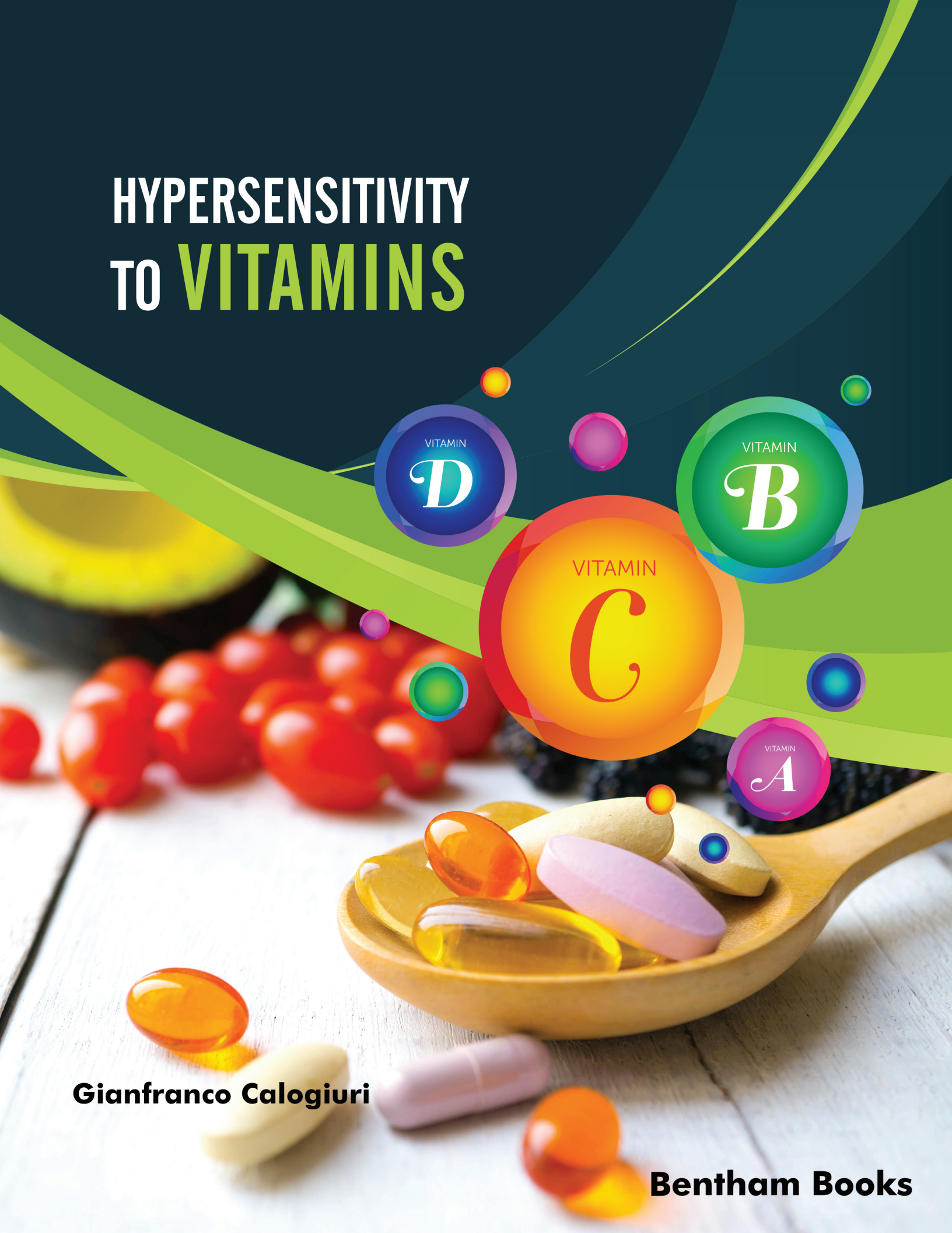
HYPERSENSITIVITY TO VITAMINS



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Hypersensitivity to Vitamins

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Hypersensitivity to Vitamins

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FOREWORD

Hypersensitivity to vitamins is rare - at least I have seen only very few cases in my life as an allergist (or did I miss some?). But now Gianfranco Calogiuri even writes a book about hypersensitivity to vitamins! It contains 13 chapters – one for each vitamin and two chapters on general and unusual aspects of hypersensitivity to vitamins. Isn`t this too much, a whole books on hypersensitivity reactions to vitamins? But as Gianfranco approached me, I was immediately fascinated and agreed to write a foreword: not because I am specialist on hypersensitivity reactions to vitamins, but because I am convinced that we, as medical community, can be happy to have someone ready to devote so much energy, passion and knowledge into a special topic. Such an enthusiasm can be immensely helpful for the medical community, as most of us do not have time or interest to become so specialised in such a topic, which we encounter only rarely, an where we need help, if we encounter it.

The book gives a comprehensive overview on function of each vitamin, its use, metabolism, pharmacological preparations, way of application and structure followed by Type I and/or Type IV hypersensitivity reactions. There are many interesting case descriptions included and referenced, and they are summarized in enough detail to allow comparison to the own case, which was probably the reason why ones looks for advise in this book. Of great help are the precise description which preparation was involved and how the hypersensitivity reaction was diagnosed. Since some vitamins are essential, desensitisations are important. The book provides much information on possible procedures and their outcome.

It is puzzling that hypersensitivity to vitamins exist at all, as we are consuming them in many foods. Various case reports illustrate quite clearly, that a slight modification of the usual substance or an abnormal way of uptake (*e.g.* parental) can be relevant. Indeed, quite many cases illustrate that the vitamin is tolerated, if applied orally, but is damaging if applied parenterally. All this information can be extremely helpful in the own case and how to help the patient.

I am happy and thankful that Gianfranco made this effort to collect all this information and to put it together. Writing a book is still the best way to spread the news to the medical community. It is a critical, highly informative review of all aspects of hypersensitivity to vitamins, and it will be the standard for this topic.

I hope the book finds its readers, and that we reader will find what he/she is looking for.

Werner J Pichler, Bern, February 2021.

PREFACE

COVID-19 infection was a frightful disgrace for all the mankind, however this book would not have been written without the SARS2 pandemic and the related lockdown and quarantine periods. When you have suddenly all the social life erased (no picnics with your family, no meals with your relatives, no parties with your friends, no travels, no meetings or congresses with your fellows, no gym, cinemas, theatres or concerts, just your work and the usual trip from home to the hospital and *viceversa,* day by day) you try to react. This book was the way I reacted to that situation. Previously, I have written an article "Hypersensitivity to vitamins with a focus on immediate type reactions: food or drug allergy?", so why do not extend that issue from an article to a book? I had already read many articles and case reports; I just needed to read some further articles and organize the chapters.

Vitamins are essential substances for life and body wellness, but they are not produced by human organism, so they need to be introduced through diet. Their deficiency may induce severe diseases like rickets or scurvy which can be even lethal as well known by the sailormen of the last centuries. Every vitamin was identified and chemically obtained as ester, thus allowing their use like medications or for industrial purposes, but as well as any other drug, vitamins may induce hypersensitivity reactions, especially in their synthetic form. However, while for an antibiotic, an antihypertensive or a chemotherapeutic agent, it is possible to find an alternative molecule, stopping the culprit drug administration, that approach is not always possible with vitamins, which need to be assumed by the patient, despite his/her sensitization. Surely, and luckily, vitamin hypersensitivity is not so common as antibiotics allergy, but probably it is also undervalued, poorly diagnosed and certainly described anecdotally.

The effort of this book has been to collect most of the case reports from literature thanks to a netsurfing research on Pubmed and Google Scholar and try to illustrate in an organic and systematic way, the mechanisms of vitamin sensitization, as understood or postulated by clinicians and researchers who have treated a vitamin sensitive patients "on the field", with a focus on the clinical aspects, the diagnostic approach and the therapeutic managements, trying to highlight much more a minor topic of drug hypersensitivity.

For each vitamin, beyond a short introduction concerning the biological activity, its use, a sketch on its metabolism and potential chemical derivatives, the most interesting part is represented by the experiences from different authors and related discussions of their case reports or studies. I limited to do some considerations of mine on the basis of the vitamins metabolism, the comprehensive literature data and my little experience with drug allergy. In future, some speculative reflections I have illustrated in this book might not be confirmed or be contradicted even by other authors experiences or by different evidences from the forthcoming case reports. For that, I apologize in anticipation. However, it would mean also this book has stimulated the curiosity of a clinician or a researcher, surely smarter than me, enough to dedicate his/her time, attention, expertise and wit to treat, solve and describe a new case of vitamin hypersensitivity from an alternative point of view or with innovative proposals I did not consider in this book. For that reason, I do not think this book is the complete or ultimate version on this topic, and I hope that nutritionists, clinical pharmacologists or other clinicians may alert me about the possible weak sides of the book, even for a future, updated and improved edition, maybe. That is all makes medical research challenging: nothing is forever in medicine and sometimes, the answers to your questions belong to another researcher, who does not image the question even.

Then, I would like to thank a research team I have ever met, personally or on the social media: Prof. Janos Zempleni and all the editors and authors of his "Handbook of vitamins" (Taylor & Francis Publisher), whom I largely cited. It was my guide, because it elucidated vitamins metabolism to me and greatly helped me to write this book. Since any vitamin is potentially a hapten, which may turn in an allergen, it is important to know and describe its chemical formula; for that reason I hope Prof. Zempleni and his biochemical team of nutritionists may excuse me if I have reported some chemical structures of the vitamins as well as they did in their book: their way was the clearest..

Lastly, a grateful thought to my wife Maria Rita, for having supported me in this project.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

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In Italy, the SARS2 pandemic required special containment policies and restrictions, like lockdowns and prohibition to leave the town where one lives or works. For that reason, I deeply thank Professor Luigi Macchia and Professor Eustachio Nettis from the School of Allergology and Clinical Immunology, Department of Emergency and Organ Transplantation, University of Bari Aldo Moro, Bari, Italy. Professor Angelo Vacca from the Department of Biomedical Sciences and Human Oncology, University of Bari Aldo Moro Medical School, Bari, Italy. Professor Caterina Foti from Dermatological Clinic of the 2nd Department of Biomedical Science and Human Oncology, University of Bari Aldo Moro, Bari, Italy. Dr Maurizio Congedo from the Section of Dermatology of Vito Fazzi Hospital, Lecce, Italy for having helped me to collect the book bibliography, since I could not leave my town to consult the Bari University Library.

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BIOGRAPHY

Gianfranco Calogiuri is born in Lecce (Italy) on March, 5th 1961. He was graduated in Medicine in November 1988 at the Chiet University Gabriele D'Annunzio (Italy) and on November 1992 and he has obtained the Board Certificate as Specialist in Allergy and Clinical Immunology at the Bari University Aldo Moro attending the Department of Allergy and Clinical Immunology directed by Professor Alfredo Tursi. In 1994 he took a master on Pediatric Allergy and Immunology at the Pediatric Department of Bari University, then he was appointed as assistant in different hospitals of the Azienda Sanitaria Lecce at First Aid Center firstly, then, in Internal Medicine, Infectious Diseases, Dermatology, Hematology, Clinical Pathology and Neurology. In 2005, he has been hired at the Pneumology Hospital in San Cesario di Lecce and in 2011 he has worked as consultant in Allergy and Pneumology at the Asthma Center of the Hospital "Ninetto Melli" in San Pietro Vernotico (Brindisi) up to 2016. In 2012, he obtained his PhD in Immunology and Infectivology at the Bari University with a thesis on the immunological status of the tracheotomy patients.

From 2016 up to 2020 he worked in the Department of Pneumology and Allergy of Hospital Sacro Cuore in Gallipoli (Lecce-Italy). For the needing of well-trained doctors because of the COVID 19 pandemic, at the beginning of 2020 he was temporarily assigned at the Pneumology Department of Civil Hospital Vito Fazzi in Lecce. He is a member of European Academy of Allergy and Clinical Immunology (EAACI) from 2003 and a member of ENDA (European Network for Drug Allergy). Besides the articles published on Italian scientific journals, he has published more than 50 articles on international scientific journals as author and co-author and a book contribution. Actually he actively collaborates with the Department of Allergy and Clinical Immunology at Bari University to investigate the pathomechanisms of drug allergy. His main fields of interest are the drug induced hypersensitivity reactions, either IgE mediated or T cell mediated, their diagnosis, management and therapy.

