
The incidence of anaphylaxis following intravenous phytonadione (vitamin K₁): a 5-year retrospective review

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Background: Phytonadione (vitamin K₁) administered intravenously (IV) has been associated with anaphylaxis, although the incidence is not known. The anaphylaxis is thought to be attributable to the solubilizing vehicle, polyethoxylated castor oil (Cremophor EL, BASF AG, Ludwingshafen, Germany).

Objective: To estimate the incidence of anaphylaxis after IV administration of phytonadione.

Methods: A retrospective review of anaphylaxis after IV phytonadione over a 58-month period at a large academic center was performed. During the period of the study a protocol for the administration of IV phytonadione was in place. A review of computerized records and survey of staff identified cases of anaphylaxis meeting predefined inclusion criteria. In addition, a literature review was performed for articles concerning anaphylaxis after IV phytonadione.

Results: Over the 58 months of the study, a total of 6,572 doses of IV phytonadione were administered. Two cases of anaphylaxis after IV phytonadione were identified. The incidence of anaphylaxis was 3 per 10,000 doses with 95% confidence intervals of 0.04 to 11 per 10,000 doses. The literature review identified 14 cases meeting inclusion criteria with no reviews of the literature or estimates of incidence.

Conclusions: The incidence of anaphylaxis after IV phytonadione is overall comparable or slightly less than other drugs known to cause anaphylaxis. We do not recommend routine pretreatment with antihistamines or corticosteroids before administration of phytonadione.

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INTRODUCTION

In the 1930s, Henrick Dam isolated a factor essential for coagulation. He termed it vitamin “K,” taking the first letter of the Danish word *koagulation*.¹ Eventually, several subtypes of vitamin K were identified. Phytonadione (vitamin K₁) is found primarily in green leafy vegetables.²

Vitamin K deficiency with resultant hypoprothrombinemia is most commonly a complication of warfarin therapy but can also be secondary to dietary deficiency, antibiotics (altering gut flora) and fat malabsorption. Of the different vitamin K congeners, only phytonadione is available for therapy. Phytonadione is available for oral, intramuscular, subcutaneous, or intravenous administration (IV).

IV phytonadione has been associated with anaphylaxis.^{3,4} The factor responsible for the anaphylaxis is not phytonadione but the *solubilizing* vehicle, polyethoxylated castor oil, PEO-CO (Cremophor EL, BASF AG, Ludwingshafen, Germany).⁵ IV Phytonadione is currently available in the United States in two formulations, both containing PEO-CO (Table 1). The reaction has been classified as anaphylactoid,⁵ but there are little experimental or clinical data. Product information, reference texts, and the literature recommend avoid-

ing IV phytonadione because of the risk of anaphylaxis.^{3,4,6,7} However, the evidence in support of this recommendation, specifically the incidence of anaphylaxis after IV phytonadione is unknown.

To determine the incidence of anaphylaxis after IV phytonadione, we performed a retrospective review over 58 months. Based on our findings and a review of the literature, we present what is known of the incidence of anaphylaxis after IV phytonadione.

METHODS

The study was conducted in a large academic medical center with an average of 913 beds occupied per day in 2000. On March 3rd, 1995, a protocol for the administration of IV phytonadione was approved and was in place during the duration of the study (Table 2).

After obtaining approval from the institutional review board, we reviewed the pharmacy records for all doses of IV phytonadione administered from March 1st, 1995 to December 31st, 2000. During this time phytonadione from Abbott Labs (North Chicago, IL) and Merck & Co (Whitehouse Station, NJ) was used.

Pharmacy records consist of doses drawn from the pharmacy. Doses of 0.5 and 1.0 mg are accurately reflected in records. However, doses of 10 mg could represent the administration of any dose from 1 to 10 mg, and 20-mg doses could represent any dose from 10 to 20 mg.

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Table 1. Phytonadione Brand Information

Brand name	Manufacturer	Vehicle/contents
Non—PEO—CO— containing Konakion MM	Roche UK	Glycocholic acid, sodium hydroxide, lecithin (phospholipin 100), hydrochloric acid 25%, water for injection
Synkavit† PEO—CO containing	Roche	Water soluble
Konakion†	Roche	PEO—CO
AquaMephyton	Merck & Co	PEO—CO*
None	Abbott Labs	PEO—CO*

* Each milliliter contains phytonadione 2 or 10 mg, polyoxyethylated fatty acid derivative 70 mg, dextrose hydrous 37.5 mg in water for injection; benzyl alcohol 9 mg added as preservative. May contain hydrochloric acid for pH adjustment. pH is 6.3 (5.0 to 7.0).

