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Core Entrustable Professional Activities in Clinical Pharmacology for Entering Residency: Common Problem Drugs and How to Prescribe Them

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Abstract

Although the medical profession strives for safe prescribing, most medications are unique challenges even when prescribed by an experienced provider. In this article we discuss the pitfalls associated with drug interactions between commonly used antibiotics and anticoagulants, the complexities associated with the administration of novel reversible anticoagulants, the often-overlooked severe adverse drug reactions from commonly used classes of medications such as corticosteroids, the nuances of managing an acetaminophen overdose, and uncommon yet serious adverse events associated with the use of contraceptive hormone drugs.

Keywords

acetaminophen, contraception, entrustable professional activities (EPA) in clinical pharmacology, ethinyl estradiol, GME, medical education, norethindrone, novel oral anticoagulants (NOAC), opioids, prescribing practices, problem drugs, psychosis, steroids, thrombosis, toxicity, UME

No medication is perfectly safe for every person. Risks and benefits must always be considered when prescribing any drug. Desperate circumstances may require desperate measures; ordinary circumstances mandate that we endeavor to do no harm.

Certain drugs are inherently dangerous because of their mechanism of action, that is, the same characteristics that make them effective also make them dangerous. Many chemotherapeutic oncology drugs kill normal cells as well as cancer cells, and it is only the relative rates at which the cells are killed (the therapeutic window) that makes these drugs useful. Anticoagulants reduce the risk of pathologic blood clotting, but increase the risk of dangerous bleeding.

Other drugs are dangerous because of unintended but intrinsic properties that they possess. Opioids are perhaps the most dramatic current example. In addition to the intended effect of reducing pain, they have an inherent effect of suppressing respiration, which can be lethal. Opioids are discussed in a separate article in this series.[1] Contraceptive hormonal medications are associated with an increased risk of thrombosis,[2] especially in patients with inherited thrombotic defects.

Still other medications are not inherently dangerous, but improper dosage, interactions with other drugs, or combination with alcohol or other substances may result in adverse consequences. Drug-drug interactions are discussed in another article in this series[3]; this

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article will focus on the toxicity of individual drugs. It is important to remember that not all dangerous drugs require a prescription. Indeed, alcohol, tobacco, and heroin are 3 commonly used toxic drugs, and acetaminophen (liver toxicity) and non-steroidal anti-inflammatory drugs (renal toxicity) are readily available over the counter.

Finally, it is important to remember that there is considerable individual variability in susceptibility to adverse outcomes. In the past we have had only rough guidelines for therapy based on patient racial or ethnic group, age, and other medical conditions,[4] all of which are associated with differences in response to various medications.

Clinicians should familiarize themselves in depth with problems associated with drugs they commonly use in their practice. When using less familiar drugs, clinicians should consult authoritative sources for such information. Searchable databases about properties of medications, including toxicity and drug-drug and food-drug interactions, are increasingly available (https://www.drugbank.ca/[5] and UpToDate [www.uptodate.com][6]), and a forthcoming article in this series[7,8] will identify reliable sources for this information. When writing a prescription for any medication, it is essential to be certain that the name of the drug is correct and perfectly clear to avoid confusion with other similarly named drugs. The dosage, frequency, route of administration, number of doses to be dispensed, and number of prescription refills permitted must also be specified.

Better understanding of the mechanisms of action of drugs and of the human-genome-transcriptome-proteome are increasingly allowing prescription medications to be individualized for optimum therapeutic effects. The promise of personalized medicine is real and continues to grow.

Clinical Vignettes

Case 1. Clinically Relevant Drug Interaction Between Trimethoprim-Sulfamethoxazole and Warfarin

A 66-year-old woman with a history of atrial fibrillation and hypertensive heart disease has been maintained on an oral dose of warfarin 5.0 mg daily for embolic stroke prevention. International normalized ratios (INRs) obtained monthly have been therapeutic at 2.5–2.7 (therapeutic range for treatment of nonvalvular atrial fibrillation, 2.0–3.0).