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CHAPTER 1

Hypersensitivity to Vitamins: General Considerations

Abstract: Vitamins include a wide range of biochemical compounds, very different from each other, whose presence is essential for the wellness and health of a human organism, given their importance in many enzymatic pathways of cell and tissue biology. However, the body cannot produce them. For that reason, their intake must be granted by a rich and highly differentiated diet which should include large amount of fresh vegetables and fruits, but also meats, wheat and natural vegetable oils from different seeds. During the years, every vitamin has been identified and produced synthetically, so allowing to treat pharmacologically the diseases related to their deficiency. The large amount of vitamin derivatives has led to development strategies of food fortification enriching common aliments and dairy products with specific vitamins but also to discover particular vitamin derived drugs, whose properties recall the original vitamin, allowing to increase their therapeutic effects or decrease the potential vitamin toxicity or their use through topical or mucosal routes even. Because of the antioxidant properties of some vitamins as vitamin C, for instance, some vitamins have been developed as food preservatives or food dyes. The increased attention and fashion for body wellness has brought to an augmented consumption of multivitamin, above all, in Western societies, believing that consumption of vitamin megadoses could be a protective factor from degenerative disease. On the contrary, vitamins may induce toxic effects as hypervitaminosis, but also, more rarely, hypersensitivity reaction.

Keywords: Allergy, Cosmetics, Fat-Soluble Vitamins, Food Excipients, Food Fortification, Hydrosoluble Vitamins, Hypersensitivity, Hypervitaminosis, Multivitamins, Vitamers, Vitamins, Vitamin Deficiency, Vitamin Toxicity,.

INTRODUCTION

With the name of vitamins, a heterogeneous group of biologically active organic substances are indicated. They are essential compounds playing an active role in numerous enzymatic pathways of the human organism [1, 2]. The name derives from the Italian *amine* [because they were reputed to be amines] *della vita* [of the life]. However, humans cannot produce vitamins *de-novo*, so they must absorb vitamins through the diet [1, 2], thus, under the name vitamins there is an highly differentiated family of compounds with various biochemical properties and

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chemical structures exhibiting antioxidant, co-enzymatic and hormonal activity, even [1, 2]. Vitamins are essentially divided into two groups [1, 2]:

- fat-soluble vitamins (ADEK complex), including
  1. pro-vitamin A and vitamin A,
  2. vitamin D,
  3. vitamin E,
  4. vitamin K;

- hydrosoluble vitamins including (mainly B complex)

1. vitamin B1 (thiamine),
2. vitamin B2 (riboflavin),
3. vitamin B3 (niacin, nicotinic acid or nicotinamide),
4. vitamin B5 (pantothenic acid),
5. vitamin B6 (pyridoxine),
6. vitamin B7 or H (biotin),
7. vitamin B9 (folic acid and folate),
8. vitamin 12 (cobalamin),
9. vitamin C (ascorbic acid).

Further substances have been indicated like the missing vitamins, such as vitamin B4 (also known as adenine), vitamin B8 (also known as inositol), vitamin B10 (paraamino benzoic acid – PABA), vitamin B11 (carnitine), but not all the nutritionists accept these compounds may be included in the group of the hydrosoluble vitamins because they are not so essential or alternatively they are so widespread and common in nature, thus their deficiency is extremely rare. Moreover, PABA, for instance, is included in the chemical structure of folic acid, so it can be absorbed with folates too. (see: Chapter 8: Vitamin B9). Vitamin deficiency may be caused by the inadequate absorption of one or more of these compounds as a consequence of both insufficient dietary intake and malnutrition [1, 2]. In Table **1**, the main diseases associated with each vitamin deficiency are reported. Vitamins act as cofactors in several cellular enzymatic pathways [1, 2], and it has been suggested that, due to their antioxidant properties, an increased daily consumption of vitamins, taken as megadoses, might protect against ageing and degenerative diseases [1, 2]. For every vitamin, nutritionists have tried to establish the dietary reference intakes (DRIs), which are a set of reference values including the estimated average requirement [EAR], recommended dietary allowance [RDA], adequate intake [AI], and tolerable upper intake level [UL]. These values are changing according to the age and health status of the patient [1]. Then, in 1988, in an eight-month double-blind clinical trial, both multivitamin and

multimineral supplements were reported to improve the performance of 30 school children in Wrexham [UK] who were administered non-verbal intelligence tests as part of an 8-month double-blind clinical trial [3]. Although the British nutrition establishment found many weaknesses in the trial, and some attempts to confirm the results failed, the myth of unnecessary intake of vitamins at high doses had started; thus, nowadays, it has become increasingly popular to consume vitamins either as multivitamin formulations or vitamin megadoses. For instance, the "Myers cocktail," which is often intravenously injected to treat or prevent various chronic diseases, contains high doses of hydroxycobalamin, pyridoxine, dexpanthenol, ascorbic acid, magnesium, and calcium gluconate [4]. Unfortunately, such empirical "do-it-yourself" multivitamin treatments may cause serious adverse effects, including accidental intoxication and hypervitaminosis [5, 6], rather than supposed benefits to the body. Moreover, vitamins and multivitamin consumption has turned to represent a business. It has been estimated that more than 90,000 dietary supplementation products, containing vitamins and minerals available on the USA market, foster an industry of about 30 bilion USD, although the real beneficial effects on the patients' health status induced by vitamins megadoses are doubtfully demonstrated [7]. From a National Health and Nutrition Examination Survey [NHANES] data survey, it has been recorded that from 2003 to 2006, 53% of the United States population aged 1 year and older took a multivitamin supplement in a given month in front of a previous survey [1988-1994] reporting consumption of only about 44% of general population [8] while in 2009, 56% of USA consumers said they comsumed vitamins or other supplements, and 44% of them told to take such compounds daily [8]. In Europe and Latin America, vitamin and supplement usage is lower with a 30% and 28%, and France, Italy and Spain bringing up the bottom with only 13-17 percent and of consumers saying that they take vitamins and supplements. The primary reason for not taking vitamins was that their diets were already balanced, so there was no need to take them [8], while 90% of the American population do not follow vitamin E intake recommendations because of the scarce consumption of green leafy vegetables in the country [9]. For that reason, in 1995, vitamin E supplements have been taken daily by more than 35 million people only in the United States [9], although 10 years later, many clinicians alerted about the potential adverse effects of vitamin E excessive consumption [10]. A report published in 2005 found no clear evidence that men and women who had vascular disease or diabetes and who took 400 I.U. of vitamin E daily for seven years reduced their risk of cancer compared to others with these conditions who took a placebo [10]. However, vitamins and multivitamin supplements are perceived as beneficial and natural substances required by the human body, but commercial vitamins rarely are "natural" products. Firstly, it is necessary to distinguish between vitamins, which naturally

CHAPTER 2

Vitamin B1 (Thiamine)

Abstract: Vitamin B1 or thiamine was the first water-soluble vitamin to be isolated. Thiamine deficiency leads to the onset of beri-beri and Wernicke encephalopathy, often associated with Korsakoff psicosis, above all, in chronic alcohol addicted patients. The necessity to administer quickly intravenous thiamine hydrochloride to restore blood thiamine level caused in some patients the onset of a severe immediate type reaction like anaphylactic shock, sometimes with lethal outcomes. The pathomechanism of hypersensitivity reaction seems to be genuinely IgE mediated and thiamine hydrochloride, that is the synthetic pharmaceutical form of thiamine, probably is a sensitizing hapten able to conjugate with azoproteins. Furthermore, patients with immediate-type hypersensitivity to parenteral thiamine may tolerate that vitamin when assumed orally. On the contrary, few cases of allergic contact dermatitis to thiamine are reported in literature, mainly following an occupational exposure and the oral intake of vitamin B1 is always associated with a flare-up of dermatitis.

Keywords: Allergic Contact Dermatitis, Anaphylaxis, Angioedema, Delayed-type Reaction, IgE, Immediate-type Reaction, Skin Tests, Thiamine, Thiamine Hydrochloride, Thiamine Mononitrate, Urticaria, Vitamin B1.

INTRODUCTION

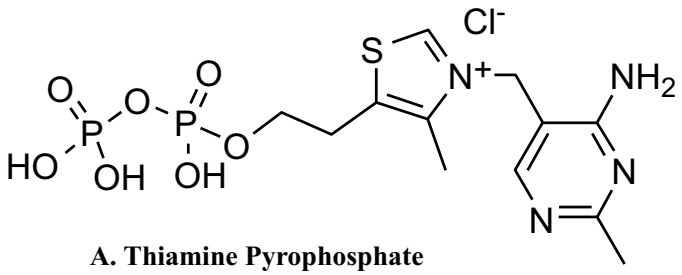
Thiamine was the first B vitamin to be identified and isolated from rice bran in 1926, thus its designation B1 [1], while its chemical name is 3-[(4-Amino-2-e-hyl-5 pyrimidinyl)methyl]-5-[2-hydroxyethyl]-4-methylthiazolium.

Thiamine participates in the metabolism of carbohydrates, alcohols, and branched-chain aminoacids. Thiamine deficiency is responsible for the onset of beri-beri disease and Wernicke Korsakoff syndrome (WKS) [1], which is an acute encephalopathy as a manifestation of severe thiamine deficiency occurring mainly in chronic alcoholists. WKS can be a life-threatening disease even.

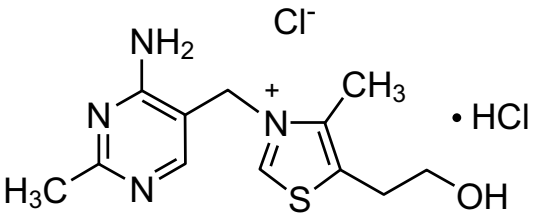
Moreover, beyond a clinical history of chronic alcoholism, thiamine deficiency may occur in malnourished patients, after bariatric surgery, but also after chronic diuretic therapy and in *hyperemesis gravidarum* [1].

Thiamine is found in various foods, including enriched bread and cereals (whole grain and enriched), peas, beans, nuts, brown rice, and meats (especially pork and

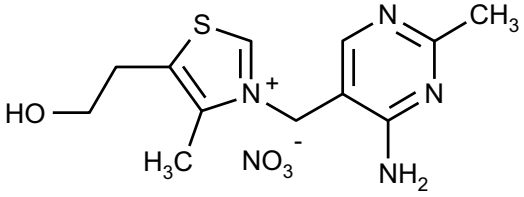
beef), and is absent in polished rice and other highly purified cereal products. Some thiamine in foods is lost with cooking. Since this is a water-soluble vitamin, it is not stored in the body and the excess is excreted in the urine. Body storage of thiamine is minimal, and a state of severe depletion in patients on a strict thiamine deficient diet becomes evident within 18 days [1]. The daily intake for a human being should be at least 1-2 mg. After intestinal resorption the thiamine is esterified with pyro-phosphoric acid and thus changed to co-carboxylase, The main molecular features of thiamine include its linked pyrimidine and thiazole rings, the presence of a hydroxyethyl side chain at position 5 of the thiazole ring, an amino group at position 4' of the pyrimidine ring, and an unsubstituted carbon at position 2 of the thiazole ring, which is capable of forming a carbanion (Fig. **1**).



A. Thiamine Pyrophosphate



B. Thiamine Hydrochloride



C. Thiamine Mononitrate

Fig. (1). Different forms of Thiamine (vitamin B1).

Thiamine pyrophosphate (TPP), where the hydroxyl group of thiamine is replaced by a diphosphate ester group (Fig. **1A**), is the active form of thiamine, and it is also known as co-carboxylase, because it participates as co-enzyme in the activity

of carboxylase. Naturally occurring vitaminB1 or thiamine, is a water-soluble vitamin found in plants and usually bound to a phosphate moiety in animals,whereas synthetic vitamin B1 [*i.e*., thiamine hydrochloride] is obtained from coal tar, ammonia, acetone, and hydrochloric acid [2]. The hydrochloride and mononitrate salts (Figs. **1B** and **1C**) are the most widely commercially produced synthetic esters.

Thiamine hydrochloride TH-HC], whose molecular weight is 337 daltons about, is a colorless, crystalline, hygroscopic, and highly water-soluble substance [2], used mainly as a drug and in multivitamin compounds, supplements or energy drinks while Thiamine mononitrate (TH-MN) is a white to yellowish crystalline powder, less hygroscopic than chloride moiety, with a faint, characteristic odour and a bitter taste and it is an alternative commercially available used often as a preferred compound in food fortification.

Both the active substances are prepared synthetically from thiothiamine which is oxidised to thiamine sulphate by use of hydrogen peroxide [1, 2]. Thiamine (vitamin B1) is the water-soluble vitamin that most frequently induces serious allergic reactions.

Immediate-type Reactions

The first cases of immediate-type hypersensitivity to thiamine hydrochloride have started to be carefully reported in the 40ies of last century [3 - 13].

Since these first case reports, it was evidenced that thiamine hydrochloride (TH-HC) was able to cause anaphylaxis following its administration subcutaneously[3, 5, 6, 9], intramuscularly [4, 7, 13] and intravenously [8, 11], sometimes with fatal consequences [8], while mild hypersensitivity such as maculopapular eruption was less common [7]. The anaphylactic reactions werepreceeded by mild symptoms like burning sensation in the site of injection, weakness or temporary general malaise, sneezing at the previous administrations [3, 5, 6, 9] and when TH-HC had been given previously as long course therapy with multiple, large, intermittent doses [3].

