Antithrombotic Drugs: Pharmacology and Implications for Dental Practice

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Appropriate preoperative assessment of the dental patient should always include an analysis of the patient's medications. This article reviews the actions and indications for the various categories of antithrombotic medications and considers actual risks for postoperative bleeding and potential interactions with drugs the dental provider might administer or prescribe.

Key Words: Drug interactions; Drug side effects; Antiplatelet drugs; Anticoagulants; Postoperative bleeding; Dental treatment.

Antithrombotic drugs are prescribed extensively in medical practice, and an impressive number of formulations have been introduced in recent years. Although these medications do not significantly impact the use of sedation or anesthesia per se, they certainly introduce concerns regarding postoperative bleeding and a potential for significant drug interactions. To evaluate and understand these risks it is essential to have an understanding of thrombogenesis and the various classes of antithrombotic drugs.

Thrombogenesis (clot formation) includes 2 principal processes: platelet aggregation and coagulation. Platelet aggregation consists of activated platelets attaching to strands of fibrinogen, whereas coagulation is a complex cascade of enzymatic events leading to the formation of fibrin strands. The proportion and sequence of these 2 processes, as well as their consequences, differ during thrombogenesis in arteries compared to veins.¹ Platelet activation is the initial event during arterial thrombogenesis. Platelets adhere to damaged vessel walls, aggregate, and provide a core around which fibrin strands accumulate. Arterial thrombi are white in appearance because of the predominance of platelets, and they

occlude arterial flow, leading to ischemia and infarction of supplied tissues and organs. In contrast, venous thrombi commence as fibrin strands, appear red in color because of entrapped red blood cells, and embolize great distances, ultimately lodging in the pulmonary arteries, ie, pulmonary embolism.

Antithrombotic drugs include those that inhibit platelet aggregation (antiplatelet drugs), inhibit formation of fibrin strands (anticoagulants), and dissolve existing clots (fibrinolytics). Antiplatelet drugs and anticoagulants target each component of clot formation and can be used to prevent thrombogenesis, but have no effect on existing clots, other than limiting their progression. Only the fibrinolytic (thrombolytic) drugs can actually dissolve an existing thrombus. (See Figure 1.)

OVERVIEW OF ANTIPLATELET DRUGS

The antiplatelet drugs are used to prevent arterial thrombogenesis. The biology of platelet activation and aggregation is becoming better understood and has provided numerous molecular targets for drugs to impart an antiplatelet effect. This in turn has led to a rational approach to prescribing single or multiple drug regimens. (See Figure 2.)

Aspirin is the most commonly prescribed antiplatelet drug for the prevention of myocardial infarction and ischemic stroke. Aspirin imparts its antiplatelet action

Received January 19, 2013; accepted for publication February 28, 2013

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Anesth Prog 60:72–80 2013

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ISSN 0003-3006/13

SSDI 0003-3006(13)

Figure 1. Thrombogenesis. A thrombus consists of 2 principal components: an aggregate of platelets and a fibrin mesh. Platelet activity consists of adherence to vessel walls (adhesion) and to one another (aggregation). The fibrin mesh is synthesized during a complex cascade of enzymatic reactions leading to the formation fibrin strands (coagulation). The body also has a natural thrombolytic system, essentially comprised of plasmin, an enzyme that cleaves fibrin strands. Antithrombotic drugs are classified according to action on each of these processes: antiplatelet drugs, anticoagulants, and thrombolytics (fibrinolytics).

within the portal system prior to any hepatic biotransformation. Once it reaches systemic circulation it lacks any antiplatelet activity. Its maximum antiplatelet effect is achieved within 1 hour following an initial dose of 325 mg, and this is the basis for its indication during an acute coronary syndrome. Aspirin's antiplatelet effect is sustained using very low doses, ~40 mg/d.² Baby aspirin (81 mg) is the most conventional dose prescribed

in the USA but dosages may range from 50 to 320 mg/d. Higher dosages do not improve efficacy and increase risks for gastrointestinal bleeding.³

Dipyridamole (Persantine) prevents platelet adherence to endothelial surfaces more than platelet aggregation. When combined with warfarin, it provides an enhanced antithrombotic effect on artificial surfaces, and the combination may be prescribed for patients having

