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Anaphylaxis (M Sanchez-Borges, Section Editor)

Vitamin-Induced Anaphylaxis

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Abstract

Purpose of review This paper aimed to summarize and review the known data on anaphylaxis and hypersensitivity reactions to vitamins.
Recent Findings Vitamins A, C, D, and E seem to be extremely safe compounds, with few or no related case of anaphylaxis to them. Vitamin B1 is considered the most allergenic vitamin. Immediate reactions are unusual, but urticaria and anaphylaxis to thiamine intravenous administration have been described. Vitamin B12 hypersensitivity is also infrequent. Reactions occur mostly in patients receiving long-term supplementation. Desensitization is mandatory for patients with hypersensitivity that have clinical indication for therapy with this vitamin. Vitamin K1 injection can induce adverse reactions that resemble hypersensitivity or anaphylaxis and may include immunologic or non-immunologic mediated mechanisms. These reactions are not well understood and can arise because of the vitamin K1 itself and/or because of the vehicle associated to it.
Summary Anaphylatic reactions to vitamins are uncommon. When they occur, a complete investigation is recommended to avoid mislabeling of patients as allergic. However, skin and provocation test protocols vary and should be standardized, as well as those for desensitization.

Introduction

Vitamins are organic compounds that play a crucial role in the organism performing a wide range of functions. They are needed in small quantities, and a healthy diet remains the best way to get them since our bodies cannot produce enough amounts of vitamins and minerals [1]. Currently, there are 13 recognized vitamins: vitamins A to E, including a range of B vitamins, and vitamin K. They are classified by their biological and chemical activities, being divided into 2 groups: water-soluble (B vitamins and vitamin C) and fat-soluble (A, D, E, K) [1].

Fat-soluble vitamins can be stored in the liver or fatty tissues until required, which means that they generally do not need to be ingested as frequently. Water-soluble vitamins, on the other hand, are not stored in the body. As such, they must be a regular part of the diet to avoid deficiency [1].

Most patients do not seek medical advice before taking vitamins or supplements. This reckless behavior can lead to several health problems, such as hypervitaminosis, adverse drug reactions, and hypersensitivity reactions.

Vitamin A

Vitamin A comprehends the family of retinoids that is available as preformed vitamin A (retinol, retinaldehyde, and retinoic acid) or as provitamin A (carotenoids). It cannot be synthesized by the human body and must be obtained from the diet, can be found in eggs, fish oils, liver, dairy products, yellow and orange fruits, and dark green leafy vegetables [1]. Until the present day, only one case of vitamin A-induced anaphylactic shock has been found in older Russian literature [2]. The significance of vitamin A in food allergy prevalence is only provided through a hypothesis that has implicated vitamin A sufficiency in the development of immune tolerance [3].

Vitamin B

B-complex vitamins are water-soluble vitamins that must be regularly supplied in the diet, except for vitamin B12 (cobalamin). They serve as coenzymes in many reactions and are essential for a healthy metabolism. Their deficiency is associated with a variety of symptoms and diseases (e.g., beriberi and pellagra) that occur more frequently in some risk groups (e.g., poor diet, elderly, pregnant women, vegetarians, alcoholism, renal or intestinal diseases) [1]. Patients with B-complex vitamin deficiency must be treated with supplemental therapy, and hypersensitivity reactions may occur.

Vitamin B1 (thiamine) is considered the most allergenic vitamin. Immediate (type I) reactions are uncommon, but there are some reports of urticaria and anaphylaxis related to intravenous administration and occupational asthma due to the use of thiamine in an industrial setting [4, 5]. Distinctive investigational approaches have been performed, including specific IgE measurement (ELISA), basophil activation tests, and skin tests. Although not standardized, positive prick and intradermal tests were reported using different concentrations of the vitamin (1 to 100 mg/mL for prick and 0.5 to 1 mg/mL for intradermal) [4, 6–8]. Oral thiamine can be a safe alternative for patients that reacted to the intramuscular preparation [9]. A few cases of delayed reactions to thiamine described as contact dermatitis or systemic contact dermatitis have also been

published. A positive patch test to thiamine hydrochloride 10% in aqua was described as well as a positive oral challenge with the vitamin, triggering systemic contact dermatitis [10–12].