The intradermal tests [3, 5 - 7, 9, 10] or indeed passive serum transfer (Prausnitz and Kustner test) [3, 6, 7, 10] resulted positive when performed with different amounts of undiluted TH-HC, suggesting a reaginic pathomechanism, given the negative results of skin tests in thepatients control group.

However, in 1952, a study performed by Jarosh *et al*. [12] proposed that anaphylaxis was caused by a thiamine overdosage with chemical toxicity due to excessive amounts of acetylcholine and possibly histamine release too.

CHAPTER 3

Vitamin B2 (Riboflavin)

Abstract: Riboflavin or vitamin B2 is rarely responsible for allergic reactions and few cases mainly immediate-type reactions are reported in literature. Despite that riboflavin is used as a coloring excipient in drinks and industrial foods in the form of sodium phosphate salt, it does not seem to cause occult sensitization or cross-reactivity with natural riboflavin naturally occurring in foodstuffs.

Keywords: Anaphylaxis, Food Excipient, Immediate-type Hypersensitivity, Riboflavin, Riboflavin Sodium Phosphate, Urticaria, Vitamin B2.

INTRODUCTION

Riboflavin is a yellow colored substance with a high degree of natural fluorescence when excited by UV light. Chemically it is identified as 7,8-dimethyl-10-[[2*S*,3*S*,4*R*]-2,3,4,5-tetrahydroxypentyl benzo[*g*]pteridine-2,4-dione, also 7,8-dimethyl-[N-10-ribityl] isoalloxazine and has a molecular weight of 376.36 [1]. The most significant dietary sources of riboflavin are meat and meat products, including poultry, fish, milk and dairy products such as eggs and cheese. Because of his high presence in milk, the vitamin was firstly named as lactoflavin. Additionally, nuts, almonds, green vegetables such as broccoli, collard greens, and turnip greens are also reasonably good sources of riboflavin. A human being necessitates an intake of about 1,3-2 mg daily. The deficiencyof riboflavin is rare in developed countries because it is a vitamin found in many common foods, however as a supplement, riboflavin is usually included in multivitamins and B-complex vitamins. Riboflavin in pure form is a yellow-orange, poorly water-soluble compound, stable to heat, acid, and oxidation, but highly reactive to light, especially ultraviolet light, which induces a photo-degradation of the vitamin. Its degradation products are both antagonists to riboflavin action and may be significantly effective when foods are stored improperly or exposed to light [1].

The molecular structure of riboflavin comprises a planar isoalloxazine ring linked to a ribitol side chain (Fig. **1**) [1]. Riboflavin is the precursor for the coenzymes, flavin-5-phosphate also called flavin mononucleotide (FMN), which was established by Theorell and flavin adenine-dinucleotide (FAD), whose structure

was established by Warburg and Christian [1]. Both FMN and FAD function as coenzymes in a wide variety of intermediary metabolism reactions of cells. The enzymes requiring FMN or FAD as cofactors are termed flavoproteins, and several flavoproteins also contain metal ions so they are known as metalloflavoproteins. Free vitamin B2 is easily absorbed from the small intestine and there mainly converted into FAD and FMN, before being distributed in all tissues, through blood circulation, predominantly as FMN [60-95%] and FAD [5-22%]. The greatest amount of B2 was found in the liver, kidney and heart, while total body reserve of B2 in adults last for 2-6 weeks. Excessive intake is eliminated in the urine, which may give it a yellow-green fluorescent glow [1]. Since pure riboflavin has poor solubility in water, riboflavin sodium phosphate, the phosphoric acid ester of riboflavin is more quickly dissolved in water and absorbed, and thus offers higher blood concentrations and it is used for vitamin B2 injection and as a bright yellow-orange colorant in food and beverage, named E101 according to the European regulation for food additives.

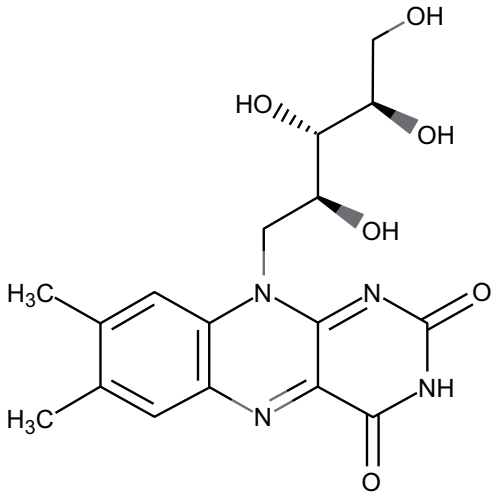


Fig. (1). Riboflavin.

Both to biotin (see Vitamin B7 – Biotin) riboflavin is probably the less allergenic vitamin from the B complex and actually, just two cases of immediate-type hypersensitivity to riboflavin are reported in literature.

Immediate-type Reactions

Ou *et al*. firstly reported in 2001 a 15 year old male boy who had an episode of anaphylaxis following the ingestion of a multivitamin tablet. In the previous 5 years, the patient had already experienced two other anaphylactic reactions induced by the consumption of a "yellow" energy drink [2]. The multivitamin

compound contained vitamins B1 [100mg of thiamine hydrochloride], B2 [100 mg of riboflavin], B6 [100 mg of pyridoxine hydrochloride], B12 [500 mg of cyanocobalamin concentrate], and vitamin C [500 mg of ascorbicacid] and the skin tests were performed as intradermal tests (Table **1**), because skin prick tests gave a doubtful result with only erythematous halo to pure riboflavin. Intradermal tests were performed 20 days later the anaphylactic episode and repeated at day 50, showing the maintenance of the sensitization. On the other hand, the previous anaphylactic reaction, in the patient's clinical history, suggested the persistence of riboflavin sensitization during the years along. The histamine release test resulted doubtful because it elicited a histamine release even in the negative control group composed by 5 healthy patients. The patient tolerated naturally occurring riboflavin in foods, which probably contributed to maintain his sensitization.

Table 1. Results of the intradermal skin tests [1,2].

S. No.	Intradermal Tests (mg/mL)	Concentration (mm)	Wheal (mm)	Erythematous Halo
1.	Thiamine	10	0	0
2.	Thiamine	1	0	0
3.	Riboflavin	1	20	50
4.	Riboflavin	0.1	12	38
5.	Ascorbic acid	50	0	0
6.	Ascorbic acid	10	0	0

Masuda *et al*. describe a case of a Japanese 23 year-old female patient who had developed an anaphylactic reaction following the consumption of 100 mL of an energy drink containing taurine, caffeine and a mix of multivitamins composed by riboflavin sodium phosphate 10 mg, pyridoxine hydrochloride 10 mg and nicotinamide 30 mg plus glucose, citric acid, malic acid and sodium benzoate. Prick test and intradermal test with the drink were negative and an oral provocation tests with that drink gave a negative result after ingestion of 10 mL of the same drink. Anaphylaxis occurred again after ingestion of 100 mL [3]. The skin tests with all the components of the drink were performed and although skin prick tests resulted negative, an intradermal test with riboflavin sodium phosphate 0,1% in aqueous solution was positive, causing a wheal with diameters of 6 mm and an erythema 30 mm. A histamine release test with the patient's basophils showed a positive response with riboflavin sodium phosphate, whereas basophils from healthy controls showed a negative response.

Three weeks later, intradermal skin tests with riboflavin adenine dinucleotide sodium (FAD) 0,1% and riboflavin tetrabutyrate 0,1% were positive only to riboflavin tetrabutyrate, suggesting a tolerance towards naturally metabolic

CHAPTER 4

Vitamin B3 (Niacin)

Abstract: Niacin is an essential nutrient necessary to the human body for numerous enzymatic pathways requiring nicotinamide adenine dinucleotide (NAD) and its derivatives for redox metabolism. Niacin can be deficient despite its fortification in flour and cereal products. Niacin deficiency can present in several different forms, although the most known and recognized is pellagra disease. Immediate type hypersensitivity to nicotinic acid is rare and it was reported with intravenous administration only. Even allergic contact dermatitis are reported exceptionally and it occurs mainly with the topical use of nicotinic acid derivatives more than vitamin B3 itself

Keywords: Allergic Contact Dermatitis, Anaphylactic Shock, Delayed-type Reaction, Immediate-type Reaction, Niacin, Nicotinamide, Nicotinic Acid, Vitamin B3-.

INTRODUCTION

Niacin or Vitamin B3 was previously known also as vitamin PP [Pellagra Preventing], because its deficiency caused the onset of pellagra or the 3D disease, characterized by Dermatitis or rough skin (from the Italian *pelle agra*) with sensitivity to sunlight, Dementia and psicosis and Diarrhea [1]. The earliest sign of vitamin B3 deficiency is often an inflammation of the oral mucosa, which progresses to include the esophagus and eventually the whole digestive tract, associated with severe diarrhea. Under the name vitamin B3 a broad variety of vitamers are included. They have the biological activity associated with nicotinamide and nicotinic acid, indeed in the past, niacin has been used to specifically refer to nicotinic acid (pyridine-3-carboxylic acid) (Fig. **1**). However, there is confusion between the use of the terms nicotinic acid/nicotinamide and niacin/niacinamide, even because nicotinic acid and nicotinamide are not directly convertible to each other [1].

Nicotinic acid is the provitamin formed in plants and it appears like a white crystalline solid, stable in air at normal temperature, while nicotinamide (niacinamide; pyridine-3-carboxamide), looks like a white crystalline substance too, highly soluble in water and in ether. Both vitamers are essentially the direct

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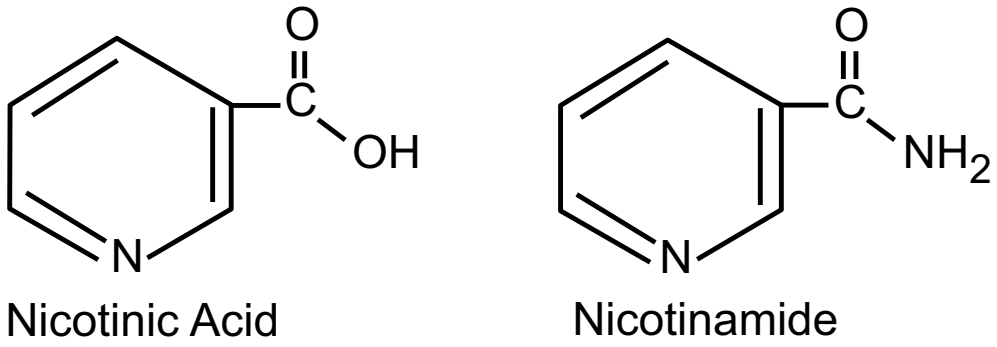

Fig. (1). Chemical structure of Vitamin B3.

dietary precursors for nicotinamide adenine dinucleotide ([NAD). In the organism, nicotinic acid is converted into nicotinamide adenine dinucleotide (NAD) and its derivatives NADH and NADP, the biologically active forms involved in many cellular redox pathways [1]. Even tryptophan can be a source for nicotinamide, because it can be converted at low efficiency to NAD in the liver, allowing nicotinamide release into the blood stream [1]. In normal adults, it has been found that about 3.3 percent of administered tryptophan is converted to niacin compounds [1]. The necessary intake of vitamin B3 to an adult is 18-30 mg daily [1]. Vitamin B3 occurs naturally in many food, but there are four different types of food sources of niacin.

Niacin in plant products is mainly in the form of nicotinic acid, therefore grains, nuts and legumes are important foodstuffs, despite their modest level of niacin, whereas muscle-based foods, such as meat, poultry, eggs and fish, have high levels of nucleotides, which release nicotinamide on digestion [1]. Many products like cereals are also fortified with niacin during manufacturing and, as well as thiamine, chronic alcoholists and cancer patients are greatly at risk for niacin deficiency [1].

One side effect of taking niacin supplements is mild flushing, described as a feeling of warmth, itching, redness or a tingly feeling under the skin. The flushing is harmless and usually subsides within one or two hours. However, in 2009, Inositol Hexanicotinate (NH) (niacin-flushing free) was introduced on the market and INH metabolism brings that molecule to release free nicotinic acid available for its physiological functions. Other esters of nicotinic acid are available.

Immediate-type Reactions

The only case reports of hypersensitivity to nicotinic acid date back to the 40ies of the last century in four patients [2 - 4]. In all the cases, the hypersensitivity reaction was represented by an anaphylactic shock following the intravenous administration of nicotinic acid [2 - 4]. A patient had previously consumed oral niacin, whereas in the other three subjects, the sensitization was induced by repeated intravenous administration of nicotinic acid. Skin tests were performed in two patients only [2, 4] and it consisted of an intradermal test with 0.05 ml. of a 1:20 dilution obtained from a compound of nicotinic acid 50 mg/ml [2]. Both the patients exhibited a positive response at the skin rests [2, 4], but no oral challenge test was performed to investigate the tolerability of niacin through a different route.

