Learning Objectives: After reading this article, the physician should be able to:
1. Identify the type of reactions to vitamin K.
2. Describe the incidence of reactions to vitamin K.
3. Discuss options that will minimize the potential for serious adverse reactions.

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By James R. Roberts, MD

Warfarin is ubiquitous, its clinical indications myriad, and its complications vast. The reversal of anticoagulation is controversial and largely unstudied in the ED for anticoagulated patients presenting with spontaneous intracranial hemorrhage. Surprisingly little data exist about interventions to rapidly obtain a normalized INR in critical patients, such as those with intracranial bleeding. Although it would seem that rapidly reversing an elevated INR in ICH would be beneficial, there is minimal evidence that emergency and aggressive intervention alter the outcome to any great extent. Prognosis is always dismal when the anticoagulated patient bleeds into the brain.

This month, I discuss the occasional hypersensitivity reactions associated with parenteral administration of vitamin K1. Oral vitamin K supplementation is relatively innocuous, and is universally considered safe. Systemic reactions to parenteral (SC, IM, or IV) vitamin K are certainly few and far between, but they are well publicized, so physicians must be aware of the possible consequences.

Adverse events defined as anaphylactoid, allergic reaction, anaphylaxis, or shock, are rare. Systemic reactions to vitamin K are possible approaches. When rapid action is required, fresh frozen plasma (FFP), administration of vitamin K and administration of a variety of coagulation factors that are deficient in patients treated with warfarin, such as prothrombin complex concentrate (PCC) and Factor VII (rFVIIa). When rapid action is required, FFP or PCC (or possibly rFVIIa), along with vitamin K, are possible approaches.

This letter to the editor is frequently cited in all reviews that discuss toxicity due to parenteral vitamin K1. Interestingly, it is assumed that this was straightforward anaphylactic shock.
disagree, and think the case was significantly overstated. The reaction appeared to be non-life-threatening in nature, short-lived, and did not require antihistamines or epinephrine. One would be hard pressed to eschew IV vitamin K based on this anecdotal report. Certainly this does not describe an immediate hypersensitivity or a classic IgE-mediated reaction. Exactly what it was is puzzling. The hypotension and hyperthermia would suggest a simple pyrogen reaction. Prohibiting subsequent vitamin K in any patient just because of a previous, possibly sensitizing dose is certainly an invalid conclusion. In fact, there are numerous reports where vitamin K has been well tolerated after a previous reaction, typical for idiosyncratic reactions.

The medical literature, however, seems to accept the concept of the serious danger of IV vitamin K as gospel, and the PDR contains a boxed warning about the possible lethal effects. No doubt some patients will experience an idiosyncratic response to vitamin K and/or its additives, and a cautious approach is prudent. Most patients requiring IV vitamin K will have multiple medical problems that can cloud the issue. Serious or even life-threatening Coumadin-induced bleeding is certainly more common than lethal reactions to vitamin K. Sometimes you just have to take some calculated risks. The medical literature does contain other case reports with similar caveats, merely finding an elevated INR, often at very high levels, is not as much of an emergency as some physicians presume. When I was a resident, finding a high PT on routine testing was considered a big deal. The standard rationale for vitamin K in this scenario was to prevent spontaneous bleeding from over-anticoagulation before it began, ostensibly because intracerebral or retroperitoneal hemorrhage could be spontaneous and fatal.

When patients presented with bleeding (usually hematuria) secondary to an elevated INR, all clinicians reflexively administered very large doses of vitamin K. The 30 mg IV dose described in the article is certainly bizarre, and that patient would be near-ly impossible to anticoagulate for weeks. The obvious downside of vitamin K in patients with DVT, mechanical heart valves, or atrial fibrillation is that they are at risk for embolic phenomena. Over the years a more conservative approach, especially to anticoagulation, has been promulgated. The current clinical approach to various scenarios associated with an elevated INR is outlined in the table. Intravenous vitamin K has been recommended only for serious bleeding secondary to Coumadin toxicity. When it is given, doses in the 5 mg to 10 mg range are recommended, but in seriously compromised patients, most would first give FFP or PCP, followed by vitamin K. If intravenous vitamin K is given, it is always recommended to be diluted and given at a slow rate (less than 1 mg/min) because of the danger of systemic reactions. Anecdotal reports suggest, however, that even slow infusion of the dilute solution, or even SC/IM doses, will not guarantee total safety. I could find no problems related to oral use.