She presented to her primary physician with recent complaints of low-grade fever, mild lower back pain, dysuria, frequency, and urgency. The primary physician obtained a urinalysis and urine culture. Urinalysis was positive for bacteria and showed 10–20 white blood cells per high-power field and 5–10 red blood cells per high-power field. Although waiting for culture results to come back, the doctor started trimethoprim/sulfamethoxazole (TMP/SMX) Double Strength (DS) at a dose of 1 tablet (160/800 mg) every 12 hours for 14 days for suspected pyelonephritis.

After 5 days of TMP/SMX therapy, the patient noticed a bloody nose and some rectal bleeding. The physician ordered another INR, and the results came back at 4.1. He held the warfarin dose for 1 day, then decreased the dose by 20% to 4.0 mg/day. Repeat INRs were 3.1, 2.8, and 2.5 at 1, 3, and 6 days following warfarin dose reduction (days 8, 10, and 13 of TMP/SMX therapy). Urine culture was reported to be positive for *E. coli* sensitive to TMP/SMX, and the patient was able to finish the 14-day antibiotic course. The physician ordered follow-up INRs 3 and 7 days following discontinuation of the 2-week course of TMP/SMX, which showed INRs of 1.9 and 1.7 (subtherapeutic for stroke prevention for atrial fibrillation). Therefore, the dose of warfarin was increased back to 5.0 mg to maintain an effective level of anticoagulation for this patient. One and 2 weeks following the dose increase back to 5 mg daily, the INRs were therapeutic, at 2.6 and 2.8. The frequency of INR determination returned to monthly.

Case 1 Discussion. Trimethoprim/sulfamethoxazole is one of the most frequently prescribed antibiotics and is used in a variety of common bacterial infections (urinary tract, respiratory, and skin). There is a high incidence of clinically significant increases in INR when patients taking warfarin are prescribed TMP/SMX. Warfarin is a racemic mixture of the S- and R-enantiomers. Although both enantiomers are pharmacologically active, S-warfarin provides the majority of the clinical effect and toxicity of warfarin as it is 5 times more potent as a vitamin K antagonist than R-warfarin.[9] S-warfarin is primarily metabolized by cytochrome P450 (CYP) 2C9, whereas R-warfarin is metabolized by CYP3A.[10,11]

SMX has been shown to be an inhibitor of CYP2C9 at therapeutic concentrations, causing a 20% or greater increase in S-warfarin plasma concentrations.[12,13] TMP normally inhibits CYP2C8 at clinically relevant doses; however, if the plasma concentrations exceed 100 μM, it can inhibit both CYP2C9 and CYP3A and therefore increase the plasma concentrations of both warfarin enantiomers.[12]

Both SMX and S-warfarin display similar stereoselectivity and regioselectivity for the binding site on CYP2C9.[10,12,14] SMX and S-warfarin compete for the same binding sites, with a limited number of binding sites on CYP2C9 available for their respective metabolisms. Therefore, SMX is a competitive inhibitor of S-warfarin metabolism.[10,12]

The drug interaction between TMP/SMX is clinically relevant, as the adjusted relative risk for over-anticoagulation when initiating TMP/SMX in a patient

on stable doses of warfarin has been reported to be 20.1 (95%CI, 10.7–37.9).[11] This translates into a significant likelihood of over-anticoagulation if there is no decrease in the warfarin dose. Many anticoagulant management clinics recommend a warfarin dose reduction strategy when adding TMP/SMX. Data suggest a preemptive short-term dose reduction of warfarin of 10%–20% as an effective strategy for maintaining a therapeutic level of anticoagulation in patients starting TMP/SMX therapy and to minimize the risk of supratherapeutic INR results and warfarin dose interruption.[14] The treating physician in this case reduced the warfarin dose by 20% only after the patient showed signs of bleeding. A preemptive approach to dose reduction is usually recommended if the patient cannot be treated with an antibiotic that shows a lesser drug interaction with warfarin. However, it must also be appreciated that the magnitude of the drug interaction between warfarin and TMP/SMX is variable and underscores the need to closely manage all patients anticoagulated with warfarin when initiating TMP/SMX antibiotic therapy.