† Production discontinued in 1987.

We identified cases from computerized records and a survey of the staff. A computerized database of patient diagnoses was searched for “vitamin K” and “anaphylaxis” or “allergy.” In addition, discharge diagnoses were searched for the International Classification of Diseases, 9th revision (ICD-9) code E964.3, adverse reaction to phytonadione.⁸ Members of the pharmacy (approximately 100 pharmacists), coagulation (6 physicians), thrombophilia (7 physicians), and allergy (9 physicians) sections present in 2000 were contacted and asked to recall any adverse reactions to IV phytonadione.

Two potential cases were identified by survey of the staff and 8 cases by the computerized search. To be included, cases had to meet the criteria for anaphylaxis by Yocum et al⁹:

1) Mediator Release

One symptom of generalized mediator release including flushing, pruritus or paresthesias of lips, axilla, hands, or feet; general pruritus; urticaria or angioedema; lip tingling or paresthesia; and conjunctivitis or chemosis.

2) Additional Symptoms

Oral and gastrointestinal symptoms include oral mucosal pruritus; intraoral angioedema of buccal mucosa, tongue,

palate, or oropharynx; nausea, emesis, dysphagia, abdominal cramps, or diarrhea. Respiratory symptoms are rhinitis, stridor, cough, hoarseness, aphonia, tightness in the throat, dyspnea, wheezing, hypopharyngeal or laryngeal edema, cyanosis. Cardiovascular symptoms include chest pain, arrhythmia, hypotension, presyncope, syncope, tachycardia, bradycardia, orthostasis, seizures, and shock.

3) Shock or Edema

Isolated laryngeal edema or immediate shock and a syncopal event after the injection of medication or a radiocontrast agent.

One symptom/sign from (1) and (2) or a clinical scenario consistent with (3) was needed for inclusion.

In addition, a review of the literature was conducted using the MEDLINE database 1966 to 2001. The search strategy cross-referenced the terms *vitamin K*, *phytonadione*, *Cremophor EL* with *anaphylaxis*, *allergy*, *drug hypersensitivity*. All relevant articles were retrieved and reviewed. Relevant references from those articles were also retrieved and reviewed. Cases were included if they met the criteria of Yocum et al.⁹

We calculated the confidence intervals around the anaphylaxis incidence estimate using the Clopper-Pearson method (StatsDirect software package, Camcode, Ashwell, UK).

RESULTS

During the 58 months the protocol had been in effect, we identified two cases of anaphylaxis after IV phytonadione meeting inclusion criteria. During the same period 6,572 doses of IV phytonadione were administered to 2,938 patients (Fig 1). The incidence of anaphylaxis was 3 per 10,000 doses (0.000304) with 95% confidence intervals of 0.04 to 11 per 10,000 doses (0.0000037 to 0.001099).

Case 1

An 84-year-old woman was admitted complaining of melena. The patient's past medical history was significant for cryptogenic cirrhosis with recent variceal bleeding, idiopathic bronchiectasis, ulcerative colitis, and panniculitis.

Pulmonary function tests performed 28 months before hospitalization demonstrated a forced expiratory volume in 1 second (FEV₁) of 1.38 L (67% of predicted), falling 15% after challenge with methacholine. There was no significant postbronchodilator response.

The patient had previously developed urticaria after cefazolin. There was no history of previously diagnosed asthma, anaphylaxis, nor environmental allergy. There was no history of previous phytonadione or PEO—CO exposure.

Pertinent medications included albuterol and ipratropium metered dose inhalers two puffs four times a day, carvedilol, doxepin, and isosorbide dinitrate.

On admission, pertinent laboratory studies included a hemoglobin of 9.5 g/dL and an international normalized ratio of 3.7. In preparation for an esophagogastroduodenoscopy, 1.0 mg of IV AquaMephyton brand phytonadione (Merck & Co) was administered per protocol (Table 1).

Shortly after the initiation of the infusion the patient began having symptoms of facial flushing and respiratory distress.