The clinical approach to an elevated INR and bleeding disorders secondary to vitamin K deficiency has come under scrutiny, and a much more conservative
**Warfarin**

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Warfarin is now the mainstream treatment of vitamin K1. The reflex vitamin K reversal syndrome has been called into question, and, in fact, it is not required nor suggested as standard of care. When intravenous vitamin K1 is indicated, it should be given with the knowledge that there is a slight but certainly a real chance for a potentially serious reaction, regardless of dose or administration technique. As with other medications given on a daily basis without a second thought, such as thiamine and naloxone, a proper observation and monitoring period should be routine following parenteral administration of vitamin K1.

I could find no guidelines on the treatment of vitamin K1-induced reactions. Moreover, I could not find a colleague who had personally witnessed such a reaction. If any reader has personal experiences, an email would be appreciated. It is impossible to ascertain the physiology of the reaction, and it seems to be idiosyncratic, usually producing alarming but poorly defined systemic reactions. Hypotension, fever, and flushing seem to predominate. It is not a true IgE-mediated event, and apparently it can occur with the first dose. This is a classic anaphylactic or idiosyncratic reaction. It is also unclear whether standard anaphylactic therapy would be helpful or would reverse the condition. I think it is reasonable to administer IV fluids and antihistamines and possibly epinephrine in severe or resistant cases if the extremely rare vitamin K1 reaction is encountered. Most current recommendations include the caution that IV vitamin K1 be administered “only in an emergency.” This is hardly a firm guideline because the definition of an emergency is certainly open to debate.

Most clinicians will never encounter a reaction to IV vitamin K1, but the seasoned clinician will be informed and cautious. I have given this vitamin many times in 10 mg IV bolus doses, and I have never seen even a hint of a reaction. Having further researched the topic, however, I have become more conservative (aka paranoid). This means using oral vitamin K and FFP more frequently, always using a diluted solution given slowly, and telling the nurse to stay in the room because the definition of an emergency is extremely rare vitamin K1 reaction is slow, and telling the nurse to stay in the room because the definition of an emergency is extremely rare vitamin K1 reaction is slow.

**Reader Feedback:**

Readers are invited to ask specific questions and offer personal experiences, comments, or observations on InFocus topics. Literature references are appreciated. Pertinent responses will be published in a future issue. Please send comments to emm@lw.com. Dr. Roberts requests feedback on this month’s column, especially personal experiences with successes, failures, and technique.

**Dr. Roberts:** I enjoyed your recent article on ICH and warfarin. In my past experiences, this has often been a lethal combination. I recently had a case of a large spontaneous intracerebral hemorrhage (INR~4.4) with a GCS of 12. I intubated this patient and gave FFP and vitamin K.

On the advice of our neurosurgeon, I also administered 1.2 mg of IV NovoSeven (recombinant Factor VII), and the INR decreased to 1.1 within 15 minutes. This patient went directly to the OR (not the ICU), and was discharged from our hospital moving all four extremities and able to communicate.

This usage is currently off-label, but I want the emergency medicine community to know about this “bridge” therapy (to reverse warfarin) that has proven to be quite effective in several case series. After the NovoSeven is administered, you still give the FFP and vitamin K. The NovoSeven just serves as a bridge until the FFP and vitamin K take effect.

Mitchell Palmer, MD, Minneapolis, MN

**Dr. Roberts responds:** You are correct about the dismal outcome of anticoagulated patients who bled into the brain. Your case, with an INR of only 4.4, is a common scenario, especially in the elderly. Many will spontaneously bleed with much lower levels of anticoagulation. NovoSeven holds promise, but so far it has not been the Holy Grail that was hoped for with regard to the warfarin/ICH issue in question. NovoSeven will immediately normalize the INR, but the literature is still too sparse to make or break the use of this expensive (more than $10,000 per dose) reversal agent for spontaneous warfarin-related ICH. It is true that rFVIIa needs to be followed by FFP and vitamin K to maintain full and lasting reversal. Most of the use of this product is now considered off-label. In one relevant but very small study (Mayo Clinic Proc 2004;79:1495), seven patients with warfarin-related spontaneous ICH (INR 1.6-5.6) were treated with rFVIIa. Two died within a week, and the five survivors had severe neurologic impairment. I am concerned that we will “save” those destined to die only to fill up our nursing homes with vegetative patients, a quintessential Pyrrhic victory.

