Pharmacology of Peripheral Arterial Disease in the Angio Suite: What Every Interventionalist Should Know

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Abstract

Keywords

- medications in PAD
- peripheral arterial disease
- pharmacology of PAD

Safe and effective treatment of peripheral arterial disease (PAD) and critical limb ischemia can be routinely performed in the angiography suite. A systematic understanding of the medications commonly used during these procedures is essential. This review discusses the traditional roles of the medications used in PAD procedures, the existing evidence basis for those roles, potential alternatives, and evolving techniques. Developing a familiarity with these medications can help improve outcomes and safety for the patients being treated.

Objectives: Upon completion of this article, the reader will be able to define common medications used in the angio suite for PAD procedures, their uses, and possible alternatives.

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As the prevalence of peripheral arterial disease (PAD) and critical limb ischemia (CLI) has continued to rise,¹ opportunities for safe and effective endovascular treatment have increased. A renewed emphasis on endovascular training of residents and fellows across multiple disciplines^{2,3} helps ensure the best possible outcomes of PAD treatment with education on patient selection, basic and advanced procedural techniques, emerging technologies, and comprehensive cardiovascular care. A key component to the overall success of an endovascular revascularization procedure and thus to a patient's eventual outcome is a comprehensive understanding of the pharmacological armamentarium available to the interventionalist in the angiographic suite.

Preprocedural Medications

Peripheral arterial procedures, including those for CLI, can be done in the angiography suite without significant alteration from the practices customary to each individual laboratory. The vast majority of these procedures can be completed under conscious sedation using the interventionalist's preferred regimen, usually intravenous (IV) fentanyl and midazolam titrated as needed to the desired effect. Clearly, if using this combination, immediate availability of flumazenil and naloxone for emergent reversal is critical.⁴ Some operators choose to supplement this combination with IV diphenhydramine, but care should be taken as it has no reversal agent and can have a disorienting effect in the elderly. Established patients can often be treated with oral anxiolytics and analgesics if a minor procedure is planned (e.g., short segment in-stent superficial femoral artery [SFA] restenosis or planned focal tibial angioplasty). In these instances, effective sedation can often be achieved with PO lorazepam and oxycodone.⁵ Essential to these patients, but important to all, is excellent local anesthesia. Traditional local subcutaneous injection is with 1% lidocaine to infiltrate the tissues around the access site to prevent transmission of pain sensation. Buffered lidocaine may preclude some of the discomfort for the patient that can be associated with the injection of the anesthetic itself. Usually 10 mL is sufficient and lidocaine toxicity (at levels of 4.5 mg/kg) does not generally come into play, but should be kept in mind.⁶ As part of a thorough history and physical exam during patient selection, care must be taken to elicit any history of a possible

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lidocaine allergy. Lidocaine is part of the amide class of local anesthetics and an ester class drug should be used as a substitute.⁷ If a suitable substitute is not available, it is possible to use the IV formulation of diphenhydramine (50 mg in 10 mL normal saline) injected in a subcutaneous manner as one would with lidocaine.⁸ It is rare that a patient would need monitored anesthesia care or general sedation for a peripheral arterial intervention but may occasionally be necessary for a prolonged procedure such as a SAFARI⁹ or recanalization of a long calcified chronic total occlusion.

Routine peripheral arterial procedures are considered clean procedures and evidence is not sufficient to recommend routine prophylactic antibiotic usage.¹⁰ This is true for procedures that include angioplasty, thrombolysis, and bare metal stenting. There is a similar lack of compelling evidence to routinely use antibiotics during the implantation of an arterial closure device.¹¹ Certain factors may predispose patients to infection and these relatively high-risk patients may be treated with antibiotics at the operator's discretion. These patients include those who have had repeat procedures within 7 days, those with an arterial sheath left in place overnight, and those who have had a prolonged duration of procedure. Cefazolin 1 g IV is generally sufficient to cover the potentially infectious organisms (coagulase-negative *Staphylococcus* species) and can be substituted with clindamycin or vancomycin in an allergic patient.¹² Alternatively, routine antibiotic prophylaxis is recommended during the placement of peripheral endografts. Covered stent infection incidence is rare but given the serious potential complications and unacceptable mortality rate of graft infection, prophylaxis is justified.¹³ The same organisms are implicated, and the same antibiotic regimen is recommended.