Vitamin B12 (cyanocobalamin and hydroxocobalamin) hypersensitivity is infrequent. Reactions occur more frequently in patients receiving long-term supplementation but can also present immediately after administration of a sensitizing dose [13, 14]. Symptoms can be triggered by both cyanocobalamin and hydroxocobalamin and vary from mild (itching and urticaria) to severe (anaphylactic shock), with a possible IgE mechanism involved. However, patients with hypersensitivity to cyanocobalamin may tolerate hydroxocobalamin and vice versa [13, 15, 16]. Delayed-type reactions have not been reported. The diagnostic workup starts with skin tests, followed by the drug provocation test when the skin tests are negative (Table 1). Allergic reactions to benzyl alcohol (preservative) must be considered [15, 17•]. Desensitization is mandatory for patients with vitamin B12 hypersensitivity that have a clinical indication for therapy with this vitamin [17]. A few protocols for cyanocobalamin have been reported, most of them using schemes ranging from 5 days to 7 weeks until the therapeutic dose is achieved [18–20]. Alves-Correia et al. reported a modified 9-step subcutaneous dose protocol that allows the patient to take the cumulative dose of 1010 mcg in 2.5 h [17]. Previously positive skin tests were reported to turn into negative after desensitization [17, 18].

No hypersensitivity reactions to the other B-complex vitamins (riboflavin, niacin, pantothenic acid, biotin and folate) are reported in the current literature.

Vitamin C (Ascorbic Acid)

Vitamin C is an essential micronutrient with many functions in the human body. It has a significant antioxidant effect and works as a cofactor for gene regulatory enzymes. Vitamin C assists with various cellular functions of the innate and adaptive immune system. It supports epithelial barrier function against pathogens and promotes antioxidant activity on the skin, therefore protecting against environmental oxidative stress and contributing to the immune defense. Vitamin C also accumulates in neutrophils, enhancing chemotaxis, phagocytosis, and generation of reactive oxygen species and promoting microbial killing [21]. The role of vitamin C in lymphocytes is less clear, but it has been shown that ascorbic acid is required for the early development of T

Table 1. Diagnostic workup proposal for vitamin B12 immediate hypersensitivity

	Cyanocobalamin	Hydroxocobalamin
Prick test	1 mg/mL	0,01 mg/mL
Intradermal test	1:100→ 1:10	0,01 mg/mL
Drug provocation test	1:100 (0,1 mL) SC 1:10 (0,1 mL) SC 1:1 (0,1 mL) SC 1:1 (0,1 mL) IM *(15 min interval between doses)*	

cells in vitro and can enhance differentiation and proliferation of both B and T cells [22].

Humans are unable to synthesize ascorbic acid and must rely on dietary sources for vitamin C. A wide variety of foods, such as oranges, lemons, broccoli, tomatoes, and potatoes, are high in ascorbic acid. Many prepared foods are already fortified with synthetic vitamin C [23].

Vitamin C can be absorbed in the stomach and along the entire small intestine. Patients with a chronic gastrointestinal disease such as Crohn's disease might have diminished absorption of vitamin C and might need oral supplementation [23]. Likewise, patients with chronic kidney disease that undergo maintenance hemodialysis are advised to get vitamin C supplementation with ascorbic acid daily to replace the losses of this vitamin during dialysis [24].

The available literature about hypersensitivity reactions to vitamin C supplementation is scarce. So far, ascorbic acid seems to be an extremely safe compound. Until present, there have been reports on two potential cases of anaphylaxis to ascorbic acid, both in the older literature. One of them describes anaphylaxis to a mixture of ascorbic acid and vitamin B rather than ascorbic acid alone, so it is uncertain which one was the actual culprit agent [25, 26].

Similarly, there are few case reports in the literature regarding contact dermatitis caused by ascorbic acid and its derivatives. Belhadjali et al. have reported allergic contact dermatitis caused by ascorbic acid in a cosmetic antiaging cream. This patient had a 3-month history of eczema with edematous erythematous lesions on the eyelids that spread to the rest of the face and neck. A patch test with the cosmetic cream was positive, and a subsequent patch test with the ingredients of this cream showed positivity only to ascorbic acid. Afterward, oral provocation tests were performed with ascorbic acid with negative results [27]. Likewise, three ~~previous~~ cases of allergic contact dermatitis caused by 3-o-ethyl-L-ascorbic acid, an ascorbic acid derivative contained in antiaging cosmetics, have been described [28–30].

