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A 76-year-old woman with erratic anticoagulation

A 76-YEAR-OLD WOMAN with a history of hypertension, osteoarthritis, gas-tropathy due to nonsteroidal anti-inflammatory drug (NSAID) use, atrial fibrillation, and stroke comes to the emergency department because of hematuria and gingival bleeding.

She is currently taking hydrochlorothiazide, warfarin, and acetaminophen. She has not recently been ill, had any infections, used antibiotics, or changed her diet.

Last month during a routine checkup, her serum transaminase and albumin levels were normal and the international normalized ratio (INR) of her prothrombin time was 2.1.

■ DIAGNOSTIC STUDIES

1 What coagulation tests should be done immediately to help determine the cause of her bleeding?

- Platelet count and INR
- Partial thromboplastin time
- Lupus anticoagulant activity
- Factor XII level
- Bleeding time

The **platelet count** (done as part of a complete blood count) and **INR** would provide the most immediately useful information, ie, her level of anticoagulation and the magnitude of her blood loss.

The INR, a standardized measure of the prothrombin time, is used to assess the extrinsic pathway of clotting, which consists of tissue factor and factor VII, and the common pathway (factor II [prothrombin], factor V,

factor X, and fibrinogen). It is useful in monitoring warfarin therapy because it is sensitive to reduced activity of the vitamin K-dependent factors II, VII, IX, and X, which warfarin inhibits.

Our patient's complete blood count is normal, but her INR is 7.0.

The **partial thromboplastin time** is used to monitor unfractionated heparin therapy, but therapeutic doses of warfarin do not usually affect it. It may be useful to measure the partial thromboplastin time in a bleeding patient if severe, chronic liver disease or diffuse intravascular coagulopathy were suspected clinically.

"**Lupus anticoagulant**" is actually a misnomer: although this immunoglobulin can elevate the partial thromboplastin time, it can be associated with excess thrombosis rather than bleeding.

Factor XII deficiency can prolong the partial thromboplastin time, but it is not associated with excessive spontaneous bleeding.¹

The **bleeding time** measures the interaction of platelets with the blood vessel wall. A normal bleeding time does not rule out the potential to bleed, nor does a prolonged bleeding time always indicate bleeding risk. Therefore, the bleeding time is not recommended as a preoperative screening test or as an initial test in a patient with spontaneous bleeding.² In fact, it is generally not a useful initial test unless von Willebrand disease or a platelet function disorder is suspected; in these situations the bleeding time or formal platelet aggregation studies may assist the evaluation.

A previously controlled patient on warfarin now has bleeding and an INR of 7. What has changed?

■ MANY THINGS CAN INCREASE THE INR

2 Which of the following does not usually increase the INR?

- Vitamin K deficiency
- Severe liver disease
- Prothrombin deficiency
- Antiphospholipid antibodies
- Heparin treatment

In addition to warfarin therapy, factors that can increase the INR include (in decreasing order of frequency):

- Vitamin K deficiency due to poor nutrition or antibiotics that alter the intestinal microflora
- Severe liver disease, which decreases the synthesis of both vitamin K-dependent and vitamin K-independent clotting factors
- Deficiency or inhibition of factor II (prothrombin), factor V, factor X, or fibrinogen
- Antiphospholipid antibodies (lupus anticoagulant phenomenon) with antiprothrombin activity (uncommon).³

Heparin treatment does not normally increase the INR because heparin-neutralizing materials are added to the reagent, but the INR may be transiently elevated after bolus doses of heparin.

■ WARFARIN: RISK OF BLEEDING VS RISK OF STROKE

In patients with atrial fibrillation, warfarin therapy must be intense enough to prevent thrombotic stroke but not so intense as to cause bleeding. Bleeding occurs in up to 2% or 3% of patients per year on warfarin therapy.⁴ In multicenter trials,^{4,5} most thrombotic strokes occurred in patients assigned to warfarin therapy with INR values lower than 2.0. At the other end of the spectrum, the bleeding risk was significantly higher in patients with INR values higher than 3.0.⁴⁻⁶

Therefore, the target INR during anticoagulation therapy for most indications (eg, prevention and treatment of venous thromboembolism, atrial fibrillation, and valvular heart disease) should be between 2.0 and 3.0.