Antiplatelet therapy has shown a proven benefit to decrease the risk of serious vascular events and increase survival in at-risk patients.¹⁴ The same therapy has a theoretical benefit to limit postprocedure restenosis due to platelet activation and aggregation in response to vascular inflammation. It is common practice to give antiplatelet therapy to peripheral arterial patients to prolong the patency of their procedures.¹⁵ The chosen agent or combination of agent as well as the length of therapy is not well standardized and not supported by strong evidence, though dual-antiplatelet therapy (DAPT) with aspirin 81 mg daily and clopidogrel 75 mg daily is most commonly used. Starting DAPT before endovascular intervention to preempt platelet aggregation¹⁶ has been suggested, but the usefulness of this practice has been extrapolated from coronary intervention data and needs further investigation to be supported for peripheral intervention. In our practice, if a patient is not on antiplatelet therapy at the time of initial consultation, aspirin therapy is started at 81 mg per day before intervention. A loading dose (generally 300 mg PO) of clopidogrel is given at the time of intervention at the operator's discretion and continued at 75 mg PO daily.

Other routine angio suite medication protocols should be followed as usual during peripheral arterial interventions. Even though in the setting of a documented contrast allergy the majority of arteriography can be completed with carbon

dioxide digital subtraction angiography technique,¹⁷ it is still prudent to premedicate these patients if the need for a small amount of contrast does arise. Multiple effective oral allergy premedication regimens have been published which usually begin the day before the procedure with a steroid formulation to be followed by at least one more dose shortly before the procedure paired with an antihistamine.¹⁸ If the procedure must be done urgently, there are multiple "quick prep" combinations that can be given IV shortly before the procedure.¹⁸ Another nuance that may be somewhat unique to these procedures is intraprocedural blood pressure management. It may be prudent to delay nonemergent IV hypertension management, given that intra-arterial nitroglycerin may prove beneficial during the procedure and would be contraindicated if the blood pressure were made too low with intraprocedural antihypertensives.

Anticoagulants and Thrombolytics

Intravenous unfractionated heparin is the mainstay of procedural anticoagulation for peripheral arterial interventions. Generally extracted from porcine intestines or bovine lungs, heparin acts to inactivate thrombin. Heparin has a variable dose-response curve and the effect should be monitored via activated partial thromboplastin time measurements.¹⁹ Since this would be impossible within the time constraints of an endovascular procedure, activated clotting time (ACT) measurements can be performed rapidly and accurately in the angio suite. An ACT of 200 to 250 seconds is generally accepted as therapeutic, though some operators prefer a higher range between 250 and 300 for tibial artery intervention. A bolus of 80 unit/kg is generally sufficient for therapeutic anticoagulation with a half-life of approximately 60 minutes.²⁰ For a prolonged procedure, continued titration of heparin to desired ACT is often necessary. Bleeding complications caused by heparin can be minimized by giving IV protamine as a reversal agent. Protamine binds to heparin and neutralizes its effect. Care must be taken to give the smallest effective dose of protamine because in larger doses, it can interfere with platelet function and cause its own anticoagulant effect. Although rare, catastrophic adverse events have been reported with protamine including severe allergic reactions and cardiovascular collapse. Risk factors for these events include repeat protamine use, high-dose administration, concomitant use of other protamine-containing medications (including neutral protamine hagedorn (NPH) insulin), prior vasectomy, hypersensitivity to certain fish, severe left ventricular dysfunction, or abnormal preoperative pulmonary hemodynamics.²¹ Rarely, a patient may develop heparin-associated antibodies and suffer from heparin-induced thrombocytopenia. These patients can develop arterial and venous thrombus and cannot receive heparin necessitating an alternative agent for anticoagulation.²²