Delayed-type Reactions

Although nicotinic acid and nicotinamide may be responsible for some dermatologic side effects during their topical and systemic use [5], like flushing and/or transient eythema, allergic contact dermatitis has been reported more frequently following the topical use of nicotinic acid esters than the pure niacin or niacinamide [6]. Audicana *et al*. [6] describe a case of a 43 year old man presenting an eczematous dermatitis of the left wrist appearing few hours after the application of a product named Finalgon, containing 2-butoxy-ethyl nicotinate 2,5% and N-vanillylnonanamide 0,4%. The authors performed open and close patch tests with a series of other structurally-related pyridine derivatives, such as 3-[aminomethyl]-pyridine, 3-[aminomethyl]-pyridyl salicylate, 3-[methylamino--pyridine, 3-[methylamino]-pyridyl salicylate and 3-aminopyridine [6].The reading at D1, D2 and D3 revealed a positive response for the substances as illustrated in Table **1**, and compared with other authors experiences.

Previously an allergic contact mucositis reported as a burning mouth syndrome induced by benzyl nicotinate and propylnicotinate contained in certain toothpastes to improve gingival microcirculation was described in literature. Patch tests with both the compound 1% aqueous and sorbic acid gave a weak but persistent response at D1, D2 and D3 [7].

Table 1. Patch tests for vitamin B3 and derivatives (extrapolated from literature).

Method and Molecule	Concentration (%)	Vehicle	References
Open	-	-	-
Benzyl nicotinate	2.5	petrolatum	[6]
Butoxyethyl nicotinate	2.5	petrolatum	[6]

CHAPTER 5

Vitamin B5 (Pantothenic Acid)

Abstract: Pantothenic acid is widely distributed in numerous foodstuffs and it is essential for normal epithelial function and as a component of coenzyme A, which serves as a cofactor for a variety of enzyme-catalyzed reactions highly important in the metabolism of carbohydrates, fatty acids, proteins, steroid hormones, and many others. However, panthotenic acid is chemically unstable, thus the stereoisomer of the alcoholic analog, dexpathenol is truly used in cosmetics or multivitamins. Although it is a hydrosoluble vitamin, its derivatives are largely used in cosmetics, moistures, hair products and regenerative emulsions for skincare, for that reason the risk of skin irritancy or sensitization is stronger than other hydrosoluble vitamins and allergic contact dermatitis to panthotenic acid and its derivatives are described in literature, whereas immediate-type reactions like anaphylaxis and contact urticaria occur less frequently.

Keywords: Allergic Contact Dermatitis, Anaphylaxis, Cosmetics, Delayed-type Reaction, Dexpanthenol, Immediate-type Reaction, Pantothenate, Pantothenic Acid, Urticaria, Vitamin B5.

INTRODUCTION

The name of pantothenic acid (Fig. **1**), or vitamin B5, originates from the Greek word "*panthos*", meaning "from everywhere" because such vitamin is widely diffused in many aliments and can be found throughout all living cells. It is synthesized by microorganisms *via* an amide linkage of pantoic acid and beta-alanine subunits [1]. It has been estimated the adequate levels for daily intake in healthy population groups should range from 3 to 10 mg in adults [1]. The richest vitamin B5 sources are yeast and organ meats [liver, kidney, heart, brain], but eggs, milk, vegetables, legumes and whole grain cereals are more common sources. In the overall diet, about 50–95% of pantothenic acid occurs as CoA or pantetheine [fatty acid synthetase complex]. It is an essential vitamin required for the biosynthesis of coenzyme A (CoA), which itself plays a role in numerous steps of cellular metabolism, *e.g.*, acylation and acetylation of proteins, transfer of C2-units, and synthesis of several substances.

Pantothenic acid has a molecular weight of 219,24 and its chemical structure consists of pantoic acid and beta-alanine bound in amide linkage. Pure pantothe-

nic acid is a light-yellowish viscous oil that is soluble in water and in ethanol. It is light-stable and stable at neutral pH, but it readily degrades in both acid and alkaline solutions, and it is unstable in heat. Calcium pantothenate, a white, odorless, crystalline substance, in the form of pantothenic acid, most often used vitamin supplements, because it is more stable than pure vitamin B5 [1]. Panthenol, (Fig. **2**) also known as pro-vitamin B5, is the alcohol analog of pantothenic acid. Panthenol is quickly oxidized to pantothenate, which has two isomers. However, only D-panthenol (dexpanthenol) is biologically active. D-panthenol is synthetically produced from 2,4-dihydroxy-3,3-dimethylbutyric acid and b-alanine.

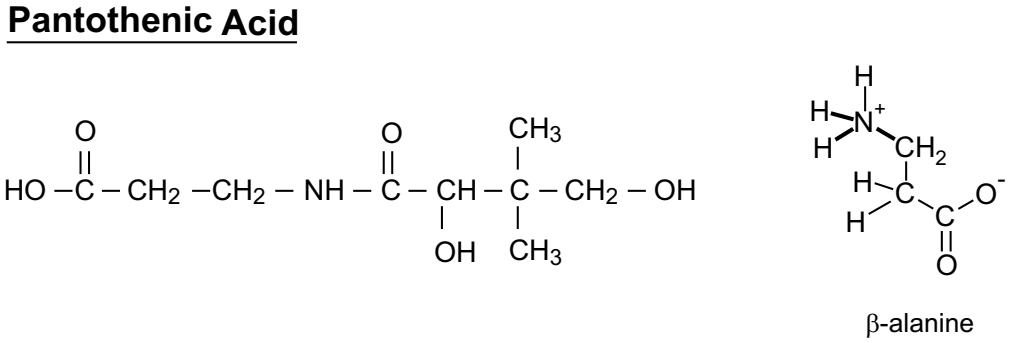

Fig. (1). Panthotenic acid.

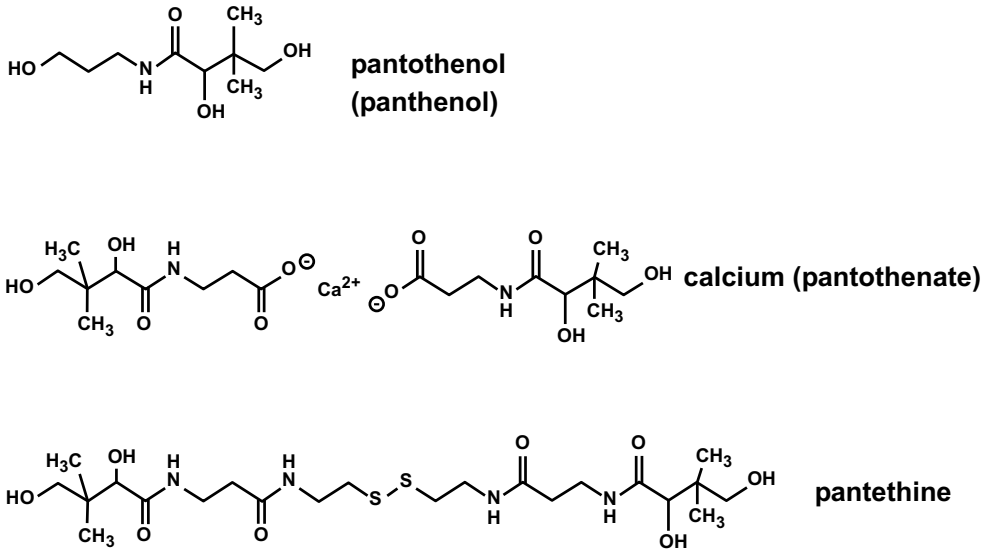

Fig. (2). Chemical Structures of Some Panthotenic Acid Derivatives.

Dexpanthenol is enzymatically cleaved to form pantothenic acid. It is an odourless, slightly bitter, highly viscous, transparent and colourless liquid. Since vitamin B5 occurs to some extent in all foods, its deficiency is extremely rare, although pantothenic acid deficiency in humans is not well studied and probably does not occur in isolation but in conjunction with deficiencies of other B vitamins [1]. Groups at risk of deficiency are alcohol addicts, women on oral contraceptives, people with insufficient food intake (*e.g*., elderly, post-operative), and people with impaired absorption (due to certain gut diseases). Symptoms of a vitamin B5 deficiency may include fatigue, insomnia, depression, irritability, vomiting, stomach pains, burning feet, and muscle cramps. Many forms of pantothenic acid were synthetized as esters, *i.e*., Panthenyl Ethyl Ether, Panthenyl Triacetate, and as salts like Calcium and Sodium Pantothenate. Beyond pharmaceutical preparations, such compounds are largely used in cosmetics as hair conditioning and skin-conditioning agents, creams, emollients, humectants, gels, lotions, oils, ointments, solutions, solvents and spray [2].

Immediate-type Reactions

The first case of immediate-type reaction induced by panthenol was a contact urticaria with facial edema and diffuse pruritus of the trunk following the application of a hair conditioner. The symptoms improved after washing off the conditioner. The patient, a 53 year-old female referred to a previous itching of the scalp caused by panthenol containing hair dyes used by her hairdresser [3]. An open application test of 30% pet at immediate reading resulted negative, but a skin prick test with an undescribed concentration of panthenol and the undiluted hair conditioner resulted in a positive response to both the skin tests. [3]. In 2005, five years later, Rockmann *et al*. described the first and actually the case of anaphylaxis caused by the ingestion of a vitamin tablet containing multiple vitamin B complex, including dexpanthenol [4]. Skin tests were performed as scratch tests, scratching the *stratum corneum* of skin and depositing a drop of different components of vitamin B complex to identify the causative ingredient in the tablets. Vitamin B1 (10 mg), B2 (10 mg), B6 (40 mg), B12 (1 mg), and folic acid (5 mg) showed no reactions compared with the positive control (histamine hydrochloride 10 mg/mL). Testing dexpanthenol by friction test (dexpanthenol 5 % in purified vaseline) led to pruritus and erythema in the tested skin area and pruritus on the lips and a coated tongue. Consequently, no further tests were performed. The patient reported that dexpanthenol-containing sun cream had caused pruritus and local urticaria previously. The report seems to suggest that the topical route from daily consumer products may induce an occult sensitization leading to a serious allergic reaction triggered by the systemic assumption of vitamin B5 [4].

CHAPTER 6

Vitamin B6 (Pyridoxine)

Abstract: The name of Vitamin B6 refers to a group of vitamers based on a core pyridine structure from which a synthetic homolog, pyridoxine hydrochloride, has been obtained, for pharmaceutical purposes. However, that synthetic compound is responsible for different allergic reactions, mainly delayed, cell-mediated-type. Because of the vitamin B6 photosensitivity, various cases of adverse cutaneous reactions, above all photoallergic, are described in the literature following the use of systemic assumption of vitamin B6 or its skin application from vitamin enriched topical products like creams and cosmetics.

Keywords: Allergic Contact Dermatitis, Anaphylaxis, Delayed-type Reaction, Immediate-type Reaction, Photo Allergy, Photosensitivity, Pyridoxine, Pyridoxine Hydrochloride, Vitamin B6.

INTRODUCTION

Vitamin B6 is an important coenzyme involved in numerous cell metabolic functions, and it is the unique B vitamin involved in metabolic pathways of all three macronutrients, proteins, lipids, and carbohydrates [1]. The chemical structure was identified as 3-hydroxy-4,5-hydroxymethyl-2-methylpyridine, which is also the first vitamer to be isolated in 1934. With the name of vitamin B6, in fact it comprises a set of three different pyridine derivatives changing each other in a variable group present at their 4'-position, thus resulting in

- Pyridoxine (PN) with a hydroxyl-methyl group,
- Pyridoxal (PL) carrying an aldehyde
- Pyridoxamine (PM) with an amino-methyl group.,

All the three B6 vitamers are phosphorylated by a kinase in the organism and converted reversibly to:

- pyridoxine-5'-phosphate (PNP)
- pyridoxal 5'- phosphate (PLP), *i.e*. the most active biological form;
- pyridoxamine-5-phosphate (PMP) as shown in Fig. (**1**).