Antiplatelet Drugs	Mechanism
Aspirin *	Inhibit TXA ₂ Synthesis
Clopidogrel (Plavix)* Prasugrel (Effient)* Ticagrelor (Brilinta)	Inhibit ADP Receptor Activation
Dipyridamole (Persantine) Cilostazol (Pletal)	Lowers Ca ⁺⁺ by elevating cAMP
Abciximab (ReoPro) Tirofiban (Aggrastat) Eptifibatide (Integrilin)	Block GPIIb/IIIa Receptors

* Permanent Inhibition

Figure 2. Platelet aggregation and actions of antiplatelet drugs.^{1,3} Resting platelets have specific receptors for ligands that trigger activation: epinephrine, thrombin, serotonin, collagen, adenosine diphosphate (ADP), and thromboxane A₂ (TXA₂). When activated, intracellular calcium levels elevate and the platelet expresses glycoprotein (GP) IIb/IIIa receptors that bind to strands of fibrinogen. This results in platelet aggregation. The various antiplatelet drugs inhibit aggregation by targeting specific aspects of this process.

mechanical heart valves.³ Dipyridamole is ineffective as an antiplatelet drug when used alone, but its combination with aspirin (Aggrenox) is effective in the secondary prevention of ischemic stroke and transient ischemic attacks. However, there is no proven advantage for its addition to aspirin when managing coronary artery disease. Dipyridamole is also a coronary vasodilator and is used by cardiologists during diagnostic procedures to assess patency of coronary arteries, ie, dipyridamole-thallium scanning.

Clopidogrel (Plavix) is among the most commonly prescribed antiplatelet drugs, second only to aspirin. It acts by blocking adenosine diphosphate receptors on platelet cell membranes and thereby prevents subsequent expression of glycoprotein IIb/IIIa receptors that bind fibrinogen. Clopidogrel is a prodrug and only 15% of an administered dose becomes activated. Patient differences in microsomal enzyme activity and potential drug interactions lead to significant interindividual variability in antiplatelet efficacy. Prasugrel (Effient) is a newer thienopyridine derivative that is also a prodrug but is almost entirely activated following administration. Although this is a notable improvement, it shares an additional disadvantage of clopidogrel, which is permanent inhibition of the adenosine diphosphate receptor for the life of the platelet. This poses a significant problem if bleeding occurs. Ticagrelor (Brilinta) is among the newest adenosine diphosphate receptor antagonists. It is active as the parent drug and its antiplatelet influence ceases upon discontinuation. However, these advantages are tempered somewhat because of side effects not associated with the thienopyridines; dyspnea, bradyarrhythmia, and elevated serum creatinine.⁴

Drugs that block the activated glycoprotein IIb/IIIa receptors, such as tirofiban (Aggrastat), impart the most absolute inhibition of platelet aggregation and therefore carry the greatest risk for hemorrhage. These drugs are administered intravenously to prevent platelet aggregation during acute coronary syndromes or postoperatively following interventional procedures such as insertion of coronary stents.

DENTAL IMPLICATIONS FOR PATIENTS MEDICATED WITH ANTIPLATELET AGENTS

Ibuprofen and naproxen have been implicated as competitive inhibitors of aspirin on platelet cyclooxygenase.^{5,6} Consideration regarding this issue may eventually prove moot because actual clinical relevance has been challenged impressively. Cryer et al⁷ found thromboxane inhibition by aspirin to be reduced only 1% after 10 days of concurrent ibuprofen use, and Patel and Goldberg⁸ found no increase in incidence of myocardial infarction

over a 10-year period in patients with coronary disease taking ibuprofen with low-dose aspirin. The antiplatelet influence of aspirin occurs within 1 hour of administration, and one solution might be to instruct patients to take their daily aspirin upon rising and delay the first dose of a nonsteroidal anti-inflammatory drug (NSAID) for 1–2 hours. By this time the antiplatelet influence of aspirin will have been established.^{6,9}

Although low-dose aspirin does not introduce a major risk for bleeding following minor dental surgery, extensive surgery may require some consideration. This may be of even greater concern for patients medicated with thienopyridines such as clopidogrel (Plavix), but it is noteworthy that it was found insignificant following peripheral vascular surgery.¹⁰ The antiplatelet influence for both aspirin and clopidogrel extends for the life of the platelet. Platelets are replenished at an approximate rate of 10% daily, and this would require these drugs to be withheld for 10–14 days for platelets to be completely replenished. However, it is generally unnecessary to interrupt either drug for minor dental surgery; risk for thrombotic events outweighs any slight risk for postoperative bleeding that can be controlled with local measures. Should a surgical procedure be so extensive that antiplatelet therapy poses a concern, consultation with the patient's physician is essential. Although complete reversal of antiplatelet influence requires ~10 days, bleeding times return to normal after interrupting aspirin therapy for only 4–5 days.^{11,12}