Case 2. Novel Oral Anticoagulants

A 68-year-old man with a medical history of hypertension, coronary artery disease, benign prostatic hypertrophy, deep venous thrombosis (DVT), and multiple previous pulmonary emboli (PE) after inferior vena cava filter placement, on chronic anticoagulation with warfarin. The patient presented to the emergency department with reports of 2 episodes of bright red blood per rectum. He denied abdominal pain, nausea, or emesis, as well as light-headedness, dizziness, shortness of breath, or chest pain. He reported full compliance with medical management. The patient had regular follow-up in the Anticoagulation Clinic, and his INR was stable in the range of 2.0–2.5. His last INR was 2.2, which was 2 weeks prior to admission. The patient reported that 10 days prior, he had a urinary tract infection (UTI) and received a 7-day course of ciprofloxacin. On presentation, he denied any fever, chills, dysuria, hematuria, urgency, or frequency. He did not have any history of medication allergies. His other medications included amlodipine, atorvastatin, carvedilol, and lisinopril. He denied current alcohol, tobacco, or drug abuse. There was no family history of hypercoagulability. On initial evaluation, the patient was stable, with a blood pressure of 140/30 mm Hg, heart rate (HR) of 60 beats per minute (bpm), respiratory rate of 16 respirations per minute, and oxygen saturation of 99% on room air. He was alert, fully oriented, and in no acute distress. His heart rate was regular; breathing was unlabored, and lungs were clear to auscultation. Abdominal examination was unremarkable, with positive bowel sounds, nondistended and nontender. Rectal examination found bright red blood in the rectum and was negative for fissure or hemorrhoids. Laboratory workup revealed creatinine (Cr), 1.0 mg/dL (creatinine clearance [CrCl] > 60 mL/min); hemoglobin (Hgb), 11.4 g/dL; hematocrit (Hct), 35.2% (previous hemoglobin, 14.7 g/dL; hematocrit, 44.6%); PT, 39.8 seconds; INR, 3.9; PTT, 42.1 seconds. Computed tomography (CT) of the abdomen and pelvis revealed diffuse sigmoid diverticulosis without signs of diverticulitis. The patient was admitted to a monitored bed. Serial hemoglobin and hematocrit were followed every 4 hours, and "type and screen" was ordered. Warfarin was discontinued, and the patient received 5 mg of oral vitamin K. The gastroenterology (GI) service was consulted and recommended further observation off anticoagulation in the setting of probable diverticulosis as the source of bleeding.

Overnight, he continued to have a bloody bowel movement every 1–2 hours. Fresh frozen plasma transfusion was given to emergently reverse anticoagulation. Follow-up hemoglobin was 8.1 g/dL, and INR was 1.4. In the early morning, the patient reported lightheadedness and dizziness, his BP was 90/56 mm Hg and pulse 104 bpm. He was given a fluid bolus and 1 unit of packed red blood cells. The GI service was summoned emergently, and the patient underwent colonoscopy. Multiple nonbleeding colonic angiodysplastic lesions were found in the right colon, and there was sigmoid diverticulosis with no signs of active bleeding. The cause of the lower GI bleeding was thought to be the angiodysplastic lesions, and most of them were cauterized, and there was no recurrent bleeding. Because of recurrent UTIs and the need for antibiotics, warfarin was thought to be an undesirable mode of anticoagulation for this patient. He was started on rivaroxaban and discharged home with oral iron supplementation.

Two months later, he presented to the emergency department with recurrent bright red blood per rectum. Symptoms were similar to his previous presentation, except that the amount of blood per bowel movement was larger. The patient denied any recent change in medications and reported compliance with current medical management. He reported that since the warfarin was discontinued, he had liberalized his diet to include more vegetables and had lost 4 pounds. His last dose of rivaroxaban was 2 hours before the onset of bleeding. On admission, the patient was stable, with a BP of 128/65 mm Hg and HR of 70 bpm. His abdominal examination was benign, and the rectal examination was positive for bright red blood. Hemoglobin was 10.1 g/dL; Hct, 30.9%; Cr, 1.1 mg/dL; and INR, 1.6. The patient was again admitted to a monitored bed. Rivaroxaban was discontinued. During the first hospital night, he continued to have bloody bowel movements every 1–2 hours. Hgb 4 hours after