Appropriate procedural anticoagulation for heparin-allergic patients includes thrombin inhibitors, bivalirudin, and argatroban. Bivalirudin is a synthetic direct thrombin inhibitor based on the natural hirudins produced by saliva of the *Hirudo medicinalis* leech. Bivalirudin is given IV as a weight-based bolus and continuous infusion. ACT is not helpful in

monitoring effect. Dose-adjusted scales are available for renal impairment.²³ Argatroban is another synthetic direct thrombin inhibitor that can be given IV. There is hepatic clearance rather than renal which may be preferable for certain patients. ACT monitoring is effective for argatroban and should be checked frequently.²⁴ Bleeding complications with both bivalirudin and argatroban can be managed with recombinant factor VIIa.²⁵

Though treatment of patients presenting with acute limb ischemia (ALI) is beyond the scope of this discussion, endovascular arterial interventions will occasionally be complicated by arterial thrombus formation. Effective strategies for thrombectomy and thrombolysis are essential for patient safety and acceptable outcomes. Mechanical and aspiration techniques for thrombectomy can be effective, but pharmacological thrombolysis can play a pivotal role. The safety and efficacy of tissue plasminogen activator (tPA) for catheter-directed thrombolysis has been long established and is the standard of care for ALI.²⁶ Judicious use of catheter-directed tPA (Alteplase) at the site of arterial thrombosis within the context of an endovascular peripheral arterial revascularization procedure can also result in effective thrombolysis. Generally, small aliquots (2–4 mg) delivered through a catheter placed within the focal thrombus or immediately proximal to it will provide adequate thrombolysis if the thrombus is acute.²⁶ Given the complex physiology of in-stent restenosis, which included neointimal hyperplasia combined with subacute and often acute thrombus,²⁷ it is also our practice to instill a dilute solution of 2 to 4 mg of tPA through occluded or nearly occluded stents through an angled end-hole catheter, depending on the length of the stents. Again, a careful preprocedural history should elicit recent intracranial hemorrhage, gastrointestinal bleed, trauma, or major surgery which would be a contraindication for tPA (→ Fig. 1).

Another class of medications that have been studied for safety and efficacy in coronary and peripheral interventions is

the glycoprotein IIb/IIIa antagonists. These drugs inhibit the final stage of platelet aggregation, leaving the ability of the platelets to adhere to the damaged vascular surfaces relatively intact.²⁸ The most commonly used medication of this class is abciximab which is given as an IV bolus and continuous infusion. Though the half-life of the drug is 30 minutes, it effectively prevents bound platelets from aggregating for 18 to 24 hours and some evidence of bound abciximab can be found in the blood stream up to 14 days after administration.²⁹ A unique property of these medications is the ability to induce dethrombosis,³⁰ or the dissolution of platelet-rich thrombus. This mechanism can be utilized when an intervention is complicated by diffuse thrombus formation. Simultaneous IV bolus can be given with intra-arterial catheter-directed administration at the location of thrombus formation (→ Fig. 2).

Vasodilators

Nitroglycerin is a safe and short-acting vasodilator that can be given intra-arterially during a peripheral arterial intervention to combat arterial vasospasm. With a half-life of 3 to 5 minutes, nitroglycerin exerts its effects via releasing nitric oxide to relax vascular smooth muscles. Its effects are dose dependent and aliquots of 100 to 200 µg are generally given when vasospasm occurs. This can be repeated until the desired effect is achieved as long as the patient's blood pressure does not become depressed between administrations. Tibial artery vasospasm is likely to occur after angioplasty and is treated effectively in this manner. Given as an intra-arterial injection via a catheter directed toward the area of spasm, there is little risk of systemic effect, but systemic depression of blood pressure can occur. It is important to note systolic blood pressure (SBP) before administration and SBP less than 90 mmHg should be considered a contraindication.