Table 2. Protocol for the Administration of IV Phytonadione

Administration guidelines
A registered nurse will administer intravenous piggyback phytonadione (vitamin K ₁). The dose of phytonadione to reverse warfarin-induced anticoagulation is 0.5–1.0 mg IV piggyback over 1 hour
Intravenous piggyback phytonadione should be administered via an infusion pump to safeguard control of the rate of infusion
Monitoring guidelines
The nurse will monitor patient's vital signs (blood pressure, pulse, and respirations) before beginning the infusion, 15 minutes later, and at completion of the infusion before the patient gets out of bed. The patient will be on bedrest during the infusion because of the potential risk of hypotension.

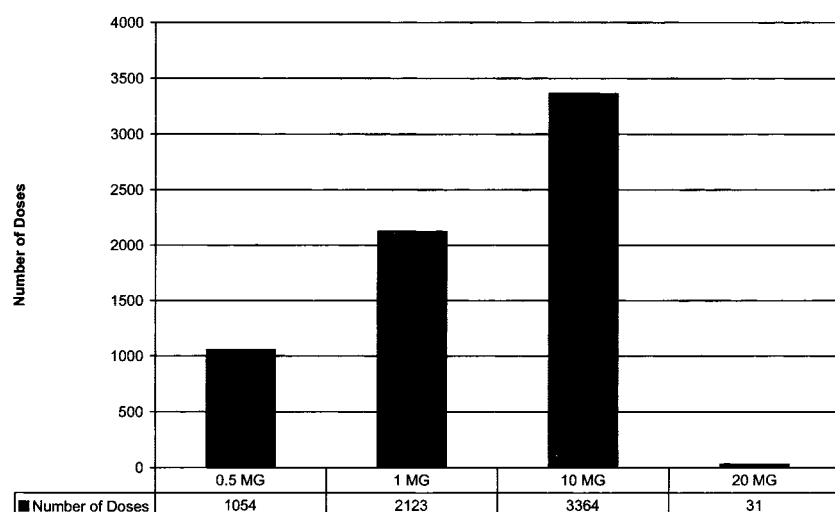


Figure 1. Distribution of doses of IV phytonadione administered over the 58-month period of the study.

The infusion continued and was completed per protocol. The flushing and respiratory distress progressed. On examination, she was hypotensive, tachycardic, hypoxic, and wheezing. An erythematous papillomacular rash was present on the chest. There was no urticaria, abdominal pain, nausea, diarrhea, abdominal pain, pruritus, or headache.

The patient was transferred to the intensive care unit. She was treated with 50 mg of IV diphenylhydramine and 125 mg of IV methylprednisolone with symptom resolution over several hours. The remainder of the patient's hospital course was unremarkable. The patient has not been rechallenged with phytonadione.

Case 2

An 89-year-old woman was admitted to hospital complaining of increasing abdominal distention and obstipation. Pertinent past medical history included a recent history of colonic pseudo-obstruction requiring central parenteral nutrition and coronary artery disease. The patient had no previous history of diagnosed asthma, anaphylaxis, or environmental allergy. There was no history of previous phytonadione or PEO-CO exposure.

Pulmonary function tests performed 6 years before presentation demonstrated a FEV₁ of 1.78 L (48% of predicted) with 22% increase following bronchodilator. Pertinent medications on admission were aspirin 81 mg daily, albuterol, and ipratropium inhalers, four puffs as needed.

Femoral vein deep thrombosis was diagnosed by duplex ultrasound and warfarin was started. On hospital day 8, the patient's international normalized ratio was 6.9. An order was written for phytonadione 0.5 mg in 50 mL 5% dextrose to be infused over 1 hour per protocol (Table 2; brand unavailable). Thirteen milliliters (0.13 mg phytonadione) had infused when patient complained of tremors, flushing, and dyspnea. On examination, respiratory rate was 40 breaths/minute. The patient's face was flushed. There was no urticaria, angioedema, abdominal pain, nausea, diarrhea, abdominal pain, pruritus, nor headache. The infusion was discontinued and

diphenhydramine 25 mg was administered intravenously. The patient's symptoms resolved within 2 minutes of stopping the infusion. Later, the same day the patient developed aspiration pneumonia. Comfort care was initiated and the patient died 2 days later.