A higher INR range (2.5–3.5) is recommended for patients with a tilting disk

mechanical heart valve or a bileaflet mechanical valve in the mitral position, or patients with a bileaflet mechanical aortic valve who have atrial fibrillation. More intense anticoagulation may also be indicated when a clot is seen to increase in size despite maintenance of a therapeutic INR.

However, keeping the INR in the goal range is much more difficult than appreciated. For example, in the third Stroke Prevention in Atrial Fibrillation (SPAF III) trial,⁷ INR values were measured every month, and a nurse adjusted the warfarin doses using a nomogram, with the help of a physician. In spite of this careful attention, only 61% of INR values were in the goal range of 2.0 to 3.0.

Predicting the risk of bleeding

Probably the most important risk factors for life-threatening bleeding complications while on warfarin therapy are advanced age (> 75 years), intense anticoagulation (especially when the INR is > 4.0), history of cerebrovascular disease (recent or remote), and concomitant use of drugs that interfere with hemostasis (aspirin or nonselective NSAIDs).⁸

Outpatient bleeding risk index. In an attempt to estimate the probability of major bleeding in outpatients taking warfarin, Beyth et al⁹ retrospectively derived a risk index in a cohort of 556 patients and prospectively validated it in a separate cohort of 264 outpatients. The index consists of the following risk factors:

- Age 65 years or older
- History of stroke
- History of gastrointestinal bleeding
- Recent myocardial infarction
- Hematocrit less than 30%
- Creatinine concentration greater than 1.5 mg/dL (133 μmol/L)
- Diabetes mellitus.

At 48 months, the cumulative incidence of major bleeding was as follows:

- With no risk factors: 3%
- With one or two risk factors: 12%
- With three or more risk factors: 53%.

Of the 18 episodes of major bleeding that occurred in patients with three or more risk factors, 17 were potentially preventable (eg, by avoiding excessive anticoagulation and the coadministration of nonselective NSAIDs).

Keeping the INR in the goal range is harder than appreciated



■ ELDERLY PATIENTS ARE AT HIGHER RISK OF BLEEDING

Elderly patients are more sensitive to the anticoagulant effect of warfarin than younger patients are. In one report,¹⁰ patients 75 years old or older needed less than half the daily warfarin dose compared with those younger than 35 years for an equivalent level of anticoagulation.

Several factors may account for this increased sensitivity in elderly patients:

- Lower body weight
- Differences in pharmacokinetics
- A tendency toward reduced drug clearance, due either to reductions in renal or hepatic blood flow and function with age or to other disease processes
- An age-related difference in the sensitivity of the vitamin K₁ receptor
- Possibly lower dietary vitamin K intake^{10,11}
- Polypharmacy. Warfarin has many drug interactions that alter its absorption or metabolism (TABLE 1),¹² and many elderly patients take more than one drug. Furthermore, some elderly patients who see more than one physician may fail to tell all their physicians that they are taking warfarin, or fail to tell the physician who is prescribing the warfarin about all the other drugs they may be taking. This can especially be a problem in patients with cognitive decline. Therefore, we must caution elderly patients taking warfarin about possible warfarin drug interactions any time we change their medications.

The risk of bleeding with warfarin may increase with age.^{13–17} Thus, the safety and tolerability of long-term anticoagulation, titrated to conventional levels, is less certain in the very elderly (older than 75 years), a group that accounts for approximately half of patients with strokes due to atrial fibrillation.

