

Anaphylactic Reactions with Intravenous Vitamin K: Lessons from the Bedside

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ABSTRACT—Vitamin K is used as a correction factor to avert the risk of bleeding due to warfarin overdose. Among the reported complications of this therapy, the most serious one is the anaphylactic cardiovascular collapse caused by intravenous infusion of the drug. We report herein a patient with over-anticoagulation from warfarin use and a subcapsular renal bleeding who developed a fatal anaphylactic shock after vitamin K administration via slow intravenous infusion. Vigilance with the intravenous formulation of this agent should always be sought in order to prevent fatal outcomes, especially in patients with severe comorbidities.

VITAMIN K was discovered by Henrick Dam in 1935, while investigating the effect of a cholesterol-free diet on baby chickens.¹ He found that hemorrhagic disease resulted from nutritional deficiency of a fat-soluble compound that he labeled as "vitamin K." Today, the members of the vitamin K family include the following: K₁ or *phytonadione* found in green leafy vegetables and considered the main source for humans; K₂ or *menaquinone* manufactured by intestinal bacteria; and K₃ or *menadione* representing the synthetic form.² Vitamin K serves as a necessary cofactor for gamma carboxylation of coagulation factors II, VII, IX and X,

as well as the proteins C and S.³ It is the carboxylation of specific glutamic acid residues of hepatically synthesized precursors that enables the clotting factors to bind calcium ions and as a result be bound to a phospholipid surface, both processes being crucial for clot formation.

Case Presentation

An 80-year-old man presented with the chief complaint of right-sided chest-pain and right upper abdominal pain for two days after tripping over a rug and falling against a back of a chair at his residence. He noticed large bruises on his chest, and decided to come to the emergency department for further evaluation. The patient had a history of coronary artery disease, hypertension, atrial fibrillation, congestive heart failure and chronic obstructive pulmonary disease. His medications included warfarin, metoprolol, losartan, torsemide, simvastatin, and an albuterol inhaler. Recording of vital signs documented tachycardia at 110 bpm, a blood pressure of 95/57 mm Hg, a respiratory rate of 23 breaths per minute and an O₂ SAT of 100% while on nasal cannula at 2 L/min. A chest examination showed decreased breath sounds at the lung bases bilaterally, with no added sounds. The heart rhythm was irregularly irregular. The patient had moderate pallor and large ecchymoses involving both upper extremities and the right side of the rib cage. The rest of his physical examination was unremarkable. Laboratory examination showed a prothrombin time of 52.5 seconds (normal range, 11–13.5 seconds) and an INR of 4.5. Blood counts showed a hemoglobin 9.7 g/dl, but normal white blood cell and platelet counts. Creatinine was 2.1 mg/dl (normal range, 0.8–1.2 mg/dl). Liver function testing and electrolytes were normal. A chest X-ray showed fractures of right sixth to the 10th ribs. While a CT scan of head was unremarkable, a CT scan of abdomen and pelvis revealed a right chest wall

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hematoma and a large subcapsular hematoma of the right kidney. In the ED, he received four units of fresh frozen plasma and five mg of oral vitamin K. Given the instability of vital signs, he was evaluated by the ICU team who administered intravenously 10 mg of vitamin K (Aqua Mephyton) via slow infusion. A few minutes into the infusion, the patient started complaining of difficulty breathing. He then became hypotensive with a systolic blood pressure of 80 mm Hg, after which he experienced a cardiopulmonary arrest and a Code Blue was called. As initially the monitor showed a pulseless electrical activity, the patient received several consecutive doses of intravenous epinephrine and atropine, with no meaningful effect. Subsequently, he went into ventricular fibrillation and was therefore defibrillated repeatedly. To reverse the suspected anaphylactic reaction to intravenous vitamin K, the patient received intravenous methyl prednisolone and diphenhydramine. Despite aggressive resuscitation, he expired soon thereafter.