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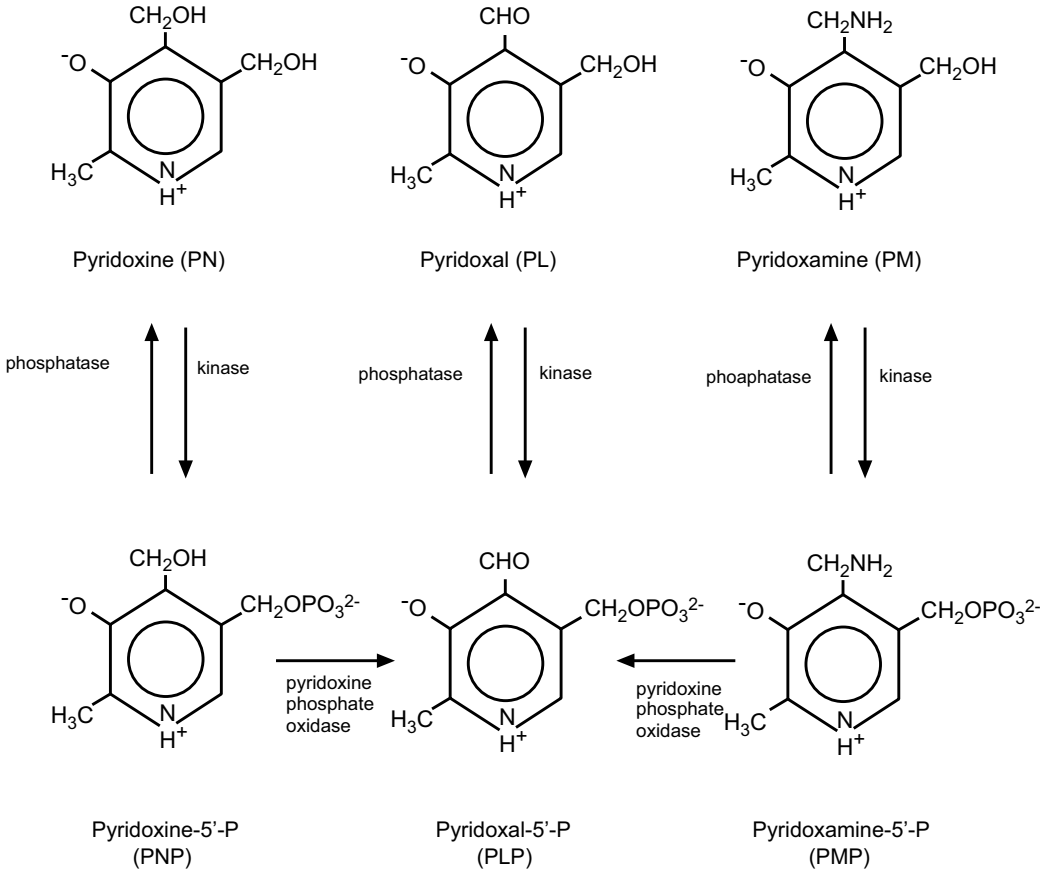

Fig. (1). The Vitamin B6 vitamers and their interconversion.

The mechanism of phosphorylation is strictly requested *in vivo* for their role as cofactors in enzymatic reactions and in the organism more than 140 enzymatic reactions requiring pyridoxine and its derivatives have been identified [1].These six forms of vitamin B6 are all present in many foodstuffs and in addition, the glycosylated form, pyridoxine-5'-β-δ-glucoside (PNG) is present in some plants and vegetables. In food supplements or drugs the most common vitamin B6 form is obtained synthetically as a salt, that is pyridoxine hydrochloride (Fig. **2**) with a molecular weight of 205,64. Pyridoxine hydrochloride (PN-HC) appears like a white or almost white crystalline powder, odorless with a slightly bitter and saline-acid taste.

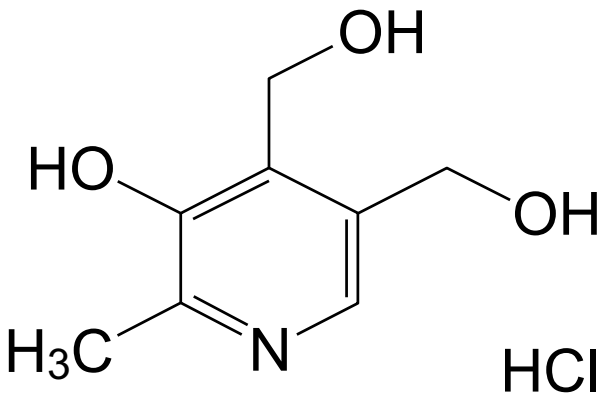

Fig. (2). Pyridoxine hydrochloride.

Vitamin B6 is present in liver, meat, fish, peanuts, bananas, walnuts, avocados, potato, eggs, and cereals. The recommended dietary intake is about 20 mg daily for an adult. The absorption of vitamin B6 occurs following the hydrolysis of the phosphorylated forms in the intestine.

The B6 vitamers and their phosphorylated derivatives are photosensitive. Food processing, including heat sterilization, results in loss of vitamin activity [1]. Furthermore, some studies have suggested that in the organism, increased levels of the B6 vitamers and their derivatives can generate toxic photoproducts as a result of Ultraviolet (UV) irradiation [2].

The deficiency of Vitamin B6 is associated to cutaneous and neurological symptoms due to demyelination of nerves, with peripheral neuropathy and neuropathic pains leading to ataxia, but surprisingly long-term use of high-dosed vitamin B6 supplements can lead to adverse health effects as sensory neuropathy, dermatological lesions, photosensitivity and gastrointestinal symptoms, such as nausea and heartburn, which are similar to the symptoms associated to vitamin B6 deficiency. It is the so-called "*vitamin B6 paradox*", because supplementation of high concentrations of the vitamer pyridoxine, used mainly as pyridoxine hydrochloride in dietary supplements and multivitamins, leads to decreased vitamin B6 function, probably for an inhibition of the enzymatic pathways, essential for vitamin B6 derivatives conversion, by a pyridoxine overload, thus resulting in the paradoxical onset of vitamin B6 deficiency symptoms [1]. Interestingly, some particular drugs like penicillamine, cycloserine and isoniazid (isonicotinic acid hydrazide) exert an anti-vitamin B6 action.

CHAPTER 7

Vitamin B7 or H (Biotin)

Abstract: From a biochemistry point of view, Biotin or vitamin B7, previously also known as vitamin H, possesses a simple chemical structure; thus it is quickly metabolized and addressed to its biological tasks. For that reason, probably, no case report of immediate- and delayed-type reactions are described in the literature. Just two cases of occupational allergic contact dermatitis to biotin and biotin precursors have been reported.

Keywords: Allergic Contact Dermatitis, Biotin, Occupational Exposure, Vitamin B7, Vitamin H.

INTRODUCTION

Biotin is known as vitamin B7 or also as vitamin B11, according to certain classifications. Previously it was named vitamin H, where H was for the German Haut, meaning “skin.” Biotin is a water-soluble vitamin found in a wide range of food such as liver, egg yolk, soybeans, nuts, legumes and cereals. It is also synthesized by enteric bacteria. For that reason, biotin deficiency is rarely found among people with an ordinary diet. In the human body, biotin acts as a coenzyme, supporting the function of carboxylase. Biotin, in fact, is an essential cofactor for five carboxylases which are respectively propionyl CoA carboxylase [PCC], methylcrotonyl CoA carboxylase [MCC], pyruvate carboxylase [PC], acetyl CoA carboxylase 1 [ACC1], and acetyl CoA carboxylase 2 [ACC2] and catalyze the incorporation of bicarbonate into a substrate as a carboxyl group [1] and their activity is fundamental for mithocondrial functions, glucose regulation and aminoacids metabolism [1] Biochemically, biotin is a heterocyclic compound, a bicyclic where an imidazolidone ring is joined to a tetrahydrothiophene ring, being composed by three asymmetric carbons, thus eight stereoisomers exist. Of these, only one (designated D-[þ]-biotin) is found in nature, that is the enzymatically active form of vitamin [1]. This compound is generally referred to as biotin simply or D-biotin. Biotin is a bicyclic compound. One of the rings contains a ureido group (–N–CO–N–) and the other is a tetrahydrothiophene ring with a valeric acid side chain (Fig. **1**). It has a molecular weight of 244.3. Biotin is soluble in water, insoluble in organic solvents, stable at pH 5 to 8, light and heat.

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Oxidation of the sulphur atom and shortening of the valeric acid side chain result in loss of vitamin activity. Actually, the daily dose of biotin oral intake has not fully established, although it has been evaluated to be approximately 35–70 μg/day for adults, however, biotin levels decrease along with the gestational stage in pregnant women. Groups at risk of biotin deficiency include patients maintained on total intravenous nutrition, hemodialysis patients, diabetic patients, patients with an impaired uptake of vitamins from food for intestinal disorders. Particularly, it has been observed that patients treated with biotin free total parenteral nutrition solutions develop, in six months up to three years, symptoms like hair loss, eczematous or seborrhoeic dermatitis, periorificial erythema, and increased susceptibility to fungal infections associated to neurologic symptoms, which are represented mainly by depression, lethargy, hallucinations, muscular pains hyperesthesia and paresthesia of the extremities occurring in most of the adult patients [1]. In the USA and Europe, biotin is used in daily food and vitamin tablets, whereas in Japan, biotin is not used as a dietary supplement, since it is not approved as a food additive.

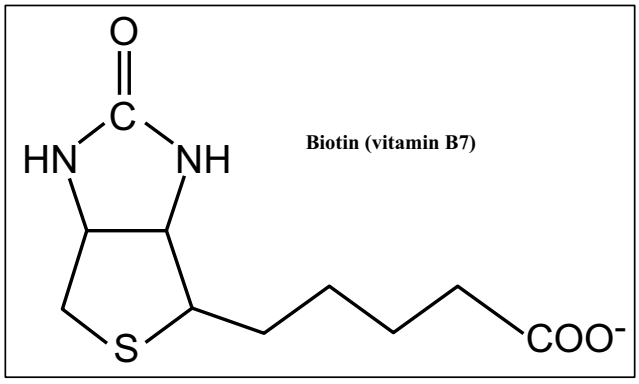

Fig. (1). Biotin (vitamin B7).

Immediate-type Reactions

Actually, no case of immediate-type reaction caused by biotin is reported in the literature.

Delayed-type Reactions

The first case of contact allergy to biotin dates back to 1942 in a pharmaceutical industry worker and it occurred because of his occupational exposure [2]. However, the description of the case report is confused, given the lack of an optimal standardization of the skin tests in that period and the poor knowledge of immunology, so the patient was patch tested with the whole multivitamin B complex, the different vitamins, crystalline nicotinic acid and biotin concentrate

on the forearm. The patch test for that last vitamin was removed after two hours because it induced itching and wheal, whereas the multivitamin compound gave a positive response at a delayed reading, 36 hours later [2], thus suggesting an occupational sensitization [2].

Nishioka *et al*. found a patient with allergic occupational contact dermatitis caused by biotin precursors [3]. The patient was a 45 year old male worker in a farm where biotin precursors were produced. The patient exhibited itchy reddish eruptions on his face and hands which appeared six months after he started to work on that plant. Furthermore, the patient was atopic with mild eosinophilia, high IgE value in the blood and sensitized to various respiratory allergens [3]. Patch tests were performed with the three main substances occurring in his workplace, *i.e*. (3aS,6aR) Hexahydro-1,3-dibenzyl-6-hydroxyfurano [3,4-d] imidazol-2,4-dione (Product A), a precursor of biotin obtained from 1,3-Dibenzy--2-oxoimidazolidine-4,5-dicarboxylic acid (Product B), thank to the use of [8*a*,9R]-cinchonan-9-ol, an optical resolving agent (Product C) [3] with dilution ranging from 0,1%, 0,5%, 1%, 5% to the last 10% petrolatum. The response was positive at D3 reading for Product B and C only, but not for Product A. A second patch tests session performed later evidenced a doubtful response towards Product B 5% pet. Even biotin was not patch tested and as soon the patient changed his workplace, no dermatitis recurrence was observed [3]. No oral challenge test with biotin was performed [3].

Another case of delayed type reaction with systemic symptoms to biotin has been reported (see. Unusual hypersensitivity reactions to vitamins), but its involvement is uncertain.

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CHAPTER 8

Vitamin B9 (Folate)

Abstract: Folic acid is the synthetic form of vitamin B9 or folate and it is not found in nature. Folate conversion to the active form requires reduction to tetrahydrofolate, a reaction that is catalyzed by dihydro-folate reductase, which is expressed in the intestine and other peripheral tissues. Folic acid is the lonely vitamin able to induce severe anaphylactic shock following its oral assumption or through any route of administration, *i.e*. intravenously or intramuscularly. The sensitizing strength of the folic acid might be due to its accumulation in blood, caused by its property to exhaust the enzymatic pathways responsible for its metabolism. Specific IgE to folic acid has been isolated by different research groups, thus suggesting immediate-type reactions to folic acid have genuinely a reaginic pathomechanism. Furthermore, derivative drugs like folinic acid or antifolate drugs like methotrexate have been produced and they may show an allergic cross-reactivity with folic acid. Isolated cases of folic acid desensitization have been performed but poorly described in literature whereas a well-elaborated desensitization protocol would be desirable, given the importance of folic acid during pregnancy to prevent neural tube malformations in the newborn

Keywords: Anaphylaxis, Calcium Folinate, Cereals, Delayed-type Reaction, Folate, Folic Acid, Folinic Acid, IgE, Immediate-type Reaction, Methotrexate, Pteroyl-glutamic Acid, Skin Tests, Urticaria, Vitamin B9.