The SPAF III investigators⁷ tried to reduce the risk of bleeding in patients with atrial fibrillation at high risk of thromboembolic stroke (with INR values 1.2–1.5) by using low, fixed doses of warfarin plus aspirin 325 mg/day. However, patients on this regimen, most of whom were older than 65 years, had a fourfold higher incidence of stroke compared with those receiving adjusted-dose warfarin (INR 2.0–3.0).

TABLE 2

Common drug interactions with warfarin

DRUG AND INTERACTION	MECHANISM OF INTERACTION
Can increase the INR	
Acetaminophen	Unknown*
Amiodarone	P450 2C9 inhibition [†]
Cimetidine	Enzyme inhibition
Ciprofloxacin	Enzyme inhibition
Clarithromycin	Enzyme inhibition
Clofibrate	Enzyme inhibition
Erythromycin	Enzyme inhibition
Fluconazole	P450 2C9 inhibition [†]
Fluvastatin	P450 2C9 inhibition
Fluvoxamine	Enzyme inhibition
Gemfibrozil	Enzyme inhibition
Isoniazid	Enzyme inhibition
Itraconazole	Enzyme inhibition
Ketoconazole	Enzyme inhibition
Lovastatin	Enzyme inhibition
Metronidazole	P450 2C9 inhibition [†]
NSAIDs	Platelet inhibition [‡]
Propafenone	Enzyme inhibition
Simvastatin	Enzyme inhibition
Tamoxifen	Enzyme inhibition
Thyroid hormone	Increased vitamin K catabolism
Tramadol	Enzyme inhibition
Trimethoprim-sulfamethoxazole	P450 2C9 inhibition [†]
Zafirlukast	P450 2C9 inhibition
Can decrease the INR	
Barbiturates	Enzyme induction
Carbamazepine	Enzyme induction
Dicloxacillin	Enzyme induction
Methimazole	Decreased vitamin K catabolism
Propylthiouracil	Decreased vitamin K catabolism
Rifampin	Enzyme induction
Initially increase, then decrease the INR	
Phenytoin	Protein displacement/enzyme induction

*Lesser effect

[†]Greater effect

[‡]Only reported with certain NSAIDs and appears to be dose-related

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When giving warfarin to elderly patients, one should take particular care and monitor the INR very closely. Given the uncertainty about the safety of INRs higher than 2.5 for patients older than 75 years, a slightly lower INR target of 2.0 may be a reasonable compromise between toxicity and efficacy for this age group. In fact, warfarin therapy with INR values of 1.6 to 2.5 has been found to be about 90% as effective in preventing stroke compared with more intense therapy.^{5,7,18,19}

■ CASE CONTINUED: DOES ACETAMINOPHEN AFFECT THE INR?

Further questioning reveals that the patient's osteoarthritis had recently flared, and she had been taking more acetaminophen to treat it.

3 True or false? Acetaminophen has no effect on coagulation.

- True
- False

If patients on warfarin need to start acetaminophen, check the INR

False. Acetaminophen, unlike the classic NSAIDs and like the newer cyclo-oxygenase II-selective NSAIDs, does not interfere with platelet function. Thus, it is not generally thought to be a common cause of gastric ulcers or bleeding. Hence, it is commonly prescribed to patients taking warfarin.

However, interactions between acetaminophen and warfarin, leading to elevated INRs and bleeding, are common, often unrecognized, and potentially fatal.^{20,21} In a case-control study,²⁰ 52 (56%) of 93 warfarin patients who had dangerously elevated INRs (> 6.0) had been taking acetaminophen, compared with 70 (36%) of 196 patients with lower INRs ($P = .001$). Patients who had taken more than 9,100 mg of acetaminophen in the preceding week (four 325-mg tablets per day) were 10 times more likely to have an INR above 6.0 than those who used no acetaminophen.

The mechanism by which acetaminophen increases the INR in patients who take warfarin is not fully understood. However, both drugs are metabolized by the cytochrome P450

2C9 enzyme system, which is competitively and noncompetitively inhibited by various substances, some as seemingly innocuous as grapefruit juice.