Preoperative assessment of platelet function, eg, PFA-100, cannot be recommended routinely but could prove useful in exceptional cases, such as urgent management of oral-maxillofacial trauma in a patient taking dual antiplatelet regimens. Low platelet activity does not promise excessive bleeding, but moderate to normal activity will assure it unlikely for any bleeding to result from inadequate platelet function.¹³

Antiplatelet drugs are prescribed for a variety of medical conditions, but the patient having coronary stents is a special consideration. In general, these patients are medicated with dual antiplatelet coverage consisting of aspirin and clopidogrel. Acute myocardial infarctions have followed interruption of antiplatelet therapy in such patients.¹⁴ Reports have accumulated and spawned a scientific advisory from the American Heart Association in collaboration with other professional organizations, including the American Dental Association.¹⁵ Antiplatelet coverage for patients having placement of coronary stents must rarely if ever be interrupted, especially if the stent is of the drug-eluting category. The most recent guidelines from the American College of Chest Physicians advise that elective surgery be delayed for 6 weeks following bare-metal stent placement and 6 months following insertion of drug-

eluting stents. If the procedure is essential, antiplatelet therapy should not be interrupted.¹⁶

Finally, the use of NSAIDs always carries a risk for mucosal damage within the gastrointestinal tract. Risk for subsequent bleeding is increased in patients taking any antithrombotic medication, including the more powerful antiplatelet drugs. Risk for gastrointestinal bleeding is increased 2–3-fold in patients medicated with clopidogrel (Plavix) who are prescribed an NSAID concurrently.¹⁷ Patients receiving monotherapy with low-dose aspirin are generally not a concern.

OVERVIEW OF ANTICOAGULANTS

Anticoagulants are used primarily to prevent thrombotic events that originate in low-pressure environments such as veins or the atria of the heart in patients with atrial fibrillation. However, combined therapy using both antiplatelet and anticoagulant drugs may be required for high-risk patients suffering either venous or arterial thrombotic events. Obviously combination therapy increases the risk for spontaneous as well as postsurgical hemorrhage. The coagulation pathway and actions of the various anticoagulants are illustrated in Figure 3.

Warfarin (Coumadin) acts in the liver competing with vitamin K to inhibit the synthesis of factors VII, IX, X and II (prothrombin). Following warfarin administration, a mild anticoagulant effect is evident within 24 hours but the peak effect is not realized for 72 hours, pending the consumption and clearance of previously synthesized factors.³ Conversely, vitamin K can be administered as an antidote for bleeding, but synthesis of replacement factors generally requires 24–72 hours. Serious hemorrhage must be managed by transfusion. Inhibiting synthesis of several factors, and to varying degrees, renders the anticoagulant activity of warfarin imprecise, and its activity must be monitored. This is accomplished using the international normalized ratio (INR), which is essentially a standardized prothrombin time (PT) and will be explained more thoroughly below. Warfarin is contraindicated during pregnancy. It crosses the placenta, where it may produce fetal or intrauterine hemorrhage, and is also associated with fetal malformations.

Unlike warfarin, heparin and most of the newer parenteral anticoagulants do not alter hepatic synthesis of factors. They act within the bloodstream by potentiating the activity of antithrombin, the body's endogenous anticoagulant. Antithrombin circulates in plasma acting as a "suicide substrate" for several activated factors but thrombin (factor IIa) and factor Xa are most significant. By consuming these 2 essential clotting factors, antithrombin prevents conversion of fibrinogen to fibrin. Heparin binds to antithrombin, potentiating its activity

instantly. Likewise, its action can be reversed immediately by administering protamine sulfate, which neutralizes heparin molecules in a simple acid-base reaction. The inhibition of multiple factors renders the anticoagulant activity of heparin imprecise and requires its effect be monitored using an activated partial thromboplastin time.