As PAD treatment continues to evolve, efforts to reduce complications, increase patient satisfaction, and improve

Fig. 1 (a) Three-vessel run-off is present below the knee of a patient before angioplasty of a thrombosed superficial femoral artery stent. (b) After revascularization of the SFA stent, thrombus is present occluding the previously patent tibioperoneal trunk. (c) After catheter-directed delivery of 2 mg of intra-arterial tPA, thrombolysis has occurred and three-vessel run-off has returned. The arrow indicates residual arteriospasm at the site where the thrombus had lodged in the posterior tibial artery.

Fig. 2 (a) Three-vessel run-off is present in an earlier atherectomy, angioplasty, and drug-eluting stenting of a focal superficial femoral artery occlusion. (b) After treatment was complete, thrombus began to actively develop throughout the popliteal artery and all three run-off vessels. An occult external iliac artery lesion was noted and the sheath had been occlusive. (c) The diffuse tibial arterial thrombosis was treated with an intravenous bolus and intra-arterial abciximab with near-immediate dissolution of the thrombus.

endovascular outcomes have helped innovate new arterial access techniques. Pedal access techniques have proven useful to treat not only tibial arterial disease but femoral and iliac disease as well. As sheaths and therapeutic devices have become smaller, many procedures traditionally done from common femoral artery access can be done entirely from access via one of the tibial arteries at or below the ankle.³¹ To prevent spasm, many operators give 200 to 400 μ g of nitroglycerin immediately upon accessing the tibial artery, depending on the systemic blood pressure.³² When placing a sheath into a tibial artery, some have advocated for the use of tibiopedal artery minimally invasive solution which contains 500 mL of heparinized saline, 1,600 μ g of nitroglycerin, and 5 mg of verapamil run through the side arm of the tibial sheath at 6 to 7 mL/min. This will continuously flush the accessed tibial artery with vasodilatory solution throughout the procedure.³³

With the increased patient satisfaction and safety of radial access techniques, their popularity has increased among interventionalists for multiple different types of arterial procedures. Given the length of traditional catheters and endovascular devices, these procedures have been limited mostly to visceral and neurological domains. Recently, multiple medical device companies have begun to create longer equipment specifically designed to reach from a patient's wrist to his or her tibial arteries. Radial access has now become an option for lower extremity peripheral arterial intervention. There are very well-established radial artery access "cocktails" to prevent radial artery spasm which have been developed over years of percutaneous coronary intervention (PCI) experience. A mixture of 2,500 units of heparin, 2.5 mg of verapamil, and 200 μ g of nitroglycerin hemodiluted to 20 mL and slowly instilled over 1 minute through the sidearm of the sheath immediately after cannulation is recommended to prevent spasm and potential thrombosis.³⁴ Multiple other formulations exist and can be tailored to operator preference, but evidence suggests that using antic-

oagulant, calcium channel blocker, and nitrate elements in combination decrease postprocedural radial artery complications.³⁵ It has also been suggested that a small amount of nitroglycerin (up to 500 μ g) can be injected subcutaneously around the radial artery access site before cannulation if spasm is suspected.³⁶

In our practice, the use of transdermal nitroglycerin paste is routine. Approximately 1 inch of paste is applied to every patient who has tibial artery access. The ointment is placed just proximally to the puncture site, above the sterile dressing, along the course of the artery. We also apply the paste liberally overlying the tibial arteries in prolonged CLI procedures that involve multiple rounds of tibial angioplasty and often atherectomy and thrombectomy. Anecdotally, results have been positive, but no evidence currently exists to support the practice ($\rightarrow$ Fig. 3).

Fig. 3 Nitro paste applied just proximal to the posterior tibial artery site after a tibiopedal artery minimally invasive procedure.