Vitamin D

No anaphylaxis cases related to vitamin D have been described so far. However, there have been studies around the world describing a possible ~~association of the~~ role of vitamin D in anaphylaxis, allergies, and asthma [31–33].

Studies in South Korea and Chile found a higher incidence of food-induced anaphylaxis in populations with lower vitamin D levels [3, 31]. A study found that food-induced anaphylaxis was more common in children born during the fall and winter. The authors suggest that vitamin D levels and UVB light exposure could explain these seasonal differences [3]. Indirect evidence suggests that variation in food allergy prevalence might be subject to ambient ultraviolet radiation exposure and, therefore, ~~with~~ to vitamin D levels [34]. Most studies point to a causal relationship between low vitamin D levels and the development of asthma and allergies, but the results are still inconclusive [35].

Current evidence suggests that vitamin D plays a role in the development and maintenance of lung structure and function [36–38]. This association with immune and airway function provides the basis for the hypothesis that vitamin D may have direct links with asthma and allergic diseases [39, 40].

Vitamin E

The number of cosmetics and skincare products containing vitamin E has increased over the last few years. A critical analysis of the literature shows that most hypersensitivity reactions to tocopherol are local contact dermatitis reactions [26, 41]. No anaphylaxis cases to tocopherol have been described so far. However, there have been studies theorizing that vitamin E supplementation might influence the risk of asthma and decrease allergic lung inflammation, though with a poor level of evidence [42, 43].

Vitamin K

Vitamin K (VK) is a fat-soluble vitamin present in plants as phylloquinone (VK1), also known as phytonadione or phytomenadione and produced by bacteria as menaquinones (VK2) [44, 45•]. It acts as a cofactor in the synthesis of coagulation factors II, VII, IX, and X and proteins C and S [45]. VK1 can be used in the treatment of anticoagulant-induced prothrombin deficiency, prothrombin deficiency secondary to drug therapy, or diseases causing limited absorption or synthesis of VK. VK1 can also be used as a prophylaxis or treatment of hemorrhagic diseases of the newborn [46].

No toxic manifestations of vitamin K have been reported so far, even when large amounts are ingested over extended periods [46]. However, VK1 injection – one of the most important preparations of VK – can induce adverse reactions, sometimes severe. Reports of adverse reactions to VK1 began to appear soon after its introduction. Although these reactions are not very common, with an estimated incidence of 3 per 10,000 doses, those occurring with intravenous route administration have been associated with death in as much as 18% of the reactions [47, 48]. The symptoms reported in adverse reactions to VK1 include facial flushing, feeling of weakness, abdominal and low back pain, nausea, vomiting, dyspnea, and chest pain. In severe reactions, these symptoms are followed within minutes by cyanosis, loss of consciousness, hypotension, and potentially cardiopulmonary arrest and death [49, 50].

It is worth mentioning that due to its poor water solubility, injectable VK1 requires formulation with an emulsifying agent such as polyoxyethylated fatty acid derivatives, polysorbate-80, or mixed micelles (MM) to keep it in solution [44].

Regarding its pathogenesis, reactions to VK1 resemble hypersensitivity or anaphylaxis and may include immunologic (allergic) and non-immunologic (non- allergic) mediated mechanisms. In general, an anaphylactic reaction due to immunologic mechanisms occurs only in previously exposed and sensitized patients. On the other hand, a non-immunologic anaphylactic reaction (anaphylactoid reaction) can occur following a single, first-time exposure, in non-sensitized patients. Unfortunately, however, concerning VK1, the reactions are not well understood or characterized and can occur because of vitamin K1 itself and/or because of the vehicle (emulsifying agent) [45, 48–50]. In this sense, growing evidence has suggested that Tween-80, used to solubilize vitamin K1, can induce anaphylactoid reactions [49, 50]. Likewise, polyoxyethylated castor oil (PEO-CO), also known as cremophor – a polyoxyethylated fatty acid

derivative commonly used as a vehicle – has been associated with anaphylactoid reactions after intravenous administration of VK1 containing PEO-CO as solubilizer [47].