Heparin can be administered subcutaneously or intravenously, as either an intermittent bolus or continuous infusion. Other than hemorrhage from its anticoagulant influence, the principal side effect attributed to short-term use of heparin is heparin-induced thrombocytopenia.^{1,3} This is attributed to an immune-mediated reaction whereby antibodies are generated against a complex formed by heparin and a platelet product called platelet factor 4. Before platelet numbers actually decline, arterial thrombosis is common because the antibodies initially trigger existing platelets to aggregate. These platelet-rich clots have a white appearance, which has spawned the term "white-clot syndrome." (Recall that fibrin-rich clots entrap red blood cells and are red in appearance.) Eventually platelets are consumed resulting in thrombocytopenia, and for this reason platelet counts are ordered periodically during treatment.

Heparin is a large polysaccharide but its most noteworthy anticoagulant action is imparted by a mere pentasaccharide segment that inhibits factor Xa. (See Figure 4.) This information led to the development of low-molecular-weight heparins (LMWH) such as enoxaparin (Lovenox) and dalteparin (Fragmin).^{3,18} These agents are as effective as heparin but are more selective in inhibiting factor Xa than thrombin (IIa). Fondaparinux (Arixtra) is a synthetic pentasaccharide that only inhibits factor Xa. These anticoagulants require less frequent dosing and are less likely to induce immunological responses that contribute to thrombosis or thrombocytopenia. Because they target only 1 or 2 factors, their activity is precise enough to exclude any need for activated partial thromboplastin time monitoring. In certain cases, these advantages offset their cost, which is 10–20 times that for heparin.

Continued research into anticoagulant mechanisms is creating novel agents having even greater specificity on the coagulation pathway. These agents act directly on specific activated factors and do not rely on potentiation of antithrombin. Newer anticoagulants include bivalirudin (Angiomax) administered parenterally and oral agents such as dabigatran (Pradaxa), apixaban (Eliquis), and rivaroxaban (Xarelto). See Figure 3.

DENTAL IMPLICATIONS FOR ANTICOAGULATED PATIENTS

The initial concern for anticoagulated patients is generally related to any risks for postoperative bleeding.

Oral Anticoagulants	
Warfarin (Coumadin)	Inhibits "Synthesis" of Multiple Factors
Dabigatran (Pradaxa)	Inhibits "Activity" of (IIa)
Rivaroxaban (Xarelto) Apixaban (Eliquis)	Inhibits "Activity" of (Xa)
Parenteral Anticoagulants	
Heparin	Inhibits "Activity" of Multiple Factors
LMWH: Enoxaparin (Lovenox) Dalteparin (Fragmin)	Inhibits "Activity" of Xa and IIa
Fondaparinux (Arixtra)	Inhibits "Activity" of Xa
Bivalirudin (Angiomax)	Inhibits "Activity" of IIa

Figure 3. The coagulation pathway and target sites for anticoagulant drugs.^{3,18} The coagulation pathway is a cascade of enzymatic conversions, each activating the next enzyme (factor) in the sequence. The final enzyme in this pathway is thrombin (factor IIa), which catalyzes the conversion of fibrinogen to fibrin strands. Warfarin acts by inhibiting synthesis of factors in the liver. In contrast, heparin acts to inhibit factors that have become activated within the bloodstream. Thrombin can be activated by either of 2 pathways. The intrinsic pathway is initiated within the bloodstream by platelet thromboplastin. Heparin influences this pathway by inhibiting factors XIIa, XIa, and IXa, which requires its activity to be monitored using the activated partial thromboplastin time. The extrinsic pathway functions outside the bloodstream, initiated by tissue thromboplastin. This pathway is influenced most by warfarin because it inhibits hepatic synthesis of factor VII, the most essential factor in the extrinsic pathway. Therefore the anticoagulant activity of warfarin must be monitored using the prothrombin time (PT), which is now standardized as the international normalized ratio (INR). Newer agents, commencing with the low-molecular-weight heparins, have greater specificity for inhibiting only factors Xa or IIa (thrombin) within the common pathway and therapeutic monitoring is not required.

For minor surgical procedures this concern is generally overstated but nevertheless deserves consideration. Warfarin is by far the most common anticoagulant in use for outpatient care, but additional agents must also be considered.