Literature Review

We identified 14 reported cases of anaphylaxis after IV phytonadione in 12 reports (Table 3). All cases met the criteria of Yocum et al.⁹ One case following intramuscular administration was identified,¹⁰ and no cases following oral or subcutaneous routes of administration were identified. No comprehensive reviews of the literature were found. We did not find other estimates of the incidence of anaphylaxis after IV phytonadione infusion.

Mention has been made of anaphylaxis and/or fatalities with IV phytonadione. No other details such as brand, dose, or clinical scenario were reported. In total this included 61 patients with three fatalities.^{11–13}

DISCUSSION

In this study, we have estimated the incidence of anaphylaxis with IV administration of phytonadione to be 3 per 10,000 doses. Our estimate of incidence is comparable with that of all forms of penicillin and high osmolality contrast dye but less than IV iron dextran (Fig 2).^{14–16} Because IV phytonadione is used less than other medications, little is known concerning the risk of anaphylaxis. This study shows that the risk is comparable with more frequently used medications which have a well documented risk of anaphylaxis.

Currently, sources recommend an infusion rate of 1 mg per minute.³ The literature reviewed supports this recommendation given that 9 of 14 cases received the IV phytonadione at rates higher than 1 mg per minute. However, this study disputes the idea that a "slow" administration is completely safe. Both cases reported by the authors occurred during very slow infusions of 1.0 and 0.5 mg per hour or 0.0167 mg and

Table 3. Reports of Anaphylaxis Associated with IV Infusion of Phytonadione

Case	Age/Sex	Form of Vitamin K ₁ /dose	Vehicle	Symptoms/signs/timing	Previous exposure/reexposure	Reference
1	84yo/F	AquaMephyton 1 mg given per protocol (Table 2)	PEO-CO	Dyspnea, flushing, wheezing during infusion	None/none	Riegert-Johnson et al
2	89yo/M	Phytonadione 0.13 mg in D5%W (either AquaMephyton or Abbott labs) given per protocol (Table 2)	PEO-CO	Flushing, tachypnea during infusion	None/none	Riegert-Johnson et al
3	41yo/F	Konakion 30 mg in 100 mL 5% dextrose over 45 minutes	PEO-CO	Facial flush, abdominal pain, hypotension, cyanosis, hyperthermia, tachycardia, and loss of consciousness during the first 2 minutes of infusion	Previously treated with 10 mg over 20 minutes without incident	De la Rubia et al ³⁷
4	68yo/F	Phytonadione 7 mg over 5–10 minutes	Not specified	Cardiovascular arrest with successful resuscitation	None/none	Rich et al ³⁸
5	67yo/F	Phytonadione 5 mg over 5 minutes	Not specified	Flushing, hypotension, dyspnea within “minutes” of completing infusion followed by cardiovascular arrest and death	Previously treated with 10 mg/10 minutes without incident	Rich et al ³⁸
6	48yo/F	Phytonadione 20 mg dose over approx. 10 minutes, with reaction occurring after approx. 20 minutes	PEO-CO	Cardiovascular arrest during infusion with successful resuscitation	None/none	Lefrère et al ³⁹
7	64yo/M	Konakion 2 mg in 0.9% normal saline over 2 minutes	PEO-CO	Urticaria, bronchospasm, hypotension during infusion	None/none	Corallo et al ¹¹
8	74yo/F	Konakion 10 mg over unspecified time	PEO-CO	Facial flush, dyspnea, hypotension, mydriasis, cyanosis, and loss of consciousness during infusion	Patient was receiving 10 mg IV twice daily for the 6 previous days	Martinez-Abad et al ⁴⁰
9	22yo/F	Konakion 20 mg “slow infusion”	PEO-CO	Brief episode of loss of consciousness without cardiopulmonary arrest, associated with sweats, collapse, and hypotension during the infusion. Symptoms resolved spontaneously within a few minutes	None/none	Labatut et al ⁴¹
10	72yo/F	Phytonadione 20 mg “slow infusion”	Not specified	Collapse with cardiopulmonary arrest and cyanosis within 2–3 minutes of completing the infusion with successful resuscitation	None/none	Labatut et al ⁴¹
11	8yo/M	Konakion 10 mg over 5 minutes	PEO-CO	Tachypnea, cyanosis, wheezing, hypoxia, bradycardia, and hypotension within 1 minute of infusion. Recovered with hydrocortisone, aminophylline, chlorpheniramine, and albumin	Konakion 5 mg IV 4 days before, Konakion 10 mg 3 days before, Konakion 500 µg/24 in Central Parental Nutrition for 1 day without reaction	Hopkin CS ⁴²

