate (5). It is, therefore, essential for the orthopaedic surgeon to fully understand the range of therapies offered, the indications for these therapies, and their pharmacology to make evidence-based decisions.

A 2015 survey of sixty-seven American orthopaedic surgeons found a wide variance in perioperative management of antiplatelet therapies. In fact, sixty-four percent of surgeons responded that there is no protocol in place at their institution to manage these patients (6). The purpose of this study is to provide a comprehensive, centralized reference of current anticoagulation medications as well as data on reversibility and half-life of elimination for each of these products as is relevant to decision making in orthopaedic surgery. Indeed, the time spent gathering such information necessary to guide an informed decision in an institution without a management plan is an unnecessary and potentially dangerous use of time.

An exhaustive list of antiplatelet and anticoagulant drugs was compiled from UpToDate (Waltham, MA), review articles, and drug information inserts. Organized by mechanism of action, this easy-to-read, comprehensive reference chart is designed to be kept on hand to plan and manage both trauma patients requiring urgent orthopaedic surgical intervention as well as non-urgent or elective orthopaedic surgeries for patients currently taking anticoagulants or antiplatelets.

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Table 1. Listing of anticoagulants along with anticoagulant specific parameters useful to orthopaedic clinical practice

	Category	Drug Name	Trade Name	Mechanism of Action	Monitoring Parameters	Metabolism	Excretion	Drug Half-Life Elimination	Duration of Effect	Reversal	Sources
ANTIPLATELETS	ADP RECEPTOR / P2Y12 INHIBITORS	Clopidogrel	Plavix	Irreversibly blocks the P2Y12 component of ADP receptors on the platelet surface, preventing platelet aggregation.	Signs of bleeding, hemoglobin & hematocrit	Hepatic conversion of pro-drug to active metabolite: CYP2C19 (major), CYP3A4 (minor)	50% renal, 46% fecal	Parent drug: ~6h; Active metabolite: ~30min	~5d after discontinuation	No specific reversal agent. Discontinue drug and consider platelet transfusion and/or desmopressin.	Frontera et al (2016), Jiang et al (2017), UpToDate
		Prasugrel	Effient	Irreversibly blocks the P2Y12 component of ADP receptors on the platelet surface, preventing platelet aggregation.	Signs of bleeding, hemoglobin & hematocrit	Intestinal and serum metabolism of pro-drug to inactive intermediate. Hepatic conversion to active metabolite: CYP2B6 (minor), CYP3A4 (minor)	68% renal, 27% fecal	Active metabolite: ~7h (range: 2-15h)	5-9d after discontinuation	No specific reversal agent. Discontinue drug and consider platelet transfusion and/or desmopressin.	Frontera et al (2016), Mousa et al (2010), UpToDate
		Ticagrelor	Brilinta	Reversible binding to P2Y12 component of ADP receptors on the platelet surface, preventing platelet aggregation	Signs of bleeding, hemoglobin, hematocrit, renal function, uric acid levels, signs/ symptoms of dyspnea	Hepatic: CYP3A4 (major)	26% renal, 58% fecal	Parent drug: ~7h; Active metabolite: ~9h	Antiplatelet effect is reduced to 30% after ~56h and 10% after ~110h. Duration of effect is 3-5d	No specific reversal agent. Discontinue drug and consider platelet transfusion and/or desmopressin.	Frontera et al (2016), Teng (2015), UpToDate