INTRODUCTION

The term “folate” is referred to a group of B9 vitamins that share the same vitamin activity based on the parent structure of folic acid. The parent structure consists of an aromatic pteridine ring joined by a methylene bridge to para-aminobenzoic acid (PABA), attached to glutamic acid by a peptide bond (Fig. **1**) [1]. Such a compound is also called folic acid or pteroyl-glutamic acid and it represents the basic molecule which is the fully oxidized and most stable form of the vitamin widely used in supplements, fortified foods and drugs.

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Natural folate differs from folic acid in three aspects:

a. Reduction to di- or tetrahydro forms of the pteridine ring at positions 7,8 and 5,6;
b. Presence of additional glutamate residues, leading to the formation of polyglutamated derivatives consisting of up to nine glutamate residues, each one joined *via* an amide linkage to the γ-carboxyl group of the preceding residue
c. The presence of an additional single carbon unit attached to the N5 or N5 nitrogen atom: methyl [-CH3], formyl [-CH=O], methylene [- CH2 -] and methenyl [-CH=], thus Folic acid is now used to denote the fully oxidized compound, and the term 'folate' is a generic term including folic acid and all naturally occurring folates [1, 2]. Folic acid, the synthetic form of vitamin folate, is not found in nature.

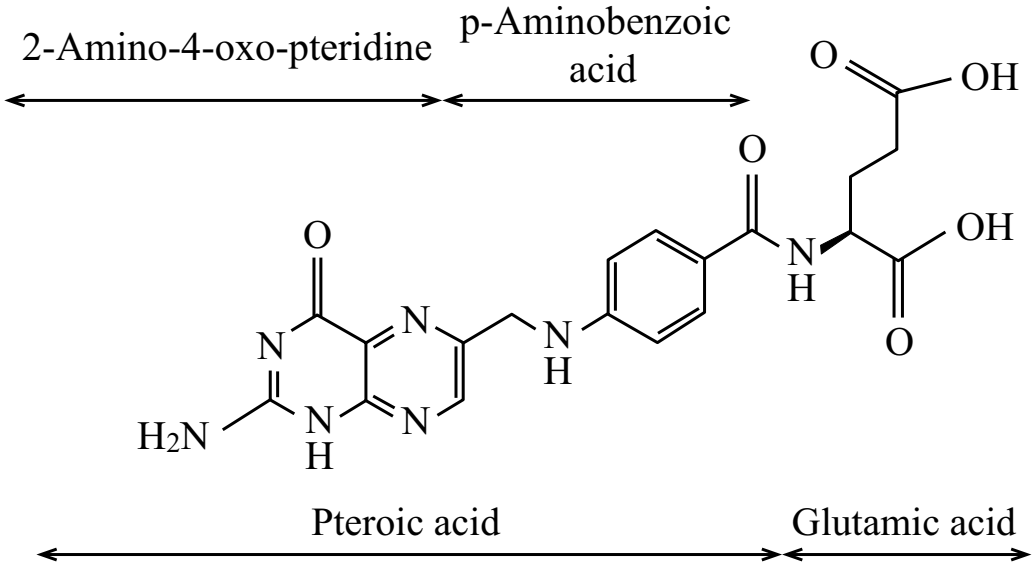

Fig. (1). Structure of folic acid (pteroyl glutamic acid).

Although it is described as "water-soluble," the acid form is only slightly soluble in water in contrast to the salt form. Folate exists naturally in foods as reduced folate polyglutamate conjugates. Synthetic folic acid is added as a fortificant to certain foods such as wheat flour, cereals, and of course multivitamin compounds.

Folic acid has a molecular weight of only 441, 4 Daltons. The recommended daily dietary intake is estimated to be 400 mcg, which can be difficult to achieve on an

average diet. Therefore, consumption of a multivitamin or folate enriched-food can be necessary, especially in pregnant women. They need 500-600 mcg of folic acid daily because folic acid prevents neural tube defect or malformation in newborns. Megaloblastic anemia is the disease truly associated with folate deficiency [2]. Folate naturally occurring in foods is concentrated in orange juice, strawberries, dark green leafy vegetables, peanuts, and dried beans such as black beans [1, 2].

Dietary folate predominantly occurs in a polyglutamate form. However, folate and folic acid undergo intracellular reduction to dihydrofolate, followed by tetrahydrofolate thanks to the activity of dihydrofolate reductase. The major dietary form obtained from folate polyglutamate is represented by 5'methyl-tetrahydrofolate, yet metabolized in methionine and tetrahydrofolate. These physiological forms of folate, *i.e*. tetrahydrofolate and dihydrofolate, work like enzyme cofactors in metabolism but they are unstable and often undergo irreversible degradation during food preparation and cooking.

Glutamates are progressively added to the gamma-carboxyl residues of tetrahydrofolate. Such folate polyglutamates are the biologically active form and serve in the synthesis of purines. 5'methyl-tetrahydrofolate (5MeTHF) is also the form which is predominantly found in blood [1]. However, because the capacity of this conversion is limited, excessive intake of folic acid saturates this capacity and results in its appearance unaltered in circulation.

Furthermore,some antifolate agents have been synthesized and they work as purine inhibitors, being similar in their chemical structure to folate, thus inhibiting key enzymatic pathways in folate metabolism and they are used as anti-cancer agents to decrease proliferation of the cancer cells [3]. Numerous antifolate agents play an essential role in the pharmacological management of different malignancies [3]. The main anti-folates are listed in Table **1**.

Table 1. Antifolate drugs (AFD).

Classic AFD	Variant AFD	Multi-targeted AFD
Methotrexate	Nolatrexed	Pemetrexed
Edametrexate	Piritrexim	-
Lometrexal	Plevitrexed	-
Pralatrexate	Trimetrexate	-
Raltratex	Talotrexin	-

CHAPTER 9

Vitamin B12 (Cobalamin)

Abstract: Vitamin B12, also known as cobalamin, is one of the few organo-metallic compounds occurring in nature and was the last hydro-soluble vitamin to be identified. The cobalamin biochemical structure and its metabolism are highly complex, and diseases related to its deficiency are associated with hematological and neurological alterations. The complex chemical structure of cobalamin gives it a high molecular weight, making cobalamin an immunogenic molecule. Moreover, the presence of the cobalt atom in the corrin ring of cobalamin may cause an allergic contact dermatitis flare-up in patients previously sensitized to cobalt. Immediate-type reactions induced by the parental administration of vitamin B12 have been reported in the literature, and they are linked to the used cobalamin moiety or its delivery route. They are reputed to be genuinely IgE mediated. Two "time patterns" of sensitization have been evidenced and probably two patterns of immune recognition also exist. Desensitization protocols have been used as an alternative method to administer vitamin B12 in patients needing it when all the other strategies fail.

Keywords: Adenosylcobalamin, Allergic Contact Dermatitis, Anaphylaxis, Cobalamin, Cobalt, Cyanocobalamin, Drug Desensitization, Hydroxocobalamin, IgE, Skin Tests, Transcobalamin II, Urticaria, Vitamin B12.

INTRODUCTION

Cobalamin was the last hydro-soluble vitamin to be isolated as, in 1948, two different research groups simultaneously announced the successful purification and crystallization of reddish needle-like crystals of a new vitamin, designated as vitamin B12. The structure and chemical properties of B12 are highly complex. Vitamin B12 is one of the few fully identified organometallic compounds with a molecular weight of 1300–1400 Da, characterized by highly unusual properties including the structural presence of a carbon–metal bond. The structure of vitamin B12 is essentially represented by a planar group and a nucleotide set. The core planar group is represented by a corrin ring, with the single cobalt atom located in the center of the ring. The nucleotide consists of a base [5,6-dimethylbenzimidazole], and a phosphorylated sugar [ribose-3-phosphate] while the corrin ring, is comprised of four pyrroles, whose nitrogens are coordinated to the central cobalt atom (Fig. **1**) [1]. The biologically active forms of vitamin B12 found in nature are represented by 5'deoxy-adenosyl-cobalamin and methylcobal-

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amin. The latter is the predominant form of human plasma, and it is used as a cofactor for the enzyme methionine synthase [1]. At the center of the tetrapyrrole ring, the chelated cobalt atom can be attached to several groups, including methyl, deoxyadenosyl, hydroxyl or cyano groups (Fig. **1**). Cyanocobalamin is both the synthetic and most stable pharmacological form of the vitamin B12. Following the exposure to the light and a source of cyanide, all forms of cobalamin are converted to cyanocobalamin [1]. For that reason, cyanocobalamin is the synthetic form of vitamin B12 used for pharmacological purposes, although hydroxocobalamin, adenosylcobalamin and methyl-cobalamin are also in use in some countries' formularies [1]. Hydroxocobalamin has a protein-binding capacity higher than that of cyanocobalamin, and has advantages due to its slower metabolism in cells. The only difference between cyanocobalamin [vitamin B_{12}] and hydroxyl-cobalamin [both referred as vitamin B_{12}] is the replacement of the cyanide [CN] group with a hydroxy [OH] group at the active site in the corrin ring [1]. Additionally, the depot preparation of cyanocobalamin [cyanocobalamin-tannin complex suspended in a sesame oil-aluminum monostearate gel [l] is metabolized even slower than hydroxocobalamin [1]. Furthermore, there are several other forms of cobalamin such as glutathionylcobalamin, sulfitocobalamin, and nitritocobalamin; however, their physiological role is unclear, and they are reputed to be artifacts of the extraction process [1]. Humans consume cobalamin contained in animal tissues, and the highest amounts of B12 are found in liver and kidney [>10 mg per 100 g wet weight]. Anyway, cobalamin is also found in shellfish, organ and muscle meats, fish, chicken, and dairy products [1].

Adenosylcobalamin and hydroxocobalamin are the predominant forms of cobalamin found in meat, whereas methylcobalamin and hydroxocobalamin are primarily contained in dairy products. Vitamin B12 is also known as the "extrinsic factor" because its absorption requires the combination with the "intrinsic factor" present in the stomach; in that way the whole complex [intrinsic and extrinsic factors] may be lastly absorbed at a special site in the terminal ileum [1].

Congenital or autoimmune "intrinsic factor" deficiency or other diseases with related functional abnormality, as in several gastric, intestinal, ileal, and autoimmune diseases can induce the onset of severe megaloblastic anemia. Moreover, such an anemia occurs in infants, more frequently than in adults who store vitamin B12 in the liver [1]. Vitamin B12 deficiency is more likely to affect patients with Crohn's disease, ileal resection, atrophic gastritis, alcohol abuse and patients 75 years old or older. Since vitamin B12 can be found in eggs, milk, meat, above all in bovine liver and oyster, total vegetarians [vegans] represent another specific group of patients at high-risk for vitamin B12 deficiency, who can manifest severe neurological symptoms too [1]. Furthermore, prolonged use of some medications such as metformin and anti-acid drugs like histamine-2

receptor antagonists and proton pump inhibitors were found to be associated with vitamin B12 deficiency. After gut absorption, cobalamin is then transported into the portal circulation and stored in the liver.

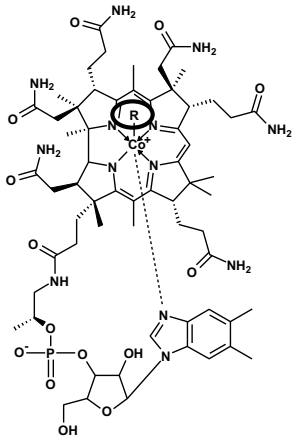


Fig. (1). Cobalamine.