admission was 7.5 g/dL. The patient reported lightheadedness and became hemodynamically unstable, with a BP of 70/53 mm Hg and HR of 112 bpm. He was transferred to the intensive care unit, received a packed red blood cell transfusion, and 4-factor prothrombin complex concentrate (Kcentra) was given for rivaroxaban reversal. Further evaluation found a diverticular bleed, and he underwent an urgent sigmoidectomy. The patient was started on heparin intravenously 24 hours after surgery. His vital signs and hemoglobin and hematocrit remained stable, but his creatinine increased to 1.5 g/dL (CrCl, 50 mL/min), indicating mild kidney injury. With his previous history recurrent DVT/PE, the patient was judged to be at high risk for recurrent thromboembolic events and continuous anticoagulation was highly recommended by the Hematology and Cardiology services. Dabigatran was recommended as the only novel oral anticoagulant (NOAC) with a US Food and Drug Administration (FDA)-approved antagonist. However, patient declined this treatment because of high out-of-pocket cost. In the setting of mild renal insufficiency (creatinine clearance less than 50 mL/min), apixaban 5 mg twice daily was recommended instead of rivaroxaban.

Case 2 Discussion. NOAC refers to several medications used to achieve systemic anticoagulation in the outpatient setting. NOACs are also called direct inhibitors because their mechanism of action involves direct blockade of 1 of 2 major proteins in the coagulation cascade. NOACs can be factor Xa inhibitors like apixaban (Eliquis), rivaroxaban (Xarelto), and edoxaban (Savaysa) or thrombin inhibitors like dabigatran (Pradaxa). This case demonstrates that both warfarin and NOACs have the same major side effect: bleeding. Given that anticoagulation is the desired therapeutic effect, this is not surprising. Despite a similar therapeutic effect and major side effect, those 2 modalities of systemic oral anticoagulation have unique advantages and disadvantages.

Warfarin has been in use for many decades, and most medical professionals are very familiar with its toxicity profile. Obvious advantages are low cost, reliable monitoring of action, and a reliable antagonist (vitamin K) that can be used even in an outpatient setting to reverse warfarin's action. However, in emergent situations, transfusion of plasma products is necessary for prompt reversal. Disadvantages are related to a relatively narrow therapeutic window and a variable dose-response relationship. Warfarin pharmacokinetics are affected by the level of vitamin K in the digestive tract (produced mostly by GI microbiota) and by the function of hepatocytes. Therefore, degree of anticoagulation can be influenced by diet, gastrointestinal disorders, antibiotic use, or liver function. The patient must consume a steady diet with limited intake of leafy vegetables (a source of vitamin K). Because of the narrow therapeutic window, warfarin effect must be closely monitored with frequent INR measurement.

Unlike warfarin, NOACs only came into use about a decade ago. Per current clinical studies, all-cause mortality from NOACs is lower than from warfarin.[15] However, unlike warfarin, there is no antagonist currently available to reverse the action of anti-Xa agents. In May 2018, the FDA approved a new agent, andexanet alfa (Andexxa) for anti-Xa agent reversal, but this medication is still unavailable for general use. Antithrombin medications (eg, dabigatran) can be reversed with idarucizumab, which is expensive and used only in the hospital setting. NOACs have less variability in bioavailability and drug effect for a given dose than does warfarin. That is why there is no requirement for close monitoring of drug levels or coagulation times. Although factor Xa antagonists could be monitored by measuring anti-factor Xa activity, this is not standardized for the outpatient setting and makes monitoring of compliance difficult.[16] NOACs are metabolized in the kidney and liver, and like warfarin, severe hepatic impairment could result in accumulation of these agents. However, unlike warfarin, NOAC pharmacokinetics are primarily affected by renal function. These medications are renally excreted to variable degrees. Of the NOACs, apixaban is the least dependent on renal clearance. In patients with moderate renal impairment (creatinine clearance, 30–50 mL/min), they are at least as safe as warfarin.[17] NOACs are not recommended for outpatients with severe renal impairment (creatinine clearance $<$ 30 mL/min). Renal impairment may require change of NOAC medication (as seen in our case) and/or dose adjustment. Despite favorable safety profiles and pharmacokinetics, NOACs are not recommended for use with prosthetic heart valves, antiphospholipid syndrome, or pregnancy because of insufficient data.