		Ticlopidine (Not available in USA)	Ticlid	Irreversibly blocks the P2Y12 component of ADP receptors on the platelet surface, preventing platelet aggregation.	Signs of bleeding, CBC, liver function tests	Hepatic: CYP3A4 (major)	60% renal, 23% fecal	13h (increased in renal failure)	Maximal effect at 3-5d, duration of effect is life of platelet (5-10d)	No specific reversal agent. Discontinue drug and consider platelet transfusion or desmopressin.	Frontera et al (2016), Saltiel et al (1987), UpToDate
	GLYCOPROTEIN IIB/IIIA INHIBITORS	Abciximab	ReoPro	Antibody irreversibly binds to platelet glycoprotein IIb/IIIa receptors, preventing platelet aggregation	PT, PTT, hemoglobin, hematocrit, platelet count, fibrinogen, fibrin split products, signs of hypersensitivity reactions, guaiac stools, Hemastix urine	None known	Proteolytic cleavage of unbound antibody	Plasma: ~30min; Dissociation from receptors: ~4h (29% and 13% bound to receptors at 8 and 15 days, respectively)	Platelet function recovery takes 24-48h. Up to 72h for restoration of normal hemostasis. Up to 7d for normal shear-dependent platelet testing	No specific reversal agent. Discontinue drug and consider platelet transfusion or desmopressin.	Frontera et al (2016), Kondo et al (2002), Schror et al (2003), UpToDate
		Eptifibatide	Integrilin	Cyclic heptapeptide reversibly blocks platelet glycoprotein IIb/IIIa receptors, preventing platelet aggregation	Signs of bleeding, PT, PTT, hemoglobin, hematocrit, serum creatinine, platelet count	None known	71.4% renal, 1.5% fecal	~2.5h	Platelet function is restored within ~4-8h following discontinuation	No specific reversal agent. Discontinue drug and consider platelet transfusion or desmopressin.	Frontera et al (2016), Tardiff et al (2001), UpToDate
		Tirofiban	Aggrastat	Reversible antagonist of glycoprotein IIb/ IIIa receptors, preventing platelet aggregation	Signs of bleeding, hemoglobin & hematocrit, platelet count	None known	65% renal, 25% fecal	~2h	Platelet function is restored within ~4-8h following discontinuation	No specific reversal agent. Discontinue drug and consider platelet transfusion or desmopressin.	Frontera et al (2016), UpToDate
	OTHER PLATELET INHIBITORS	Dipyridamole	Persantine	Reversibly inhibits adenosine deaminase & phosphodiesterase, preventing platelet aggregation	IV: blood pressure, heart rate, ECG, respiration, signs of poor perfusion	Hepatic: conjugated to glucuronic acid & excreted in bile	Fecal	~10-12h	Platelet aggregation returns to near baseline ~3h following discontinuation	No specific reversal agent. Aminophylline may be considered to treat symptoms of vasodilation caused by dipyrimadole. Discontinue drug and consider platelet transfusion or desmopressin.	Frontera et al (2016), Granato et al (1990), Gregov et al (1987), UpToDate
		Aspirin	(Various)	Irreversible inhibitor of COX-1 & 2, leading to decreased thromboxane A2, preventing platelet aggregation	Signs of bleeding and GI ulcers	Hydrolyzed to active metaboite in GI mucosa, RBCs, synovial fluid & blood. Metabolism of active metabolite occurs by hepatic conjugation: CYP2C9 (minor)	5.6-35.6% renal	Parent drug: ~15-20min; Active metabolite: ~3-10h depending on dose	Platelet lifetime (~10d)	No specific reversal agent. Discontinue drug and consider platelet transfusion or desmopressin.	Altman et al (2004), Frontera et al (2016), UpToDate
		Extended Release Aspirin/ Dipyridamole	Aggrenox	Refer to individual components above	Signs of bleeding, GI ulcers, stroke or TIA	Refer to individual components above	Refer to individual components above	Refer to individual components above	Refer to individual components above	Refer to individual components above	Altman et al (2004), Frontera et al (2016), Granato et al (1990), Gregov et al (1987), UpToDate