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**In Brief**

**Risk for Sickle Cell Children with Early Complications**

Children with sickle cell disease who experience major complications such as pain and lung disease early in life are at no greater risk for stroke or death during later childhood, new research from UT Southwestern Medical Center shows. Children with sickle cell who have pain crises or dactylitis as infants or toddlers are at no greater risk of having those symptoms recur later in childhood. The study’s results, however, showed that children hospitalized for chest problems early on are more likely to see those problems recur up to adulthood.

The study followed more than 200 children with sickle cell disease from birth through teenage years, and appears in the January issue of Blood, the scientific journal of the American Society of Hematology. The findings are an important step in trying to identify predictors that reveal how the mysterious disease will progress as children age, said Charles Quinn, MD, an assistant professor of pediatrics at UT Southwestern and the study’s lead author.

The myriad medical issues make it difficult when counseling parents of babies with sickle cell disease about what they can expect, Quinn said. UT Southwestern researchers at Children’s Medical Center and at the National Institutes of Health-funded Southwestern Comprehensive Sickle Cell Center launched the study to try to determine whether problems from the disease in the first three years of life offered any indication of later problems. They initially looked at whether some of the more common problems associated with sickle cell disease — pain events, dactylitis, and acute chest syndrome — predicted early death or stroke.

Researchers found that none of those factors result in higher risk. But they did find that acute chest syndrome did correlate with recurrent episodes throughout the remainder of their childhood. That may indicate a need for closer follow-up for those children and perhaps justify more aggressive treatment strategies. Children hospitalized for acute chest syndrome and early painful events in the first three years also were at slightly higher risk for later painful episodes. Dactylitis did not indicate any greater likelihood of pain episodes or lung events up adulthood, the UT Southwestern researchers found.

Researchers reviewed cases of 264 children who are part of the Dallas Newborn Cohort, a unique patient pool started in 1983 when newborn screening for sickle cell disease was mandated by the state. Researchers have been able to follow children with the disease to track how sickle cell patients fare. Earlier findings showed that children with sickle cell disease are living longer, dying less often from their disease, and contracting fewer infections than ever before. Dr. Quinn said this latest step of identifying potential clinical signs is an important one for predicting the future for sickle-cell patients.

**Drug Controls High-Altitude Illness**

Acetazolamide, a drug used to manage fluid retention in heart failure, controlled the serious effects of pulmonary edema and improved brain oxygenation during a randomized, double-blind and placebo-controlled study. The results appear in the February American Journal of Respiratory and Critical Care Medicine. Marc J. Poulin, PhD, of the departments of physiology, biophysics and clinical neuroscience at the University of Calgary in Canada and associates showed that acetazolamide had complex effects on ventilation, pulmonary vascular resistance, and cerebral blood flow in optimizing brain oxygenation during simulated high-altitude tests on nine subjects. The researchers concluded that the drug could be a valuable means of treating high-altitude pulmonary edema.

Acute mountain sickness is growing more common as more than several million sea-level residents visit areas higher than 2,500 meters each year. The authors found that among those susceptible to high-altitude pulmonary edema, acetazolamide decreases lung edema, facilitates the diffusion of oxygen, and improves cerebral blood flow in the lung. They also noted that those with the lowest mountain sickness scores after being exposed to a simulated altitude of slightly over 16,000 feet showed the lowest rate of fluid retention. By directly acting on smooth muscle cells, acetazolamide appears to cause dilation of vessels involved in cerebral blood flow.