Case 3. Steroid Psychosis

A 47-year-old white woman presented to an orthopedic surgery practice with the chief complaint of right shoulder pain. One month earlier, the patient had slipped on a staircase and fallen down 2 steps. During the fall, she experienced a cracking sensation in her right shoulder, followed by excruciating pain that dissipated over time to nearly normal shoulder function, and she therefore did not seek immediate medical attention. A few days before the clinic visit, her pain returned after a light upper body workout. The patient reported no clinical improvement after self-medication with ibuprofen 600 mg. Her medical history included mild asthma and an episode of major depression and anxiety 6 years earlier for which she had completed treatment. She was not

currently taking any medications and did not report any allergies.

After physical examination and x-ray, the patient was diagnosed with right rotator cuff tendinitis. The orthopedic surgeon prescribed anti-inflammatory therapy with a corticosteroid, and the patient was given methylprednisolone acetate injectable crystal suspension 80 mg in the subacromial space of the right shoulder. She was provided with rotator cuff exercises and asked to return for magnetic resonance imaging in 3–4 weeks if no pain improvement occurred.

Within 2 days, the patient complained to her family about dizziness and light-headedness. Within 7 days, she had developed severe anxiety and depression with suicidal ideation and could not attend work on 2 consecutive days because of severe anxiety.

The patient requested an appointment with her psychiatrist but was informed that the earliest appointment was in 9 days. The patient had citalopram (a selective serotonin reuptake inhibitor) and lorazepam (an anxiolytic benzodiazepine) remaining from previous treatment for depression and decided on her own to start taking citalopram 40 mg and lorazepam 0.5 mg.

Without improvement of her condition, the patient contacted her primary care physician the following day and was seen by a physician assistant the same day. She was diagnosed with severe anxiety/depression, most likely related to the methylprednisolone injection. The patient was instructed to continue on citalopram 40 mg daily and lorazepam as needed and to follow up with the psychiatrist as scheduled. The patient was counseled that the symptoms should improve in 1–2 weeks and that she should be free of depression in about 4 weeks when the methylprednisolone was eliminated and the SSRI therapy had established efficacy. She also provided the patient with emergency phone numbers of treatment centers in case the severity of depression became unmanageable.

The patient visited her psychiatrist who confirmed that the corticosteroid injection was most likely the cause of the depression episode and recommended continuation of citalopram with additional psychological treatment sessions and with follow-up visits. The patient's depression improved. She was symptom free 6 weeks after the corticosteroid injection. Her shoulder symptoms were treated with physical therapy and improved over time.

Case 3 Discussion. This case study highlights a frequently encountered challenge related to pharmacotherapy in medical practice: the occurrence of unexpected off-target side effects of commonly used therapeutics, in this case corticosteroids.

Steroid psychosis and other mental disturbances because of corticosteroid therapy have been known since the introduction of cortisone into therapy in the 1950s.[18] The magnitude and potential severity of these effects may be underestimated. The manifestations of these drug-induced adverse events range from an increased sense of well-being to hypomania, mania, depression, and frank psychosis. Incidence rates of mild to moderate psychiatric symptoms have been described as 27.5% and as 5.7% for severe psychiatric symptoms.[19] There is an increased incidence rate with increasing doses of prednisone from <40, to 40–80 to >80 mg.[20] Although the association between corticosteroids and disturbances in mood, behavior, and cognition is well known, little is known about the underlying precise mechanism of action.[21]

The primary treatment for steroid psychosis is discontinuation of steroid therapy, followed by antipsychotic medication.[22] Discontinuation of the root cause for the depression is complicated in this specific case by administration of methylprednisolone suspension. Uptake into the systemic circulation is protracted and can occur over multiple days to weeks, based on slow dissolution of the methylprednisolone crystal suspension in the subacromial space.[23] Thus, resolution of the symptoms is not expected within 2–3 weeks after initial injection, despite the initiation of SSRI therapy, which also needs an induction phase of 2–3 weeks to establish efficacy.