The recommended dose and route of administration depends on the clinical indication. Reactions can still happen despite precautions to minimize them, such as the use of adequate dilution, appropriate dosing, and a slow administration. Indeed, there are reports of reactions occurring at doses ranging from 0.5 to 100 mg (only in 3 patients the reaction occurred at doses above those recommended, > 10 mg). Most of the patients experienced a reaction with intravenous administration, although intramuscular and subcutaneous routes were also reported in the literature [44].

Fiore et al. analyzed all unpublished reports obtained using the Spontaneous Reporting System Adverse Reaction database of the United States Food and Drug Administration (FDA) between August 1968 and September 1997. All adverse drug reactions to vitamin K were categorized by route of administration, dose, and standard adverse reaction code. The review uncovered a total of 23 cases (3 fatal) of anaphylactic reactions from intravenous vitamin K. The database contained a total of 2236 adverse drug reactions reported in 1019 patients receiving vitamin K by all routes of administration. Of the 192 patients with reactions reported for intravenous VK1, 132 patients (69%) had an anaphylactic reaction, with 24 fatalities (18%) attributed to the vitamin K reaction. There were 21 reactions and 4 fatalities reported with vitamin K doses lower than 5 mg. For the 217 patients with reactions reported due to vitamin K via a non-intravenous route of administration, 38 patients had anaphylaxis (18%), with 1 fatality (3%) attributed to the drug [47].

Pereira and Williams compared adverse events associated with a conventional VK1 preparation (solubilized in PEO-CO: Konakion) with a mixed micellar MM formulation (Konakion MM). According to the surveillance, during the period 1974 to July 1995, an estimated 635 million adults and 728 million children were prescribed with one of the two drugs. Of the 404 adverse events in 286 subjects reported, 387 (96%) and 17 (4%) were associated with Konakion and Konakion MM, respectively. Thirteen of the 17 adverse events (76%) reported for Konakion MM were minor injection site reactions. Overall, 120 of the adverse events were severe, of which 117 (98%) were associated with Konakion. Eighty-five probable anaphylactic reactions (six were fatal) were reported for conventional Konakion, compared with one non-fatal anaphylaxis reaction for Konakion MM [48].

To determine the safety and efficacy of intravenously administered VK1 in patients on routine oral warfarin anticoagulation, Shields et al. conducted a retrospective cohort study that included adult inpatients who received intravenous VK1 before a diagnostic or surgical procedure. The primary outcome measures included adverse reactions to intravenously VK1. Two (1.9%) of the 105 patients studied had suspected adverse drug reaction to intravenous VK1 characterized by dyspnea and chest tightness during infusion of an initial 0.5 mg dose, both resolving 15 min after stopping the infusion [51].

Riegert-Johnson and Volcheck looking for an estimated incidence of anaphylaxis to intravenous Vitamin K1 performed a retrospective analysis of anaphylaxis after intravenous Vitamin K1 at a large academic center. To be included, patients had to meet the criteria for anaphylaxis. Over the 58 months of the

study, a total of 6572 doses of intravenous VK1 were administered to 2938 patients. Two cases of anaphylaxis were identified [52].

Conclusions

Allergy to vitamins, while rare, has been reported in the literature, particularly to vitamin K and B12. Even though the incidence is slight, any suspected case should be properly investigated. Desensitization is an option for patients with vitamin hypersensitivity that need oral or intravenous supplementation and have no other therapeutic option.

Compliance with Ethical Standards

Conflict of Interest
Luis Felipe Ensina, Fernanda Sales da Cunha, Patricia Guerzet Ayres Bastos, Fabiana Andrade Nunes, and Inês Cristina Camelo-Nunes declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance

1. Thomas DR. Vitamins in aging, health, and longevity. Clin Interv Aging. 2006;1:81–91. https://doi.org/10.2147/ciia.2006.1.1.81.
2. Danilov LN, Finogenov LN. Anaphylactic shock following administration of vitamin a. Klin Med (Mosk). 1977;55:122–3.
3. Zakariaeeabkoo R, Allen KJ, Koplin JJ, Vuillermin P, Greaves RF. Are vitamins A and D important in the development of food allergy and how are they best measured? Clin Biochem. 2014;47:804–11. https://doi.org/10.1016/j.clinbiochem.2014.01.033.
4. Rodriguez-Fernandez A, Sanchez-Domingues M, Noguerado-Mellado B, Rojas-Perez-Esquerra P. Urticaria by thiamine (vitamin B1). Allergol Int. 2018;67:276–7. https://doi.org/10.1016/j.alit.2017.07.008.
5. Drought VJ, Francis HC, McLNiven R, Burge PS. Occupational asthma induced by thiamine in a vitamin supplement for breakfast cereals. Allergy. 2005;60:1213–4. https://doi.org/10.1111/j.1398-9995.2005.00848.x.
6. Fernandez M, Blanca M, Torrecillas M, Mufios C, Garcia J. Anaphylactic response to thiamine (vitamin B1). J Allergy Clin Immunol. 1996;97:350. https://doi.org/10.1016/s0091-6749(96)80887-6.
7. Fernandez M, Barcelo M, Munoz C, Torrecillas M, Blanca M. Anaphylaxis to thiamine (vitamin B1). Allergy. 1997;52:958–60. https://doi.org/10.1111/j.1398-9995.1997.tb01258.x.
8. Proebstle TM, Gall H, Jugert FK, Merk HF, Sterry W. Specific IgE and IgG serum antibodies to thiamine associated with anaphylactic reaction. J allergy Clin Immunol. 1995; 95(5 Pt 1):1059-60. Doi. https://doi.org/10.1016/S0091-6749(95)70111-7.
9. Aurich S, Simon JC, Treudler R. A case of anaphylaxis to intramuscular but not to oral application of thiamine (vitamin B1). Iran J Allergy Asthma Immunol. 2018;17:94–6.
10. Arruti N, Bernedo N, Audicana MT, Villarreal O, Uriel O, Muñoz D. Systemic allergic dermatitis caused by thiamine after iontophoresis. Contact Dermatitis. 2013;69:375–6. https://doi.org/10.1111/cod.12115.
11. Hjorth N. Contact dermatitis from vitamin B1 (thiamine); relapse after ingestion of thiamine, cross-sensitisation to cocarboxylase. J Invest Dermatol. 1958;30:261–4. https://doi.org/10.1038/jid.1958.51.

12. Larsen AI, Jepsen JR, Thulin H. Allergic contact dermatitis from thiamine. Contact Dermatitis. 1989;20:387–8. https://doi.org/10.1111/j.1600-0536.1989.tb03186.x.
13. Moloney FJ, Hughes R, O'Shea D, Kirby B. Type I immediate hypersensitivity reaction to cyanocobalamin but not hydroxycobalamin. Clin Exp Dermatol. 2008;33:412–4. https://doi.org/10.1111/j.1365-2230.2007.02584.x.
14. Wajih Ullah M, Amray A, Qaseem A, et al. Anaphylactic reaction to cyanocobalamin: a case report. Cureus. 2018;10:e2582. https://doi.org/10.7759/cureus.2582.
15. Djuric V, Bogic M, Popadic AP, Spiric VT, Raskovic S. Anaphylactic reaction to hydroxycobalamin with tolerance to cyanocobalamin. Ann Allergy Asthma Immunol. 2012;108:207–8. https://doi.org/10.1016/j.anai.2011.12.009.
16. Vidal C, Lorenzo A. Anaphylactoid reaction to hydroxycobalamin with tolerance of cyanocobalamin. Postgrad Med J. 1998;74:702. https://doi.org/10.1136/pgmj.74.877.702.
17.• Alves-Correia M, Gaspar A, Borrego LM, Mota I, Morais-Almeida M. Desensitization to cyanocobalamin: rush protocol. J Investig Allergol Clin Immunol. 2017;27:196–7. https://doi.org/10.18176/jiaci.0160.

The authors suggest an effective desensitization protocol to cyanocobalamin hypersensitivity.