In human plasma, two main vitamin B12 carrier proteins have been identified: haptocorrin, previously known also as transcobalamin I, and transcobalamin II [1]. In serum circulation the majority of cobalamin is bound to haptocorrin, while a smaller amount is bound to transcobalamin II, with a very small amount of circulating free cobalamin [1]. The liver stores enough cobalamin, thus vitamin B12 deficiency becomes symptomatic after several months. Because of the importance of this vitamin, many extraction methods have been developed, although in most of the cases, vitamin B12 is produced industrially *via* microbial fermentation, by bacterial means using different strains of *Propionibacterium*, *Pseudomonas* and *Sinorhizobium* [2]. Moreover, hydroxocobalamin is used as an antidote in case of cyanide poisoning, above all in European countries. It complexes with cyanide on a mole-to-mole ratio to form cyanocobalamin. The required antidotal dose of hydroxocobalamin is about five thousand higher than the physiological dose, and it should be quickly administered intravenously, then both the cyanocobalamin and hydroxocobalamin are excreted by the kidney [3]. Previously in the USA cyanocobalamin was the only form of vitamin B12 commercially available. The necessity to have hydroxocobalamin as antidote led

CHAPTER 10

Vitamin C (Ascorbic Acid)

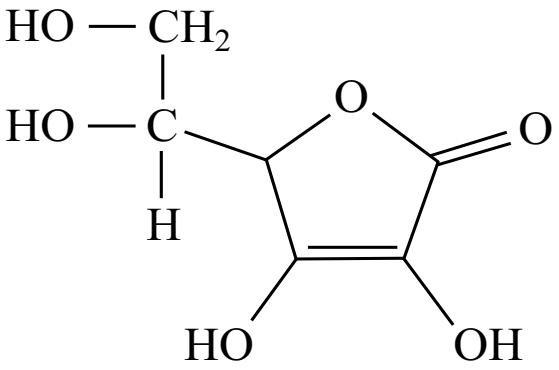
Abstract: Vitamin C, (ascorbic acid), is a water-soluble, highly labile compound, easily lost during food processing. It is one of the most common and essential vitamins, involved in numerous metabolic pathways in the human body and has a protective and preventive role against the damages of free radicals. Vitamin C deficiency is responsible for the onset of scurvy. Ascorbic acid has a high tolerability, due to its short half-life and rarely induces hypersensitivity reactions. Because of its antioxidant properties, ascorbate salts and other ascorbic acid derivatives are largely used as food preservatives in industrial beverages or more recently like whitening agents in cosmetics, thus the first case reports involving products like 3-O-ethyl-L-ascorbic acid or ascorbyl tetraisopalmitate, have been described in the literature. Such allergic contact dermatitis seems to be caused by the side chains of these compounds rather than the ascorbic acid core structure.

Keywords: Allergic Contact Dermatitis, Anaphylaxis, Ascorbates, Ascorbic Acid, Ascorbyl Tetraisopalmitate, 3-*O*-ethyl-L-ascorbic Acid, Delayed type Reaction, Immediate-type Reaction, Scurvy, Urticaria, Vitamin C.

INTRODUCTION

The ascorbic acid [2-oxo-L-theo-hexono-4-lactone-2,3-enediol] is a reduced form of vitamin C synthesized from hexose sugar. Chemically, the vitamin occurs in 3 isomeric forms, *i.e*. L-ascorbic acid, D-arabo-ascorbic acid and L-arabo–ascorbic acid, but, among them, the commercially used form is the L-ascorbic acid, which is widely known as the water-soluble vitamin C.

L-Ascorbic acid molecule has a molecular weight of 176 g/mol and is formed of asymmetrical six-carbon atoms, which is structurally related to glucose (Fig. **1**). It shows two L-isomers: ascorbic acid [vitamin C] in the reduced state and dehydro-ascorbic acid [DHA] in the oxidized state. Ascorbic acid is a potent reducing and antioxidant agent that functions in fighting bacterial infections, in detoxifying reactions, and in the formation of collagen in fibrous tissue, teeth, bones, connective tissue, skin, and capillaries. Vitamin C cannot be produced or stored by humans, so it must be obtained through diet and its dietary deficiency led to the onset of scurvy. Green vegetables and fresh fruit, above all agrumes, are the main sources of vitamin C in the human diet [1]. Ascorbic acid is a colorless and



Ascorbic acid
(Vitamin C)

Fig. (1). Ascobic acid (vitamin C).

odorless crystalline substance, slightly sour in taste and heat labile [1]. It is the third most commonly single vitamin, consumed in supplement form by 9.4% of adults [2]. The recommended dose intake is 300-1000 mg daily.

Although ascorbic acid is a powerful antioxidant, it easily undergoes degradation especially in an aqueous environment as well as in food and the degradation rate depends on various factors such as pH, temperature, light, concentration. It has been demonstrated that there is a decrease of ascorbic acid content in fresh fruit secondary to its storage period and environmental conditions [3]. As consequence, ascorbic acid degradation products like dehydro-ascorbic acid [DHAA] and other compounds affecting food ingredient stability. To prevent its deterioration, fruit is treated with coating solution of ascorbic acid 2% during the harvest or storage [4].

Since vitamin C is a good preservative to add to foods, it was authorized in Europe as a food additive like ascorbic acid [E300] or one of its salt forms, commonly sodium ascorbate [E301] or calcium ascorbate [E302], which are more stable, although there are some chemical differences between the two salts [5]. Moreover, even fatty acid esters of ascorbic acid as ascorbylpalmitate [E304] and stearate are allowed as food additives too [5]. Other synthetic esters of ascorbic acid have been produced such as tetra-hexyldecyl ascorbate, which is a form of vitamin C modified to be soluble in oil or lipids, or other lipophilic forms of ascorbic acid like 3-O-ethylascorbic acid, which is an L-ascorbic acid derivative with an ethyl group at the 3' carbon position, and ascorbyl-tetraisopalmitate whose topical use is allowed in cosmetics and anti-aging products, in the light of increased attention of vitamin C activity on skin wellness [6].

Immediate-type Reactions

Ascorbic acid is usually a well-tolerated vitamin, which rarely induces immediate-type allergic reactions. Furthermore, it is reputed an anti-allergic agent because of its anti-histaminic properties [7]. In the seventies, a Russian author has firstly described an anaphylactic reaction following the 7th dose of vitamin C 5% solution administered intravenously in a 43-year-old female patient [8]. The fatal outcome did not allow any further investigation [8]. A retrospective study investigated the onset of adverse reactions due to the use of intravenous vitamin C among patients receiving the vitamin C by complementary and alternative medicine practitioners [9]. 172 practitioners on 199 accepted to be enrolled in the study and they admitted to having administered vitamin C intravenously to 11,233 patients in 2006 and 8,876 patients in 2008 [9] with an average dose of 28 gr every 4 days. Among the 9,328 patients for whom data is available, 101 reported adverse reactions, mostly mild, although 52 reported something more serious as lethargy, phlebitis due to venous irritation from ascorbic acid, metabolic changes as hyperglycemia or oxalate accumulation leading to renal deficiency, one case of syncope, yet no hypersensitivity was reported, so confirming the safety of ascorbic acid as a poorly allergenic drug [9]. However, recently, a case of allergic hypersensitivity to vitamin C in the same patient was reported by two different research groups in English literature [10, 11]. In both the reports, authors described that a 51-year-old male patient had undervalued his hypersensitivity to ascorbic acid and did not undergo any medical observation until he developed scurvy. The diagnosis of scurvy was suspected on the basis of clinical symptoms [petechiae effusion, mucosal involvement] and confirmed by the restricted diet followed by the patient, by the dosage of plasma ascorbic acid, whose level resulted in 0,1 mg/dl whereas the normal range was 0,6-2,0 mg/dl and by a punch cutaneous biopsy. Patient reported a clinical history of widespread urticaria following the ingestion of citrus fruit with positive skin tests to orange, and also following the consumption of ascorbic acid tablets or multivitamin products containing vitamin C. No other symptoms were associated with the urticarial rash appearing within an hour after vitamin C intake. No skin tests with ascorbic acid were performed, because acid substances may give an irritant response to the *in vivo* tests. So a desensitization protocol to ascorbic acid was carried out starting from a 1/10.000 up to a final dose of 100 mg with the incremental steps after 30 minutes, as shown in Table **1**. When the full dose was reached, the patient received 1000 mg full doses every 8 hours to replenish body store sufficiently [10, 11]. Previously Thumm *et al*. described a 62-year-old man with frequent episodes of angioneurotic edema with systemic symptoms [12]. The patient showed a positive scratch test with ascorbic acid and citric acid which elicited angioneurotic edema with glottis swelling, erythema of face and hands, itching, vertigo and hypotension with tachycardia twenty minutes after testing [12]. The authors

CHAPTER 11

Vitamin A (Retinoids)

Abstract: The name of vitamin A designates the group of retinoids, *i.e*., some lipophilic substances, which include carotenoids, retinol, retinal and retinoic acid and their synthetic derivatives. Carotenoids and retinoids have several similar biological activities such as antioxidant properties, beneficial effects on the skin, the inhibition of malignant tumor growth and the induction of apoptosis. Retinoic acid [RA] is the active form of the retinol isoform of vitamin A, while retinol is its vitamer form found in food and is converted in the body to 11-trans-retinal by an oxidative process where the hydroxyl group is converted into an aldehyde. 11-trans-retinal is subsequently isomerized into 11-cis-retinal, the functional isomer of the vitamin important in the physiology of vision. Among carotenoids, beta carotene is the pro-vitamin A form obtained from vegetables. Hypervitaminosis A and the relative toxicity usually occur as a consequence of the administration of large amounts of vitamin A preparations, usually for therapeutic purposes. Many esters of vitamin A have been isolated and produced and following their topical use in cosmetics, allergic contact dermatitis has been reported. Furthermore, from retinoic acid, a new class of drugs largely used in dermatology have been produced and the first representant was the cis-retinoic acid or isotretinoin and many others which can be assumed orally to treat severe acne. Such drugs have induced contact dermatitis, photodermatitis, but also urticaria/angioedema with a pseudoallergic mechanism due to the imbalance of inflammatory prostaglandins. On the contrary, true allergic reactions like anaphylaxis from these vitamin A derivative drugs are attributed to their emulsifier, the soybean oil, able to induce severe reactions in peanut allergic patients.

Keywords: Allergic Contact Dermatitis, Anaphylaxis, Angioedema, Beta-Carotene, Food Allergy, Food Dyes, Isotretinoin, Patch Tests, Peanut, Pro-vitamin A, Retinoic Acid, Retinoids, Retinol, Retinyl Acetate, Retinyl Palmitate, Skin Tests, Soybean, Tretinoin, Urticaria, Vitamin A.

INTRODUCTION

The generic name of Vitamin A is used to indicate a group of lipohilic biomolecules with the biological activity of retinol. These compounds include the preformed vitamin A that exists in three major forms: retinol (the alcohol isoform), retinal (the aldehyde isoform), retinoic acid (the irreversibly oxidized form of retinol) and the provitamin A or carotenoids, mainly alpha-carotene, beta-carotene and beta-cryptoxanthin [1].

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Beta-carotene, the yellowish-orange pigment of carrots, is the major plant source of vitamin A precursor and it is obtained from carrots, sweet potatoes, sweet red or yellow peppers and from yellow fruits like mangoes, melons, apricots, peaches and blueberries. whereas the preformed vitamin A can be absorbed from the diet in food of animal origin, such as meat, eggs, liver, butter, milk and cod liver and it is the most abundant form of vitamin A [1]. Also, the dark green leafy vegetables such as spinach contain carotenoids, but they are masked by green pigment of chlorophyll [1].

Carotenoids include carotenes (β-carotene and lycopene) and xanthophylls (lutein, zeaxanthin, capsanthin, canthaxanthin, astaxanthin, and violaxanthin), in that way they can also be distinguished into pro-vitamin A and non-provitamin A carotenoids.

Foods containing pro-vitamin A carotenoids tend to have less biologically available vitamin A but are more affordable than animal products, especially in the diets of economically deprived populations. Moreover, the pro-vitamin A, *i.e*., beta-carotene is either water or fat soluble, so it can be excreted and usually is not associated with any toxic effect [1].

Retinol has a molecular weight of 486.2 and looks like yellow crystals insoluble in water, but soluble in oil and organic solvents, while, from the chemical point of view, Vitamin A is a 20 carbon molecule composed of three parts: a trimethylated cyclohexenyl ring, a conjugated tetraene [isoprenoid] side chain side with four double bonds, *i.e*., the retinyl group, and lastly a polar carbon–oxygen end functional group [1] (Fig. **1**). The oxidation of the alcohol end group of retinol results in the formation of an aldehyde (all-trans retinaldehyde or retinal), which can be further oxidized to a carboxylic acid (all-trans retinoic acid or tretinoin) [1]; thus, the retinal C-15 terminal group oxidation, undergoing a physiological process, leads to the irreversible production of retinoic acid, *i.e*., the main metabolite of vitamin A [1]. *Beta*-carotene is the major source of vitamin A precursor from plants and it is a dimeric molecule, represented as two connected retinyl groups (Fig. **1**). A central cleavage is required in *beta*-carotene molecules to obtain all trans-retinal; however, the bioconversion shows a 1:12 ratio [1].

Vitamin A family may exist in either the *trans*- or *cis*-isomeric form (Fig. **1**), but a large number of retinoid isomers is possible [1].

Retinol, but also retinyl esters, and pro-vitamin A carotenoids are absorbed in the gut through the chylomicrons and secreted into the lymphatic system. Most dietary vitamin A (in chylomicrons and chylomicron remnants) is taken up by the liver, which is the major site of retinol metabolism and storage [1].