More than 95% of warfarin in the blood is protein-bound, and only the other 5% is pharmacologically active.^{20,21} When the degradation of warfarin is slowed through the interaction of acetaminophen with the P450 system, the amount of active unbound warfarin can double or triple.^{20,21}

If patients taking warfarin need nonnarcotic analgesics such as acetaminophen long-term, the INR should be monitored at least once a week. Adding acetaminophen to a stable dose of warfarin can increase the prothrombin time in as little as 18 hours.^{20,21} We suggest that the acetaminophen be used in a regular daily dosage as opposed to a sporadic manner.

■ THE PATIENT RETURNS WITH A NOSEBLEED

The patient was cautioned about acetaminophen, and she began more frequent monitoring of her INR, which remained in the therapeutic range for the next 6 months.

Subsequently, however, she again came to the emergency department because of epistaxis. Her INR was 10, although her doses of warfarin and use of other long-term medications (including acetaminophen, aspirin, and NSAIDs) had stayed the same, and she had not been ill.

After more detailed questioning, the patient revealed that she had recently begun eating pieces of ginger root and drinking tea made from ginger powder as a natural remedy for an upset stomach.

Herbal medicine on the rise

There has been a huge rise in consumption of herbal products. In 1998, retail sales of just seven of the most popular herbal products exceeded \$150 billion.²²

Many people believe “natural” is better.²³ Patients often don't tell their physicians about herbal products because they believe herbal products are not medicines.²⁴ They may also think their doctor will chastise them for pursuing alternative treatments.



Ginger: More than a spice

Ginger (*Zingiber officinale*) is grown in the tropics and is used as a spice. Herbalists also use it to treat nausea, abdominal pain, diarrhea, motion sickness, and cough.

Like other herbal remedies, ginger may have serious side effects, and clinicians should remember to ask about their use. Cases of possible interactions between warfarin and garlic, ginger, ginkgo, or ginseng have been reported, but the true risks of these interactions are difficult to assess, owing to a paucity of data.²⁵

In vitro, ginger inhibits platelet aggregation in a mechanism akin to aspirin's—by inhibiting thromboxane generation via the arachidonic acid pathway.^{26,27} It also increases fibrinolytic activity.²⁸ However, this antiplatelet effect has not been reproducible in human studies.²⁹

Significant adverse effects for ginger have been reported,²⁹ but may not be as widely appreciated as those of St. John's wort, for example.²⁵ We suspect that the increased INR in our patient was due to an interaction between ginger and warfarin involving either the intestinal or hepatic P450 enzyme system.

■ REVERSING ANTICOAGULATION

4 How should this patient's excess anticoagulation be reversed?

- Reduce her warfarin dose by half
- Omit the next warfarin dose, then resume at half the dose
- Hold warfarin temporarily, give one dose of oral vitamin K, then resume warfarin at a lower dose when the INR is in the therapeutic range
- Stop warfarin, give vitamin K intravenously

A small increase in INR is associated with a large increase in the risk of bleeding.^{30,31}

Excessive anticoagulation without bleeding or with only minor bleeding can be remedied by reducing the warfarin dose or stopping it entirely. The risk of bleeding is decreased by lowering the INR from the range of 3.0 to 4.5 down to the range of 2.0 to 3.0, which generally can be achieved by reducing warfarin by only 1 mg/day.³²

If the INR is above the therapeutic range but less than 5.0 and no clinically significant bleeding is apparent, the next dose of warfarin should be omitted, or the maintenance dose of warfarin should be reduced, or both.


If the INR is between 5.0 and 9.0 and no clinically significant bleeding is present, several options are available, including stopping warfarin temporarily or stopping warfarin temporarily plus adding a low oral dose of vitamin K (2–5 mg). Low-dose vitamin K will not significantly block the effect of warfarin when anticoagulation is reinstated.