Discussion

In vitamin K deficiency, clotting factors do not contain carboxylated glutamic acid residues, which results in a deficiency of the clotting system that prolongs prothrombin time and can cause severe bleeding. Vitamin K is commonly used as a correction factor to avert the risk of severe bleeding due to vitamin K deficiency as a result of a warfarin overdose. The patient received Aqua Mephyton, which is an aqueous colloidal solution of phytonadione and inactive ingredients including polyethoxylated castor oil.

Adverse reactions to intravenous administration of vitamin K were observed soon after its introduction to the U.S. market in 1960, but it was not until 1963 when cases of severe side effects including several fatalities were reported. The vitamin K preparations involved contained propylene glycol and castor oil as an emulsifying agent. The documented reactions included facial flushing, altered sense of taste, diaphoresis, chest pain, shortness of breath, cyanosis, respiratory and cardiac arrest.^{4,5} To avoid these adverse reactions with intravenous vitamin K administration, some investigators recommended diluting the drug and infusing it at a rate of no greater than five mg/min.^{4,6} However, even with these precautions, cases of severe reactions including death have been reported since 1976.⁷⁻¹⁰ Cardiovascular collapse is thought to be secondary to an anaphylactic response, yet it is not clear whether these reactions are caused by the vitamin K itself or by one of the emulsifiers used in the intravenous preparation. The anaphylactic response could also be a

result of immediate hypersensitivity to the new antigen formation between vitamin K (as a hapten) and one of the emulsifying compounds.⁹

Over-anticoagulation with warfarin is a commonly encountered medical problem. The intravenous vitamin K administration is generally reserved for cases of active, potentially life-threatening bleeding or a very high INR value of greater than 20. While lifesaving, this treatment carries the potential risk of anaphylaxis/cardiovascular collapse similar to the situation in our case. In spite of aggressive intervention provided, our patient's life could not be saved. We believe a contributing factor to his important renal subcapsular bleeding was the chronic azotemia. His important and multiple comorbidities, along with the advanced age, must have also played a role in the dismal outcome. However, it remains unclear whether the anaphylactic reaction was caused by the vitamin K itself or by one of the emulsifiers/polyethoxylated castor oil.

This case emphasizes that IV administration of vitamin K preparation can be dangerous and, if feasible, an alternative route of administration should be used whenever possible. It also demonstrates that whenever signs of cardiovascular instability develop, anaphylactic drug reaction should always be considered in the forefront of differential diagnosis. As intravenous vitamin K can lead to life-threatening complications and even demise, it should be used cautiously and conservatively. Today, just as several decades ago, vigilance with this agent remains mandatory in order to prevent life-threatening outcomes.

REFERENCES:

1. Dam H: The antihemorrhagic vitamin of the chick. *Biochem J* 1935; 29:1273-85.
2. Lipsky JJ: Nutritional sources of vitamin K. *Mayo Clin Proc* 1994; 69:462-6.
3. Johnson BC: Post-translational carboxylation of preprothrombin. *Molec Cell Biochem* 1981; 38:77-121.
4. Vitamin K. *Br Med J* 1969; 2:40.
5. Shearer MJ, Mallinson C, Webster GR, et al: Studies in man with tritiated vitamin K1 administered intravenously. *Clin Sci* 1971; 40:23.
6. Lefere JJ, Girot R: Acute cardiovascular collapse during intravenous vitamin K1 injection. *Thromb Haemost* 1987; 58:790.
7. Barash P, Kitahata LM, Mandel S: Acute cardiovascular collapse after intravenous phytonadione. *Anesth Analg* 1976; 55:304-6.
8. Ich EC, Drage CW: Severe complication of intravenous phytonadione therapy. Two cases, with one fatality. *Postgrad Med* 1982; 72:303-6.
9. Havel M, Muller M, Graninger W, et al: Tolerability of a new vitamin K1 preparation for parenteral administration to adults: One case of anaphylactoid reaction. *Clin Ther* 1987; 9:373-9.
10. de la Rubia J, Grau E, Montserrat I, et al: Anaphylactic shock and vitamin K1. *Ann Intern Med* 1989; 110:943.

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