Study participants took either 250 mg of acetazolamide or a placebo every eight hours for three days. On the fourth test day, the researchers measured the subjects’ responses to ventilation, pulmonary vascular resistance, and cerebral blood flow during simulated high-altitude tests. Each treatment period was separated by a 10-day washout to overcome any potential crossover effects from acetazolamide. In the test group were six men and three women who were slightly over age 28. All were non-smokers with no history of cardio-respiratory disease. They were instructed to abstain from caffeine, alcohol, or strenuous exercise throughout the test period.
the room for the first few minutes when the infusion is begun. I would be interested in hearing from any readers who have encountered an adverse reaction from intravenous vitamin K. Any reaction to oral vitamin K probably represents a case report.

Acute Cardiovascular Collapse after Intravenous Phytonadione
Barash P, et al

This article seems to document cardiovascular collapse after IV vitamin K. On careful reading, however, this is a confusing case, and the facts may not substantiate the conclusions. A 43-year-old man with cancer of the pharynx underwent uneventful surgery for a laryngectomy. Because of some bleeding postoperatively, he was given 10 mg of phytonadione, infused intravenously over 10 minutes.

Five minutes following the infusion, the blood pressure and pulmonary artery pressure dropped precipitously. The patient was treated with vasopressors and IV fluids, and a relationship to the vitamin K was suspected. Curiously, within the next two days, he was again administered vitamin K on two separate occasions following this incident without complications. Doses included 25 mg IM and 10 mg IV in a dilute solution run over one hour.

The authors agreed that this is not firm evidence for anaphylaxis, nor is there a proven cause-and-effect relationship, but they are convinced that this case illustrates previously described reactions. Certainly this was not a classic allergic reaction because the patient received subsequent injections without adverse effects. It is postulated that severe hypotension due to vasodilation was the culprit. The additives (fat emulsions, now removed) in the vitamin K were possibly contributory.

Comment: This is another anecdotes report frequently quoted as evidence for severe reactions related to parenteral vitamin K. I do not think unsubstatiated reports should be published; they tend to cloud the issues and are fodder for frivolous litigation. The authors state that as of the writing of this report (1976) no fatalities had been reported with the parenteral use of vitamin K analogues. Fatalities have, however, been reported to the FDA. Although this patient did not suffer any significant consequences, he appeared to experience significant vasodilation and hypotension that was temporarily related to the vitamin K infusion. “Cardiovascular collapse” in the title is a tad misleading. I would not underplay the potential of vitamin K to produce real pathology, but when other commonly quoted articles are studied in detail, I have found that some authors have drawn similar misleading conclusions. (See Hosp Pharm 1981;16:224.)

Finally, as a further depressing observation on the shortcomings and inaccuracies of the medical literature, it is instructive to note that the current edition of a major toxicology textbook states that “death secondary to anaphylactoid reactions” has resulted from parenteral vitamin K. The author of this quote cites the articles I have reviewed, and clearly these reports do not document a fatal outcome. The message is clear, however. Parenteral vitamin K is not without risk, albeit it extremely small, but why take the chance if better alternatives are available?

CME Participation Instructions

To earn CME credit, you must read the article in Emergency Medicine News, and complete the quiz, answering at least 80 percent of the questions correctly. Mail the completed quiz with your check for $10 payable to Lippincott Continuing Medical Education Institute, Inc., 770 Township Line Road, Suite 300, Yardley, PA 19067. Only the first entry will be considered for credit and must be received by Lippincott Continuing Medical Education Institute, Inc. by May 31, 2008. Acknowledgment will be sent to you within six to eight weeks of participation.

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Questions:
1. Vitamin K administration has been associated with fatal anaphylactoid reactions.
   - True  - False
2. Reactions are limited to the intravenous route of administration.
   - True  - False
3. A slow infusion of a dilute solution of IV vitamin K eliminates anaphylactoid reactions.
   - True  - False
4. Serious reactions are only associated with doses of vitamin K more than 20 mg.
   - True  - False
5. Serious reactions have been identified as classic IgE-mediated immediate hypersensitive reactions that can be prevented with prophylactic antihistamine/corticosteroid use.
   - True  - False

Your evaluation of this CME activity will help guide future planning. Please respond to the following questions:

1. Did the content of this activity meet the stated learning objectives?
   - Yes  - No
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   - 1  - 2  - 3  - 4  - 5
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4. Did you perceive any evidence of bias for or against any commercial products? If yes, please explain.
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