(Table continues)

Table 3. *Continued*

Case	Age/Sex	Form of Vitamin K ₁ /dose	Vehicle	Symptoms/signs/timing	Previous exposure/reexposure	Reference
12	54yo/M	Konakion 20 mg over 2 minutes	PEO-CO	Generalized malaise 2 minutes after the end of the infusion followed by cardiopulmonary arrest with successful resuscitation	None/none	Pelletier et al ⁴³
13	9yo/F	10 mg phytonadione over 3 minutes	*	Rash, pulseless with successful resuscitation	None/none	Aziz et al ⁴⁴
14	44yo/M	10 mg phytonadione in mixed micelles preparation over 1 minute	Mixed micelles	Flushing, hypotension, wheezing 3 minutes after treatment. Successfully resuscitated with steroids, antihistamines, and calcium	10 mg/d Konakion for 6 days followed by three doses of 10 mg mixed micelles preparation Postexposure intradermal skin testing positive to both PEO-CO and mixed micelles preparation	Havel et al ⁴⁵
15	43yo/M	AquaMephyton 10 mg over 10 minutes	PEO-CO	Hypotension 5 minutes after infusion	Patient rechallenged with 25 mg IM and 10 mg/1 hour without incident	Barash et al ⁴⁶
16	62yo/M	1st dose AquaMephyton 10 mg in 100 mL of crystalloid given over 10 minutes	PEO-CO	Severe hypotension, bradycardia, asystole successfully treated with CPR and epinephrine	None/none	Songy et al ⁴⁷
		2nd dose AquaMephyton 10 mg in 100 mL of crystalloid given over 10 minutes	PEO-CO	Hypotension, tachycardia, wheezing, rash successfully treated with epinephrine, diphenhydramine and famotidine		

Specific brand information provided where available. See Table 1 for manufacturer affiliation.

* Polysorbate 80, dextrose BP, benzyl alcohol BP for injection by Promediapharm Sdn Bhd, Bandar Baru Bangi, Selangor, Malaysia.

0.008 mg per minute, respectively, approximately 100 times slower than recommended.

Both patients had risk factors for a severe/fatal allergic reaction. These included advanced age,¹⁷ β blocker therapy (in one patient),¹⁸ and underlying lung disease.¹⁹

The primary weakness of this study is its retrospective design in identifying cases. Despite a thorough search of the records performed with a supplemental survey of pharmacists and physicians, studies have shown anaphylaxis is underreported.²⁰ The true rate of anaphylaxis is likely higher than estimated here.

Safety data are available from other studies evaluating the reversal of anticoagulation using IV phytonadione. A review of phytonadione therapy for excessive anticoagulation examined seven studies with 124 patients treated intravenously.²¹ There were no adverse events. The authors concluded that IV

phytonadione is "safe and effective." There were no adverse events in 100 patients treated with IV phytonadione in a prospective study of anticoagulation reversal.²² In a retrospective review of 105 patients at our institution treated with IV phytonadione, 2 patients experienced dyspnea and chest tightness with no other signs of anaphylaxis.²³ None of the studies reported the rate of administration of phytonadione.

It has been suggested that the underlying cause of the reaction is not the phytonadione but the vehicle: PEO-CO.⁵ Several other drugs also compounded with PEO-CO have been associated with anaphylaxis including paclitaxel,²⁴ alphaxalone,²⁵ propanidid,²⁵ cyclosporine A,²⁶ teniposide,²⁷ and didemnin B.²⁸ The drug most associated with hypersensitivity reactions and containing the highest concentration of PEO-CO is paclitaxel. Paclitaxel contains 527 mg/mL of PEO-CO compared with phytonadione, with 70 mg/mL.²⁹