The reason for the underappreciation of psychiatric adverse events such as depression after injection of corticosteroids may partially be related to the treating physician often not being faced with the side effects of his pharmacotherapeutic intervention. In this specific case, the treating orthopedic surgeon was not consulted about the experienced adverse event (ie, depression). This may similarly be the case in other medical specialties in which corticosteroids are widely used, such as dermatology, dentistry, rheumatology, and gastroenterology. Therefore, the prescribing physician may never be confronted with the consequences of his pharmacotherapeutic intervention (unless in a legal framework) and thus may not receive feedback on his initial assessment of the case and his decision to intervene. This may lead to substantial disruption in the learning process about efficacy and safety of prescribed medications and may lead to underappreciation of potential medication-related problems. In the specific case study, it remained unknown to the orthopedic surgeon that his pharmacotherapeutic intervention had triggered a major psychiatric event and that the patient needed to seek care from multiple medical specialists to cope with the adverse drug reaction triggered by the orthopedic surgeon's decision.

Overall, corticosteroids are an excellent example of a commonly used class of medications that are used across a wide range of medical specialties and are generally considered safe, but have the potential to cause

severe adverse drug reactions. Risk factors (in the case study, history of depression) and the risk-to-benefit ratio have to be carefully evaluated, in full disclosure to the patient, to ensure a safe and efficacious treatment outcome that is acceptable to all involved stakeholders.

Case 4. Acetaminophen Overdose

A 16-year-old female adolescent presented at the emergency department 4 hours after she ingested acetaminophen 15 g after her boyfriend left her unexpectedly. She complained of nausea without vomiting or abdominal pain. She was immediately seen by a physician. Her vital signs and physical examination were unremarkable.

Acetaminophen (N-acetyl-p-aminophenol [APAP]) is the most commonly used analgesic and antipyretic available without a prescription and is found in many single and combination products. As a result, acetaminophen overdose results in more hospitalizations than an overdose of any other drug.[24] Oral absorption of acetaminophen is rapid (peak concentration after 30–45 minutes) and shows excellent bioavailability of 60%–98%. After absorption, the majority (85%–95%) is eliminated through hepatic conjugation generating nontoxic glucuronide or sulfate metabolites.[25] The remaining 5%–15% is oxidized by several cytochrome P450 drug-metabolizing enzymes, resulting in the formation of the potentially harmful metabolite N-acetyl-p-benzoquinone imine (NAPQI). If this metabolite is not eliminated, it can bind to critical cell proteins in liver cells, ultimately resulting in cell death.[26] In the liver, glutathione (GSH) combines rapidly with NAPQI, resulting in its detoxification. The amount of GSH available in the liver far exceeds the amount needed to detoxify NAPQI produced by the ingestion of therapeutic amounts of acetaminophen. However, in this case with a massive acetaminophen dose, free NAPQI will be around because the existing elimination pathways become saturated and the available GSH depleted. The clinical effects of the overdose are produced by this free NAPQI.[27]

Case 4 Discussion. Clinical symptoms of acetaminophen overdose are variable and depend on the amount ingested and time since ingestion. Initially, patients may be asymptomatic or complain of symptoms such as nausea, vomiting, abdominal pain, or general malaise. Later, symptoms of fulminant hepatic failure might dominate the clinical picture.[28] In addition to supportive therapy such as airway, breathing, and circulation measures, there is a need to monitor renal function, treat coingestions, and refer for liver transplant if there is evidence of hepatic failure. More specific measures are decontamination and/or antidotal treatment with N-acetylcysteine (NAC). Decontamination is indicated for early oral ingestion of APAP (<4 hours). Activated charcoal (1 g/kg) may be administered if the patient's airway is secure. For this 16-year-old female, the time between ingestion and arrival at the emergency department was 4 hours. As such, decontamination was no longer indicated.[29] Antidotal therapy is indicated if the APAP concentration is still above the treatment line in the Rumack-Matthew nomogram,[30] a handy tool that allows timely management of overdose with immediate-release acetaminophen. According to the nomogram, a serum/plasma concentration of 140–150 μg/mL 4 hours postingestion (when absorption is considered complete) warrants NAC treatment. For this patient, a blood sample that was immediately taken would determine if she needed to be treated with NAC. Four hours after the ingestion, the APAP concentration was above the treatment line, but she had no signs of hepatic failure, and as such she was treated with oral NAC for 72 hours. It is advisable to add an antiemetic during this treatment because significant vomiting may occur. Only if there are signs of hepatic failure is NAC administered intravenously.[31] This patient did not develop irreversible hepatic failure, and she recovered completely.