18. Kartal O, Gulec M, Demirel F, Yesillik S, Caliskaner Z, Sener O. Vitamin B12 allergy and successful desensitisation with cyanocobalamin: a case report. Allergol Immunopathol (Madr). 2012;40:324–5. https://doi.org/10.1016/j.aller.2011.10.003.
19. Costa AC, Branco-Ferreira M, Spínola-Santos A, Pedro E, Palma-Carlos A, Pereira-Barbosa M. Hipersensibilidade à Vitamina B12 - A possibilidade de dessensibilização. Rev Port Imunoalergologia. 2005;13:177–85.
20. Caballero MR, Lukawska J, Lee TH, Dugué P. Allergy to vitamin B12: two cases of successful desensitization with cyanocobalamin. Allergy. 2007;62:1341–2. https://doi.org/10.1111/j.1398-9995.2007.01389.x.
21. Carr A, Maggini S. Vitamin C and immune function. Nutrients. 2017;9:1211. https://doi.org/10.3390/nu9111211.
22. Van Gorkom G, Klein Wolterink R, Van Elssen C, Wieten L, Germeraad W, Bos G. Influence of vitamin C on lymphocytes: an overview. Antioxidants (Basel). 2018;7:–41. https://doi.org/10.3390/antiox7030041.
23. Aditi A, Graham DY. Vitamin C, Gastritis, and gastric disease: a historical review and update. Dig Dis Sci. 2012;57:2504–15. https://doi.org/10.1007/s10620-012-2203-7.
24. Steiber AL, Kopple JD. Vitamin status and needs for people with stages 3-5 chronic kidney disease. J Ren Nutr. 2011;21:355–68. https://doi.org/10.1053/j.jrn.2010.12.004.
25. Severova E. Anaphylactic shock due to sensitization to ascorbic acid. Klin Med (Mosk). 1972;50:130–1.
26. Rafter D. Anaphylactic shock reaction to intravenous parentrovite. Ir Med J. 1987;80:329.
27. Belhadjali H, Giordano-Labadie F, Bazex J. Contact dermatitis from vitamin C in a cosmetic anti-aging cream. Contact Dermatitis. 2001;45:317. https://doi.org/10.1034/j.1600-0536.2001.450523.x.
28. Yagami A, Suzuki K, Morita Y, Iwata Y, Sano A, Matsunaga K. Allergic contact dermatitis caused by 3-o-ethyl-l-ascorbic acid (vitamin C ethyl). Contact Dermatitis. 2014;70:376–7. https://doi.org/10.1111/cod.12161.
29. Numata T, Kobayashi Y, Ito T, Harada K, Tsuboi R, Okubo Y. Two cases of allergic contact dermatitis due to skin-whitening cosmetics. Allergol Int. 2015;64:194–5. https://doi.org/10.1016/j.alit.2014.10.007.
30. Victoria-Martínez AM, Mercader-García P. Allergic contact dermatitis to 3-o-ethyl-L-ascorbic acid in skin-lightening cosmetics. Dermatitis. 2017;28:89. https://doi.org/10.1097/DER.0000000000000260.
31. Hoyos-Bachiloglu R, Morales PS, Cerda J, Talesnik E, González G, Camargo CA Jr, et al. Higher latitude and lower solar radiation influence on anaphylaxis in Chilean children. Pediatr Allergy Immunol. 2014;25:338–43. https://doi.org/10.1111/pai.12211.
32. Brehm JM, Schuemann B, Fuhlbrigge AL, Hollis BW, Strunk RC, Zeiger RS, et al. Serum vitamin D levels and severe asthma exacerbations in the childhood asthma management program study. J Allergy Clin Immunol. 2010;126:52–58.e5. https://doi.org/10.1016/j.jaci.2010.03.043.
33. Litonjua AA. Childhood asthma may be a consequence of vitamin D deficiency. Curr Opin Allergy Clin Immunol. 2009;9:202–7. https://doi.org/10.1097/ACI.0b013e32832b36cd.
34. Rudders SA, Banerji A, Vassallo MF, Clark S, Camargo CA Jr. Trends in pediatric emergency department visits for food-induced anaphylaxis. J Allergy Clin Immunol. 2010;126:385–8. https://doi.org/10.1016/j.jaci.2010.05.018.
35. Douros K, Loukou I, Boutopoulou B, Fouzas S. Does vitamin D deficiency epidemic parallel with allergy and asthma epidemic? Mini-Rev Med Chem. 2015;15:967–73. https://doi.org/10.2174/1389557515121507311108827.
36. Li F, Peng M, Jiang L, Sun Q, Zhang K, Liam F, et al. Vitamin D deficiency is associated with decreased lung function in Chinese adults with asthma. Respiration. 2011;81:469–75. https://doi.org/10.1159/000322008.
37. Zosky GR, Berry LJ, Elliot JG, James AL, Gorman S, Hart PH. Vitamin D deficiency causes deficits in lung function and alters lung structure. Am J Respir Crit Care Med. 2011;183:1336–43. https://doi.org/10.1164/rccm.201010-1596OC.
38. Black PN, Scragg R. Relationship between serum 25-hydroxyvitamin d and pulmonary function in the third national health and nutrition examination survey.