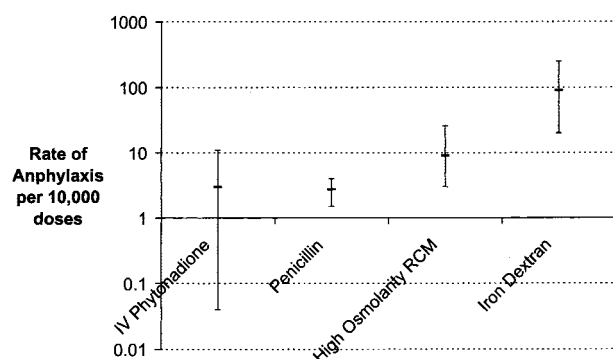


Figure 2. Incidence of anaphylaxis of IV phytonadione compared with three other agents well known to cause anaphylaxis/anaphylactoid reactions. IV phytonadione: 3 of 10,000 (95% CI 0.04 to 11 per 10,000) Riegert-Johnson et al; Penicillin (all forms): 2.75 of 10,000 (4 to 1.5 per 10,000*) Idsøe et al²⁵; High-osmolality radio contrast media (RCM): 9 of 10,000 (95% CI 3 to 26 per 10,000*) Caro et al²⁶; IV iron dextran: 90 of 10,000 (95% CI 20 to 250 per 10,000†) Hamstra et al²⁷. *Confidence interval noted from reference. †Confidence interval calculated by authors.

Approximately 3% of patients receiving paclitaxel have major hypersensitivity reactions despite infusion over 24 hours and premedication.³⁰ Premedication, ensuring adequate mixing, and increasing the duration of the infusion may decrease the incidence of anaphylaxis after paclitaxel/PEO-CO infusions.³¹ Alphaxalone and propanidid, two IV anesthetics, were withdrawn from the market because of anaphylactoid reactions.

Experimental and other evidence suggests PEO-CO may cause anaphylaxis by several pathways. Moneret-Vautrin et al³² demonstrated an immunoglobulin G antibody to PEO-CO in a patient with anaphylaxis to alphaxalone. Other evidence suggests PEO-CO can cause complement activation, and elevated plasma histamine levels have been demonstrated in dogs after administration of PEO-CO.³³ Neither of our patients and 10 of the 14 patients identified by literature review had a history of exposure to phytonadione or PEO-CO. This suggests that the reaction is not immunoglobulin E-mediated. In a canine model, infusion of small amounts of PEO-CO causes a rapid drop in blood pressure and cardiac output.³⁴

PEO-CO may not be responsible for all anaphylactic events after IV phytonadione. Our review of the literature found two cases of anaphylaxis after administration of formulations not containing PEO-CO (Table 3: cases 13 and 14). Also, the prescribing information for Konakion MM (Roche Pharmaceuticals, Malveran, PA), a water-soluble phytonadione, states that a few anaphylactic events have been reported (no other details were available).³⁵

The utility of IV phytonadione to reverse anticoagulation is beyond the scope of this report. However, the American College of Chest Physicians, in their most recent review, recommends using *oral* phytonadione (non-PEO-containing) to reverse warfarin induced hypoprothrombinemia except in extreme circumstances.⁷

The incidence of anaphylaxis after phytonadione is comparable with other commonly used medications known to cause anaphylaxis. Physicians should be aware that the risk for hypersensitivity reaction exists but is low. It should be noted, there have been no anaphylactic reactions reported after subcutaneous or oral administration. These reactions have typically been in the adult population as seen in Table 3.

If IV phytonadione is to be used, we make the following suggestions. These points should be interpreted as expert opinion rather than experimental conclusions. 1) Phytonadione should be administered according to a standardized protocol similar to the one in Table 2. Patients should be listed in an ongoing registry to monitor adverse events and identify predictors of anaphylaxis. All patients should be evaluated for a history of reaction to phytonadione or other products containing PEO-CO before treatment. We advise extreme caution in patients with a history of reaction. It is unknown if pretreatment with antihistamines and/or corticosteroids would be helpful in this situation. 2) We recommend an infusion rate of 1 mg per hour or less. 3) We do not recommend premedication with steroids or antihistamines. 4) For patients with risk factors for severe/fatal anaphylaxis such as asthma, advanced age, and β -blocker therapy, we recommend caution and close monitoring. It is unknown if pretreatment with antihistamines and/or corticosteroids would be helpful in this situation. 5) If anaphylaxis occurs after IV phytonadione, we recommend treatment according to the Joint Task Force practice parameter on anaphylaxis.³⁶

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