Case 5. Ethinyl Estradiol/Norethindrone and Thrombosis

Although regulated by the FDA as drugs distinct from biologics,[32] therapeutic hormones have much in common with biologics. They are exogenous agents that mimic the action of natural hormones. This vignette on contraceptive hormone drugs is included because they are widely prescribed and because patients are at risk for uncommon yet serious adverse events.

A 20-year-old woman presented to the emergency department with acute right-sided chest pain and shortness of breath. She reported 1 week of right lower extremity swelling and pain. She has been followed at the women's health clinic and prescribed ethinyl estradiol/norethisterone for mild dysmenorrhea and contraception. She had no history of tobacco use, no significant medical history, and was not on any other prescription or over-the-counter medications or supplements. Urgent evaluation included a chest CT with contrast that confirmed the presence of multiple PE without right heart strain. She was started on enoxaparin 1 mg/kg subcutaneously twice daily and admitted to the general internal medicine service. Lower extremity doppler ultrasound confirmed the presence of right lower extremity DVT. Hematology was consulted and recommended the transition to oral rivaroxaban and permanent discontinuation of her oral contraceptive. She was uncertain of any significant family history. On detailed questioning, she said that her father had been on an oral "blood thinner" several years earlier but did not know the reason. She underwent hypercoagulability testing that was notable for depressed activated protein

C resistance testing. Subsequent mutational testing revealed factor V Leiden heterozygosity.[25–28]

Case 5 Discussion. Estrogen-progestin contraceptives are frequently prescribed for contraception, dysmenorrhea, hyperandrogenism, and other disorders. Oral contraceptives are associated with a 2- to 3-fold increase in the risk of thrombosis,[33] depending on the estrogen dose and formulation. Given that the de novo risk of thromboembolic events in a young, healthy population is quite low (5–10 events per 10 000 woman-years[34]), the absolute risk of thromboembolic events in young women using a combined oral contraceptive is low (10–14 thromboembolic events per 10 000 woman-years).[34] For patients with multiple inherited thrombotic defects who are also taking combined oral contraceptives, the relative risk of venothromboembolism is up to 35 times greater than baseline.[35]

Prior to prescribing an oral contraceptive, an assessment of thrombosis risk is recommended. Factors contributing to thrombosis risk include smoking, personal history of thrombosis, recent pregnancy, family history of thrombosis, and obesity. In this case, it was later clarified that her father had a single episode of lower extremity deep venous thrombosis following hip surgery. Factor V Leiden is a common mutation in whites (approximately 5%) and is associated with a 5-fold increased risk of thrombosis. This mutation, as well as the oral contraceptive, increased this patient's risk of thrombosis. Familial thrombosis was previously considered an autosomal-dominant trait caused by a dominant gene defect with a reduced penetrance for the disease. Today, familial thrombophilia is considered a complex genetic disorder caused by the segregation of 2 or more gene defects (both known and unknown). Known defects include protein C, protein S, antithrombin deficiency, and activated protein C resistance associated with factor V Leiden.[35] If a positive family history is known prior to prescribing an oral contraceptive, the patient may have been identified as at increased risk of thrombosis, and alternative, nonestrogen contraceptives or nonhormonal methods for contraception could have been considered. Other medications associated with hypercoagulability include glucocorticoids,[36–38] bevacizumab, sorafenib, sunitinib, lenalidomide, testosterone,[39] thalidomide, and tamoxifen.[40] Progesterone when used in combination with an estrogen in postmenopausal women may also be associated with hypercoagulation, although the evidence is less clear. Because immobility is a risk factor for venous thromboembolism, one should consider the above discussions when prescribing contraception and hormone therapy to postsurgical or mobility-impaired patients.

After release from the hospital, the patient returned to her women's health clinic. She was not immediately interested in conception and recognized that pregnancy would increase her risk of thromboembolic event 5- to 50-fold.[41] She and her provider reviewed the United States Medical Eligibility Criteria for Contraceptive Use.[42] Given her current DVT/PE and high risk for recurrence, she was no longer a candidate for estrogen-containing methods of contraception. However, she was still a candidate for methods such as injectable medroxy-progesterone and long-acting reversible contraceptive methods including the etonogestrel implant, levonorgestrel intrauterine device (IUD), and the copper IUD.[42]

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