The anticoagulant influence of warfarin is generally monitored every 2–4 weeks initially, but in stable patients may be evaluated every 2–3 months.¹⁶ PT was formerly used for monitoring and is expressed as a ratio compared to normal. If the normal PT is 12 seconds, a PT ratio of 1.5 would correspond to 18 seconds. This test is rarely used for continual monitoring of warfarin because the thromboplastins used by laboratories vary in their sensitivity and results cannot be compared. In 1983, the World Health Organization adopted the INR, designed to improve patient monitoring. Now most laboratories standardize their results by using a computation that adjusts the sensitivity of their particular thromboplastin to that of an international

standardized thromboplastin. (These sensitivities are expressed as international sensitivity index.) The INR is the result of this calculation, and the value is identical to that had a universal standard thromboplastin been used for the test. The actual intensity of anticoagulation a physician desires will vary according to a patient's risk for thromboembolic events. For example, INR values as low as 1.3–2.0 may be effective prophylaxis for deep vein thrombosis, but 2.0–3.0 is the target for most indications, including atrial fibrillation. Higher values such as 2.5–3.5 are required for patients at greater risk, such as those with mechanical mitral valves.¹⁶

For minor surgical procedures there is no evidence of increased risk for postoperative hemorrhage in patients taking warfarin and having a therapeutic INR <3.5.^{19,20} It is wiser to limit procedures to quadrants and multiple appointments than to perform a single generalized procedure and interrupt anticoagulant coverage. Ideally, the procedure should be scheduled within a few days of

Figure 4. Actions of heparin and derivatives.³ Heparin and its derivatives impart their anticoagulant effect indirectly by facilitating the interaction of antithrombin with activated factors, primarily Xa and thrombin (IIa). (A) Heparin is a large polysaccharide capable of surrounding and potentiating antithrombin against both factors Xa and thrombin (IIa). (B) The low-molecular-weight heparins (LMWH) are smaller in size and are more active in potentiating antithrombin against factor Xa than thrombin (IIa). (C) Fondaparinux is a synthetic pentasaccharide that only potentiates antithrombin activity against factor Xa.

their most recent INR and the procedure delayed if it is above 3.5. This protocol is wise also when providing nonsurgical procedures when nerve blocks or deep infiltrations of local anesthetics may be required. Actual decisions are empiric, however, and if the provider remains concerned regarding hemorrhage any adjustment in the anticoagulant must be determined by the prescribing physician. In this case current guidelines published by the American College of Chest Physicians suggest either continuing warfarin and coadministering vitamin K or interrupting warfarin 2–3 days before the procedure and restarting 12–24 hours postoperatively.¹⁶

Although most patients are managed with warfarin, there are 3 alternative oral anticoagulants now available,

none of which can be reversed by vitamin K or other antidotes. Dabigatran (Pradaxa) selectively inhibits thrombin (factor IIa) and Rivaroxaban (Xarelto) and Apixaban (Eliquis) are selective factor Xa inhibitors. None of these agents require laboratory monitoring because of their selectivity, and the duration of their anticoagulant effect is determined by their rates of elimination. If any of these agents must be discontinued, recommendations are 1–2 days for minor procedures and 3–5 days for major surgery.²¹ However, any decision in this regard must be made by the prescribing physician.

For patients requiring extensive surgery, but at significant risk for thromboembolic events, consideration

Exemplary Protocol for Warfarin Bridging Using LMWH*

<i>Intervention</i>	<i>Explanation</i>
Discontinue warfarin 3–4 days preoperatively	Synthesis of renewed factors requires 3–4 days after warfarin discontinued
Commence LMWH 3 days preoperatively	Provides anticoagulant effect as influence of warfarin declines
Skip PM dose of LMWH night before surgery	Assures no anticoagulant influence at surgery
Restart warfarin and LMWH evening on day of surgery	Anticoagulant effect commences immediately with LMWH
Continue LMWH for 3 days postoperatively and check INR to confirm warfarin activity	Anticoagulant protection is provided by the LMWH while warfarin effects develop
Discontinue LMWH when INR confirms warfarin activity	

* So-called bridge therapy must be in consultation with and managed by the patient's physician. This regimen limits the time patient is not anticoagulated to the perioperative period. LMWH indicates low-molecular-weight heparins; and INR, international normalized ratio.

should be given to the use of “bridge therapy” in consultation with the physician. This strategy employs injectable anticoagulants while the patient discontinues and restarts warfarin. Experience with the newer oral anticoagulants is limited and is generally not considered at this time. In the extremely high-risk patient bridging may require hospital admission, but the introduction of LMWH has allowed bridging of warfarin to be accomplished safely on an outpatient basis. An exemplary protocol is presented in the Table. Fondaparinux (Arixtra) may be substituted for the LMWH, but at greater expense.