If the INR is greater than 9.0 and the patient is without clinically significant bleeding, as in our patient, warfarin should be stopped and 2 to 5 mg of oral vitamin K given, which should reduce the INR within 24 to 48 hours. The INR should be monitored closely, and repeat doses of oral vitamin K should be given as necessary. Warfarin should be restarted at a reduced maintenance dose when the INR falls to the therapeutic range, unless some dietary or medication cause for the higher INR can be identified.

A small controlled trial³³ indicated that oral vitamin K probably reverses warfarin-associated coagulopathy faster than subcutaneous vitamin K.

If the INR is higher than 20 or if the patient has serious bleeding at any degree of anticoagulation, then anticoagulation should be rapidly reversed. Warfarin should be stopped, and vitamin K 2 to 5 mg should be given by a slow intravenous infusion (eg, over 20 to 60 minutes). If the bleeding is life-threatening, this treatment should be supplemented by transfusions of fresh frozen plasma or concentrated prothrombin complex. The INR should be monitored, and repeat intravenous doses of vitamin K may be required at 12-hour intervals.

■ CASE CONCLUDED

Our patient stopped all ginger consumption, and the excessive anticoagulation was partially reversed with intravenous vitamin K. Currently, her INR remains in the therapeutic range with no change in her other medicines, and with more frequent INR monitoring when she needs extra acetaminophen for a flare of her osteoarthritis. 