Table 1 Drug table

Drug	Class	Dosing	Half-Life	Intent
Fentanyl	Narcotic Analgesic	25–50 mcg IV, repeat as necessary titrated to desired sedation effect	7 hours	Intraprocedural analgesia and sedation
Midazolam	Short-acting Benzodiazepine	0.5–1 ml IV, repeat as necessary titrated to desired sedation effect	Approximately 3 hours	Intraprocedural anxiolysis and sedation
Diphenhydramine	Antihistamine	25–50 mg IV or PO; 50 mg in 10ml saline SQ	1–4 hours	Supplemental sedation, allergy pre-medication; alternate form of local anesthesia
Lorazepam	Oral Benzodiazepine	0.5–1 mg PO	2 hours when taken orally	Oral pre-procedural sedation
Oxycodone	Oral Narcotic Analgesic	5–10 mg PO	4.5 hours	Oral pre-procedure analgesia
Cefazolin	First Generation Cephalosporin	1 g IV	1.8 hours	Peri-procedural antibiotic prophylaxis
Aspirin	Irreversible COX Inhibitor	81–325 mg PO daily	Approximately 3 hours	Platelet aggregation inhibition
Clopidogrel	Selective Anti-platelet drug	300 mg PO loading dose; 75 mg PO daily	8 hours	Platelet aggregation inhibition
Heparin	Anticoagulant	80 units/kg IV bolus	Approximately 1 hour	Intraprocedural anticoagulation
Protamine	Heparin Binder	1–1.5 mg/100 units of heparin IV. Not to exceed 50mg.	Approximately 5 minutes	Heparin reversal
Bivalirudin	Naturally Occurring Thrombin Inhibitor	0.75 mg/kg IV bolus, and then immediately 1.75 mg/kg/hr IV infusion for duration of procedure	25 minutes, renal function dependent	Heparin substitute
Argatroban	Synthetic Direct Thrombin Inhibitor	2 mcg/kg/min IV continuous infusion over 1–3 hours until steady-state aPTT is 1.5–3 times initial baseline value	Approximately 45 minutes	Heparin substitute
Alteplase	Purified and glycosylated tPa	2 mg IA bolus, repeat as necessary	5 minutes	Thrombolysis
Abciximab	Monoclonal Antibody (G2) IIb/IIIa Inhibitor	0.25 mg/kg IV bolus over at least 1 minute, THEN 0.125 mcg/kg/min IV continuous infusion terminating 1 hour post-procedure; not to exceed 10 mcg/min	30 minutes in plasma; effect can last for 10 days	Detthrombosis
Nitroglycerin	Vasodilator	50–100 mcg IA, repeat as needed.	3 minutes	Relieve arteriospasm
Verapamil	Calcium Channel Blocker	2.5 mg IA during radial or tibial arterial access	2.8–7.4 hours	Prevent arteriospasm
Thrombin	Coagulation Factor II	200–1000 IU into pseudoaneurysm in 0.1 ml aliquots	1 minute	Thrombosis of arterial pseudoaneurysm
Naloxone	Opioid Antagonist	0.4–2 mg IV or IM; repeat q2–3 min PRN; not to exceed 10 mg (0.01 mg/kg)	1.24 hours	Narcotic reversal
Flumazenil	Benzodiazepine Receptor Antagonist	0.2 mg IV over 15 second. May repeat at 1 minute intervals; not to exceed 1mg total	40–80 minutes	Benzodiazepine reversal

Other Medications

Although with experience and careful attention to detail, endovascular peripheral arterial interventions are able to be performed safely the vast majority of times, it is still imperative to be prepared for complications. A full complement of advanced cardiovascular life support drugs is critical, as patients who have severe enough PAD to require intervention will have other manifestations of cardiovascular disease (– **Table 1**). Appropriate reversal medications, as described previously, are necessary for the sedation and anticoagulation medications being used to treat an indi-

vidual patient. Another medication which is useful to have in the angio suite is thrombin. Postangiography pseudoaneurysm has been reported in up to 5% of cases, though most studies show significantly lower rates.³⁷ These complications can cause discomfort and can result in morbidity and potentially mortality if catastrophic rupture were to occur. Ultrasound-guided thrombin injection into an arterial pseudoaneurysm is a safe and effective method of inducing immediate thrombosis via injection of 200 to 1,000 IU via 22G needle in 0.1 mL aliquots until thrombosis has occurred. Risks of the procedure are minimal and success rate is nearly 100%.³⁸

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