Potential drug interactions must always be considered when managing anticoagulated patients, especially those using warfarin. The principal isomer of warfarin is metabolized by CYP2C9 microsomal enzymes. Drugs that inhibit this system should be avoided, including metronidazole, the macrolide antibiotics, and the azole antifungals such as ketoconazole.^{22,23} Antibiotics having a wide spectrum may diminish gut flora responsible for vitamin K synthesis, and this reduction may further enhance the anticoagulant effect of warfarin.²³ Of those classes implicated, only the tetracyclines are used in dental practice and should be avoided. Penicillin V, amoxicillin, cephalexin, and clindamycin administered in conventional dosages are acceptable. However, amoxicillin/clavulanic acid and large intravenous doses of penicillins and cephalosporins should be used cautiously.

Anticoagulant therapy presents a contraindication to the use of NSAIDs for postoperative pain and inflammation. This is true for all anticoagulants, not only warfarin. The reasoning for this concern is often misstated as a concern that the added antiplatelet effect of NSAIDs significantly enhances antithrombotic influences. However, with the exception of aspirin, most NSAIDs have minimal influence on platelet aggregation. In fact, the antiplatelet influence of low-dose aspirin is combined with warfarin when managing patients at significant risk for thromboembolic events. The major concern with NSAIDs is their risk for producing erosions and ulcerations of gastric mucosa that may bleed more

profusely in patients who are anticoagulated. This is rarely a consideration with low-dose aspirin, but is significant with analgesic and antiinflammatory doses of aspirin or other NSAIDs. The use of NSAIDs by patients receiving warfarin therapy increases the risk for gastrointestinal bleeding 4–5-fold.¹⁷ This is likely an equal concern for any of the newer anticoagulants as well.

Finally, it should be mentioned that both acetaminophen and tramadol have been reported to increase the INR in patients taking warfarin.^{23,24} Documentation is sparse and mechanisms have not been clearly defined, but the metabolite of acetaminophen responsible for liver toxicity is also known to inhibit activity of vitamin K. This interaction is likely insignificant with short-term regimens prescribed for postoperative pain.

FIBRINOLYTIC (THROMBOLYTIC) DRUGS

This category of antithrombotic drug is not encountered in outpatient practice but will be addressed briefly for completeness of the topic. Thrombi are normally dissolved by the action of an endogenous fibrinolytic system. This consists of plasminogen, which circulates free in the plasma and binds to both fibrinogen and fibrin. When activated, plasminogen is converted to the proteolytic enzyme, plasmin, which inactivates fibrinogen and lyses any existing fibrin strands. All fibrinolytic drugs in current use act by converting plasminogen to plasmin, either in the circulation or on the surface of existing thrombi. They are all effective “clot busters” during the early stages of myocardial infarction or ischemic stroke and thus preserve viable tissues. Currently, tissue plasminogen activator is the most common agent used in the USA.

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CONTINUING EDUCATION QUESTIONS

1. Which of the following are accurate statements regarding antiplatelet drugs?
(1) They are most effective in preventing arterial thrombosis (2) They all inhibit platelet activity for the lifespan of the platelet (3) They act by inhibiting platelet binding to fibrinogen strands
 - A. 1 and 2
 - B. 1 and 3
 - C. 2 and 3
 - D. 1, 2, and 3
2. The anticoagulant effect of warfarin may be increased by concurrent use of all the following medications EXCEPT:
 - A. ibuprofen
 - B. metronidazole
 - C. erythromycin
 - D. doxycycline
3. The use of nonsteroidal anti-inflammatory drugs (NSAIDs) for postoperative pain is contraindicated in patients taking warfarin. Which of the following is the principal basis for this contraindication?
 - A. Added antiplatelet influence of NSAIDs may prolong bleeding.
 - B. NSAIDs may elevate warfarin serum levels.
 - C. Gastrointestinal irritation may be more likely to result in excessive bleeding.
 - D. NSAIDs inhibit renal excretion of warfarin.
4. Which of the following provides the rationale for “bridging” anticoagulant therapy?
 - A. It enhances anticoagulation by combining 2 mechanisms.
 - B. It minimizes the time in which a patient is not anticoagulated.
 - C. It provides greater protection from surgically induced thrombosis.
 - D. It minimizes the risk for drug interactions that enhance bleeding.