Table 1. Continued

ANTICOAGULANTS	VITAMIN K ANTAGONISTS	Warfarin	Coumadin, Jantoven	VKOR subunit 1 inhibitor, thus depleting active vitamin K reserves and reducing synthesis of factors II,VII,IX & X	PT/INR, hematocrit, genotyping of CYP2C9 and VKORC1 prior to initiation of therapy	Hepatic: CYP2C9 (major), CYP1A2 (minor), CYP2C19 (minor), CYP3A4 (minor)	92% renal	Highly variable: ~40h (range: 20-60h)	~2-5d	If surgery can be delayed for 6-12h consider IV vitamin K administration. If surgery cannot be delayed, consider PCC administration with concurrent vitamin K	Curtis et al (2015), Frontera et al (2016), UpToDate
	HEPARIN AND LMWH	Unfractionated Heparin	N/A	Potentiates the action of antithrombin III, inactivating thrombin (and factors IX, X, XI, XII & plasmin) and preventing fibrin formation	Signs of bleeing, hemoglobin, hematocrit, FOBT, PTT, ACT, platelet count	Thought to occur by depolymerization & desulfation via reticuloendothelial system primarily in liver & spleen	Renal	~1.5h (range: 1-2h). Affected by obesity, renal function, malignancy, PE & infections. Shorter in premature neonates	Variable	IV protamine sulfate rapidly reverses	Frontera et al (2016), Garcia et al (2012), UpToDate
		Enoxaparin	Lovenox	LMWH, potentiates the action of antithrombin III. Has a higher ratio of antifactor Xa to antifactor IIa than UFH	Platelet count, FOBT, anti-Xa, serum creatinine	Hepatic via depolymerization and desulfation	40% renal	Based on anti-Xa activity: ~4.5-7h (2-4x longer than UFH)	Antifactor Xa activity: ~12h (40mg)	IV protamine sufate partially reverses the effects of LMWH	Frontera et al (2016), Garcia et al (2012), UpToDate
		Dalteparin	Fragmin	LMWH, potentiates the action of antithrombin III. Has a higher ratio of antifactor Xa to antifactor IIa than UFH	Platelet count, FOBT, anti-Xa, signs of neurological impairment	None known	Renal	IV: ~2.1-2.3h; SubQ: ~3-5h	>12h	IV protamine sufate partially reverses the effects of LMWH. May also consider rFVIIa if protamine is contraindicated	Frontera et al (2016), Garcia et al (2012), UpToDate
		Tinzaparin (Not available in USA)	Innohep	LMWH, potentiates the action of antithrombin III. Has a higher ratio of antifactor Xa to antifactor IIa than UFH	Platelet count, renal function, hepatic function, potassium, FOBT, anti-Xa in certain patients	None known	Renal	82min (prolonged in renal insufficiency)	Antifactor Xa activity: ~24h	IV protamine sufate partially reverses the effects of LMWH. May also consider rFVIIa if protamine is contraindicated	Frontera et al (2016), Garcia et al (2012), UpToDate
	PENTASACCHARIDES	Fondaparinux	Arixtra	Pentasaccharide causing an antithrombin III-mediated inhibition of factor Xa, disrupting thrombin formation	CBC, platelet count, serum creatinine, FOBT, anti-Xa, signs of neurological impairment	None known	50-77% renal	~17-21h (prolonged in elderly & renal insufficiency)	~2-4d with normal renal function	No specific reversal agent. Discontinue drug and consider PCC or rFVIIa	Frontera et al (2016), Garcia et al (2012), UpToDate
	DIRECT FACTOR Xa INHIBITORS	Apixaban	Eliquis	Reversible factor Xa inhibitor, preventing conversion of prothrombin to thrombin	Renal function, CBC, hepatic function, signs of bleeding	Hepatic: BCRP/ABCG2, CYP1A2 (minor), CYP2C19 (minor), CYP2C8 (minor), CYP2C9 (minor), CYP3A4 (major), P-glycoprotein/ABCB1	Majority fecal, 27% renal	~12h (range: 8-15h)	INR, PT & PTT return to normal after ~12h	No specific reversal agent. Discontinue drug and consider activated charcoal, tranexamic acid and PCC. Andexanet Alfa is a potential reversal agent (clinical trials)	Frontera et al (2016), Frost et al (2012), Raval et al (2017), Siegal et al (2015), UpToDate
		Edoxaban	Savaysa	Reversible factor Xa inhibitor, preventing conversion of prothrombin to thrombin	Renal function, CBC, hepatic function, signs of bleeding	Hepatic: P-glycoprotein/ABCB1 (minimal CYP3A4)	50% renal	~10-14h	~24h	No specific reversal agent. Discontinue drug and consider activated charcoal, tranexamic acid and PCC. Andexanet Alfa is a potential reversal agent (clinical trials)	Frontera et al (2016), Parasrampuria et al (2016), Raval et al (2017), Siegal et al (2015), UpToDate
		Rivaroxaban	Xarelto	Reversible factor Xa inhibitor, preventing conversion of prothrombin to thrombin	Renal function, CBC, hepatic function	Hepatic: BCRP/ABCG2, CYP2J2 (minor), CYP3A4 (major), P-glycoprotein/ABCB1	66% renal, 28% fecal	~5-9h (prolonged in elderly)	~24h	No specific reversal agent. Discontinue drug and consider activated charcoal, tranexamic acid and PCC. Andexanet Alfa is a potential reversal agent (clinical trials)	Frontera et al (2016), Mueck et al (2013), Raval et al (2017), Siegal et al (2015), UpToDate
	DIRECT THROMBIN INHIBITORS	Argatroban	N/A	Reversible thrombin inhibitor	Signs of bleeding, hemoglobin, hematocrit	Hepatic: hydroxylation and aromatization, CYP3A4/5 (minor route)	22% renal, 65% fecal	~39-51min (prolonged in hepatic impairment)	~2-4h	No specific reversal agent. Discontinue drug and consider PCC or rFVIIa	Frontera et al (2016), Garcia et al (2012), Koster et al (2007), UpToDate
		Bivalirudin	Angiomax	Reversible thrombin inhibitor	ACT or PTT depending on use	Proteases in blood	20% renal	~25min (prolonged in renal insufficiency)	Coagulation times return to baseline ~1h after stopping infusion	No specific reversal agent. Discontinue drug and consider PCC or rFVIIa	Frontera et al (2016), Garcia et al (2012), UpToDate
		Dabigatran	Pradaxa	Reversible thrombin inhibitor	CBC, renal function	Inactive form hydrolyzed to active form by plasma and hepatic esterases. Active form undergoes glucuronidation. Involves P-glycoprotein/ABCB1	>80% renal	~12-17h (prolonged in elderly & renal impairment)	>24h (prolonged in renal insufficiency)	IV Idarucizumab rapidly reverses. May also consider activated charcoal if acute ingestion	Frontera et al (2016), Pollack et al (2015), Stangier (2012), UpToDate

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