Ask patients on warfarin about all their other medications, including herbals



REFERENCES

1. **Bermas BL, Schur PH.** Clinical manifestations and diagnosis of the antiphospholipid antibody syndrome. In: Rose BD, editor. Up-To-Date. Wellesley, MA: Up-To-Date, 2003.
2. **Drews RE.** Approach to the patient with a bleeding diathesis. In: Rose BD, editor. Up-To-Date. Wellesley, MA: Up-To-Date, 2003.
3. **Zehnder JL.** Clinical use of coagulation tests. In: Rose BD, editor. Up-To-Date. Wellesley, MA: Up-To-Date, 2003.
4. **The Stroke Prevention in Atrial Fibrillation Investigators.** Bleeding during antithrombotic therapy in patients with atrial fibrillation. *Arch Intern Med* 1996; 156:409–416.
5. **Hylek EM, Skates SJ, Sheehan MA, et al.** An analysis of the lowest effective intensity of prophylactic anticoagulation for patients with non-rheumatic atrial fibrillation. *N Engl J Med* 1996; 335:540–546.
6. **The European Atrial Fibrillation Trial Study Group.** Optimal oral anticoagulant therapy in patients with nonrheumatic atrial fibrillation and recent cerebral ischemia. *N Engl J Med* 1995; 333:5–10.
7. **Adjusted-dose warfarin versus low-intensity, fixed-dose warfarin plus aspirin for high-risk patients with atrial fibrillation: Stroke Prevention in Atrial Fibrillation III randomized clinical trial.** *Lancet* 1996; 348:633–638.
8. **Levine MN, Raskob G, Hirsh J.** Hemorrhagic complications of long-term anticoagulant therapy. *Chest* 1989; 95:26s–36s.
9. **Beyth RJ, Quinn LM, Landefeld CS.** Prospective evaluation of an index for predicting the risk of major bleeding in outpatients treated with warfarin. *Am J Med* 1998; 105:91–99.
10. **Routledge PA, Chapman PH, Davies DM, et al.** Factors affecting warfarin requirements. *Eur J Clin Pharmacol* 1979; 15:319–322.
11. **Routledge PA, Chapman PH, Davies DM, Rawlins MD.** Pharmacokinetics and pharmacodynamics of warfarin at steady state. *Br J Clin Pharmacol* 1979; 8:243–247.
12. **Brater DC.** Warfarin drug interactions. In: Rose BD, editor. Up-To-Date. Wellesley, MA: Up-To-Date, 2003.
13. **Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation: Stroke Prevention in Atrial Fibrillation II Study.** *Lancet* 1994; 343:687–691.
14. **Coon WW, Willis PW III.** Hemorrhagic complication of anticoagulant therapy. *Arch Intern Med* 1974; 133:386–392.
15. **Wintzen AR, de Jonge H, Loeliger EA, et al.** The risk of intracerebral hemorrhage during oral anticoagulation treatment: a population study. *Ann Neurol* 1984; 16:553–558.
16. **Pengo V, Legnani C, Noventa F, Palareti G.** Oral anticoagulant therapy in patients with nonrheumatic atrial fibrillation and risk of bleeding. A multicenter inception cohort study. *ISCAT Study Group. Italian Study on Complications of Oral Anticoagulant Therapy. Thromb Haemost* 2001; 85:418–422.
17. **Wells PS, Forgie MA, Simms M, et al.** The outpatient bleeding risk index: validation of a tool for predicting bleeding rates in patients treated for deep venous thrombosis and pulmonary embolism. *Arch Intern Med* 2003; 163:917–920.
18. **Brass LM, Krumholz HM, Scinto JD, Mathur D, Radford M.** Warfarin use following ischemic stroke among Medicare patients with atrial fibrillation. *Arch Intern Med* 1998; 158:2093–2100.
19. **Hart GH.** Intensity of anticoagulation to prevent stroke in patients with atrial fibrillation [letter]. *Ann Intern Med* 1998; 128:408.
20. **Hylek EM, Heiman H, Skates SJ, Sheehan MA, Singer DE.** Acetaminophen and other risk factors for excessive warfarin anticoagulation. *JAMA* 1998; 279:657–662.
21. **Sabin JE, Daniels N.** Acetaminophen and warfarin. Undesirable synergy. *JAMA* 1998; 279:702–703.
22. **Ernst E.** The risk-benefit profile of commonly used herbal therapies: ginkgo, St. John's wort, ginseng, echinacea, saw palmetto, and kava. *Ann Intern Med* 2002; 136:42–53.
23. **Palareti G, Hirsh J, Legnani C, et al.** Oral anticoagulation treatment in the elderly: a nested, prospective, case-control study. *Arch Intern Med* 2000; 160:470–478.
24. **Torpy JM.** Integrating complementary therapy into care. *JAMA* 2002; 287:306–308.
25. **Vaes LP, Chyka PA.** Interactions of warfarin with garlic, ginger, ginkgo, or ginseng: nature of the evidence. *Ann Pharmacother* 2000; 34:1478–1482.
26. **Koo KL, Ammit AJ, Tran VH, Duke CC, Roufogalis BD.** Gingerols and related analogues inhibit arachidonic acid-induced human platelet serotonin release and aggregation. *Thromb Res* 2001; 103:387–397.
27. **Verma SK, Bordia A.** Ginger, fat and fibrinolysis. *Indian J Med Sci* 2001; 55:83–86.
28. **Pribitkin ED, Boger G.** Herbal therapy: what every facial plastic surgeon must know. *Arch Facial Plast Surg* 2001; 3:127–132.
29. **Hodges PJ, Kam PCA.** The peri-operative implications of herbal medicines. *Anaesthesia* 2002; 57:889–899.
30. **Second report of the Sixty Plus Reinfarction Study Research Group.** Risks of long-term oral anticoagulant therapy in elderly patients after myocardial infarction. *Lancet* 1982; 1:64–68.
31. **Hylek EM, Chang YC, Skates SJ, Hughes RA, Singer DE.** Prospective study of the outcomes of ambulatory patients with excessive warfarin anticoagulation. *Arch Intern Med* 2000; 160:1612–1617.
32. **Hirsh J, Fuster V.** Guide to anticoagulant therapy. Part 2: Oral anticoagulants. *Circulation* 1994; 89:1469–1480.
33. **Crowther MA, Douketis JD, Schnurr T, et al.** Oral vitamin K reversed warfarin-associated coagulopathy faster than subcutaneous vitamin K. *Ann Intern Med* 2002; 137:251–254.

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