Chest. 2005;128:3792–8. https://doi.org/10.1378/chest.128.6.3792.
39. Erkkola M, Kaila M, Nwaru BI, Kronberg-Kippilä C, Ahonen S, Nevalainen J, et al. Maternal vitamin D intake during pregnancy is inversely associated with asthma and allergic rhinitis in 5-year-old children. Clin Exp Allergy. 2009;39:875–82. https://doi.org/10.1111/j.1365-2222.2009.03234.x.
40. Krstic G. Asthma prevalence associated with geographical latitude and regional insolation in the United States of America and Australia. PLoS One. 2011;6:e18492. https://doi.org/10.1371/journal.pone.0018492.
41. Sanz-Sánchez T, Núñez Acevedo B, Rubio Flores C, Díaz-Díaz RM. Contact urticaria caused by tocopherol. Contact Dermatitis. 2018;79:395. https://doi.org/10.1111/cod.13099.
42. Adams AK, Connolly SM. Allergic contact dermatitis from vitamin E: the experience at Mayo Clinic Arizona, 1987 to 2007. Dermatitis. 2010;21:199–202. https://doi.org/10.2310/6620.2010.10018.
43. McCary CA, Abdala-Valencia H, Berdnikovs S, Cook-Mills JM. Supplemental and highly elevated tocopherol doses differentially regulate allergic inflammation: reversibility of alpha-tocopherol and gamma-tocopherol's effects. J Immunol. 2011;186:3674–85. https://doi.org/10.4049/jimmunol.1003037.
44. Rachel B, Britt RB, Brown JN. Characterizing the severe reactions of parenteral vitamin K1. Clin Appl Thromb Hemost. 2018;24:5–12. https://doi.org/10.1177/1076029616674825.
45.• Mi Y, Ping N, Li B, Xiao X, Zhu Y, Cao L, et al. Finding the optimal dose of vitamin K1 to treat vitamin K deficiency and to avoid anaphylactoid reactions. Fundam Clin Pharmacol. 2017;31:495–505. https://doi.org/10.1111/fcp.12290.
It is suggested by the authors, based in studies with animals, that a small dose of vitamin K1 could be effective in improving vitamin K deficiency and prevent anaphylaxis reactions simultaneously.
46. Helphingstine CJ, Bistrian BR. New Food and Drug Administration requirements for inclusion of vitamin K in adult parenteral multivitamins. J Parenter Enter Nutr. 2003;27:220–4. https://doi.org/10.1177/0148607103027003220.
47. Fiore LD, Scola MA, Cantillon CE, Brophy MT. Anaphylactoid reactions to vitamin K. J Thromb Thrombolysis. 2001;11:175–83. https://doi.org/10.1023/a:1011237019082.
48. Pereira SP, Williams R. Adverse events associated with vitamin K1: results of a worldwide postmarketing surveillance programme. Pharmacoepidemiol Drug Saf. 1998; 7:173–182.n https://doi.org/10.1002/(SICI)1099-1557(199805/06)7:3<173::AID-PDS343>3.0.CO;2-8
49. Qiu S, Liu Z, Hou L, Li Y, Wang J, Wang H, et al. Complement activation associated with polysorbate 80 in beagle dogs. Int Immunopharmacol. 2013;15:144–9. https://doi.org/10.1016/j.intimp.2012.10.021.
50. Coors EA, Seybold H, Merk HF, Mahler V. Polysorbate 80 in medical products and nonimmunologic anaphylactoid reactions. Ann Allergy Asthma Immunol. 2005;95:593–9. https://doi.org/10.1016/S1081-1206(10)61024-1.
51. Shields RC, McBane RD, Kuiper JD, Li H, Heit JA. Efficacy and safety of intravenous phytonadione (vitamin K1) in patients on long-term oral anticoagulant therapy. Mayo Clin Proc. 2001;76:260–6. https://doi.org/10.4065/76.3.260.
52. Riegert-Johnson DL, Volcheck GW. The incidence of anaphylaxis following intravenous phytonadione (vitamin K1): a 5-year retrospective review. Ann Allergy Asthma Immunol. 2002;89:400–6. https://doi.org/10.1016/S1081-1206(10)62042-X.

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