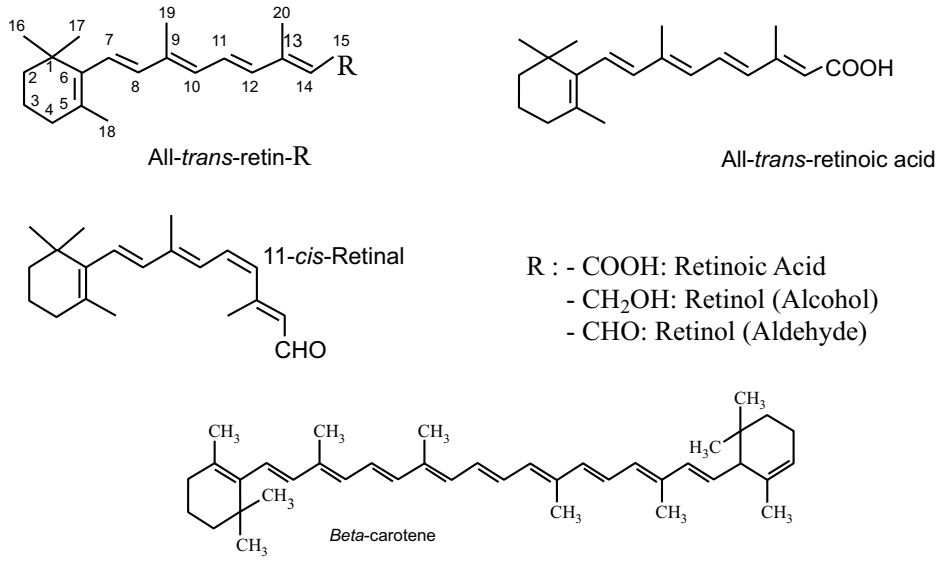

Fig. (1). The different forms of vitam A.

Anyway, once absorbed, a metabolic activation is required to convert retinol to biologically active metabolites, *e.g.*, all-trans-retinoic acid and its cis-isomers, although retinoids tend to be most stable in the all-trans configuration, the retinyl esters are converted to retinol before absorption from the intestine and then back to retinyl esters for their storage in the liver or fat tissue. Retinyl palmitate (RP) (Fig. **2**) is the main storage form of retinol in humans and animals and can be enzymatically hydrolyzed back to retinol *in vivo*. All-trans-retinoic acid is the most bioactive form of vitamin A; however, being an alcohol, retinol is known to be an unstable compound. As seen, Vitamin A is mainly found in human tissues as retinyl esters, and that explains why vitamin A is commercially produced and administered for nutritional or medical purposes in the ester forms of retinyl acetate or palmitate [1]. Since vitamin A tends to be stored in the liver, in case of excessive or chronic intake, toxic hepatitis is the major problem [2]. Other typical manifestations of vitamin A toxicity are dry skin, cheilosis, dermatitis, joint and bone pain, headaches, and fatigue. Also, *beta*-carotene is stored at relatively low concentrations in liver and fatty tissues, indeed its accumulation is responsible for yellow color of adipose tissue [1].

Vitamin A family is also known as retinoids. Although, the name retinoid was originally used to identify the synthetic products which were structurally analogs of the natural vitamin A, actually the term is used for natural and synthetic derivatives of vitamin A, including the esters such as retinyl-palmitate, -propionate and -acetate, retinyl-retinoate, retinyl *N*-formyl aspartamate and

CHAPTER 12

Vitamin D (Ergocalciferol/ Cholecalciferol)

Abstract: Vitamin D has many benefits for body and human health. Vitamin D is involved in calcium homeostasis and bone metabolism, and it can be obtained from food, but it is produced by the human body too. Vitamin D from foodstuffs is available in two forms; vitamin D2 [ergocalciferol,] is contained in plants, and vitamin D3 [cholecalciferol] is contained in animals. Furthermore, the vitamin D produced by human body, is synthesized mainly in the skin. The synthesis of vitamin D in the skin starts with the conversion of 7-dehydrocholesterol [provitamin D3] to previtamin D by UVB. Some of the formed vitamin D3 in the skin is transported to the liver and metabolized to become $25(OH)D_3$ (calcidiol), then furtherly converted in two steps to $1,25(OH)_2D_3$ (calcitriol), *i.e.*, the biologically active form of vitamin D. Being produced by the organism, vitamin D shows a high tolerability; thus hypersensitivity reactions to vitamin D are rarely reported in the literature. From vitamin D, many analogs have been used successfully to treat secondary hyperparathyroidism or other derivatives synthetically produced like calcipotriol, calcitriol and maxcalcitol that are used in dermatologic field as topical therapeutic agents for psoriasis. For this last class of compounds, given the external use on the skin, cases of allergic contact dermatitis are described.

Keywords: Allergic Contact Dermatitis, Anaphylaxis, Calcipotrion, Calcitriol, Cholecalciferol, Delayed-type Reaction, Desensitization, Ergocalciferol, Immediate-type Reaction, Pro-vitamin D, Vitamin D, Vitamin D3, Vitamin D Analogs.

INTRODUCTION

The generic term of vitamin D includes a group of six chemically related compounds possessing antirachitic activity. Although various naturally occurring members of vitamin D, ranging from vitamin D2 to vitamin D7 are differentiated only by the structures of their side chains, the most prominent vitamers from the group are the two soluble forms: vitamin D2 [ergocalciferol] and vitamin D3 [cholecalciferol], which are biologically active compounds too. The first one, vitamin D2, is produced by plants and it has got a structure derived from plant steroid, ergosterol; whereas vitamin D3 is the form of vitamin D produced by animals and derived from cholesterol. It is obtained when skin is exposed to sunlight, thus converting its precursor, 7-dehydrocholesterol to calcidiol [1].

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The exposure of 7-dehydrocholesterol [7-DHC] to ultraviolet radiation B [UVB] results in the formation of previtamin D in the skin, which is thermally isomerized to the stabler vitamin D [cholecalciferol]. The vitamin D, whether synthesized in the skin or obtained from the diet, undergoes two hydroxylation reactions: first in the liver by vitamin D 25-hydroxylase [CYP2R1] enzyme to form 25-hydroxyvitamin D, 25[OH]D, also known as calcidiol and then in the kidney by 1α-hydroxylase [CYP27B1] to form an active metabolite, 1,25-dihydroxyvitamin D, $1,25(OH)_2D$, also known as calcitriol. Therefore cholecalciferol undergoes a double hydroxylation in the liver and then in kidney to get the active form of vitamin D is 1,25-dihydroxyvitamin D ($1\alpha,25(OH)_2D_3$) [calcitriol] [1]. On the pharmaceutical market synthetic vitamin D can be found as cholecalciferol, viz the pro-drug but also as calcitriol [1]. The biologically active vitamin D2 and D3 are illustrated in Fig. (**1**). Since the body is capable of producing vitamin D3, it does not meet the classical definition of a vitamin. For that reason, Vitamin D can also be considered a hormone, because members of the D vitamin family share the cyclopentano-perhydro-phenanthrene ring structure derived from cholesterol, as well as steroid hormones, thus vitamins D compounds are also designated as secosteroids [1]. Vitamin D possesses endocrine, paracrine and autocrine actions. From a chemical point of view, in comparison with cholesterol, vitamin D has only three intact rings, A ring being not rigidly fused to the B ring.

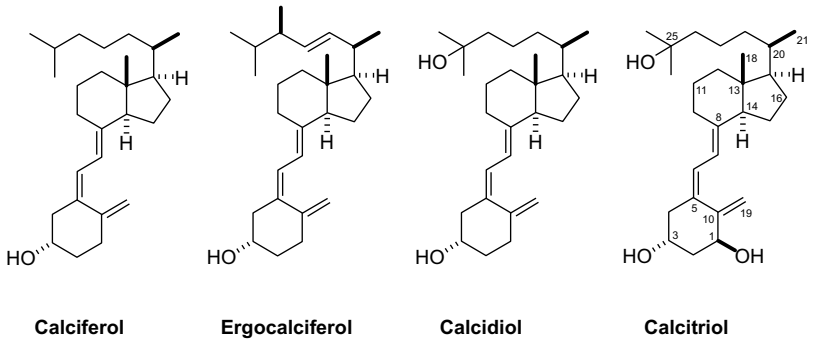

Fig. (1). Vitamin D2 and vitamin D3.

Due to the rotation on the 6,7 carbon–carbon bond of the B ring, in solution, vitamin D may exhibit two spatial conformations: the 6-s-cis form, *i.e.*, the steroid-like shape, and the 6-s-trans, *i.e.*, the extended shape. Such forms are present in both vitamin D2 and vitamin D3 [1].

Being a hormone, vitamin D is strongly involved in Calcium/Phosphorus homeostasis both for calcitonin and parathyroid hormone [PTH], so its deficiency causes mainly rickets, although vitamins D plays an important role in many other

systems [skeletal and cardiac muscles, immune system, skin, pancreas] requiring Ca^{++} for their correct functions [1].

Vitamin D occurs naturally in food derived mainly from animal products. Salt-water fish such as codfish, herring, salmon, and sardines contain substantial amounts of vitamin D, and fish-liver oils are extremely rich sources, while eggs, veal, beef, unfortified milk, and butter supply only small quantities of that vitamin.

Since vitamin D is partially produced by humans exposed to sunlight, the fair requirement of healthy adults has never been precisely established. However, the World Health Organization [WHO] has established that vitamin D deficiency occurs as serum 25[OH]D is lower than 20 ng/mL [50 nmol/L] and its oral intake is important when sunlight decreases, is absent or serum level is lower than suggested by WHO guidelines [1]. Actually, the current adequate intake allowance of vitamin D according to the USA Food and Nutrition Board of the Institute of Medicine is 200 IU daily [5 mg/day] for infants, children, adult males, and females [including during pregnancy and lactation] up to age 5, then for males and females aged 51–70 or more, the adequate indicated level is set at 400 IU/day [10 mg/day] or 600 IU/day [15 mg/day], respectively. However, there are patients whose ability to generate vitamin D in the skin is compromised as well as albinos and patients with chronic kidney diseases because uremia affects vitamin D skin and kidney metabolism [2], so they need vitamin D supplements. To reduce vitamin D hypercalcemic and phosphatemic properties, or to increase some immune-modulation abilities, various synthetic analogs have been developed [3] and, beyond cholecalciferol, calcitriol, and ergocalciferol, about 10 vitamin D structurally modified derivatives are available on the market as shown in Figs. (**2** and **3**).

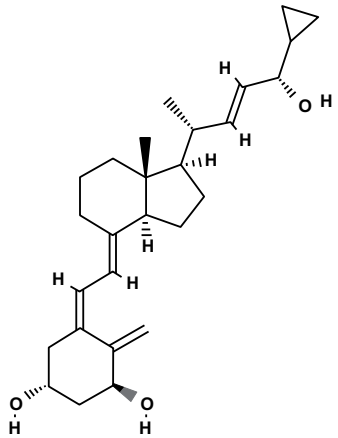

Fig. (2). Calcipotriol.

CHAPTER 13

Vitamin E (Tocopherols)

Abstract: Vitamin E refers to a family of compounds that function as lipid-soluble antioxidants capable of preventing lipid peroxidation. Naturally occurring forms of vitamin E include tocopherols and tocotrienols. The form of vitamin E most studied is natural *alpha*-tocopherol, which is the form more adapted for humanorganism requirements. It is possible to distinguish two isomers, the D-alpha tocopherol, the natural form and the synthetic form of vitamin E, *DL-alpha*-tocopherol, which has allowed the synthesis of various esters like the *alpha*-tocopheryl acetate, succinate, nicotinate and many others to increase vitamin E hydrosolubilty and its penetration throughthe skin in cosmetic applications as antioxidant and anti-aging agent. Consecutively, allergic contact dermatitis represents the most common form of hypersensitivity induced by vitamin E and its derivatives and vitamin E is the third most frequent contact allergen found in moisturizers. Despite the first cases of contact allergy to vitamin E were described in the 60ies, concentrations, and vehicles for the diagnostic patch tets to vitamin E are very far from being well standardized.

Keywords: Allergic Contact Dermatitis, Contact Urticaria, Delayed-type Reaction, Patch Tests, Repeated Open Application Test, Skin Tests, Tocopherols, Tocopherol Acetate, Tocopheryl Acetate, Tocopheryl Linoleate, Tocopheryl Nicotinate, Vitamin E.

INTRODUCTION

Vitamin E is the name for a group of eight natural structurally related molecules [*i.e*., chroman-6-ols], collectively termed toco-chromanols which are divided into tocopherols and tocotrienols, and qualitatively exhibit the biological activity of d-*alpha*-tocopherol. These compounds have a similar structure with a chromanol ring as head and a tail represented by a phytyl side chain, attached at the 2-position of the chromane ring [1]. Such a phytyl chain is a saturated isoprenoid C16 side chain for tocopherols and unsaturated for tocotrienols, so they are named *alpha-,beta-,gamma-* and *delta*-tocopherol and *alpha-, beta-, gamma-* and *delta*-tocotrienol, differing also in the number and the position of methyl groups substituted on the chromanol ring, as shown in Fig. (**1**). The structural differences between tocopherol and tocotrienols result in a different penetration of these compounds into tissues [1]. However, it has been conventionally defined *alpha*

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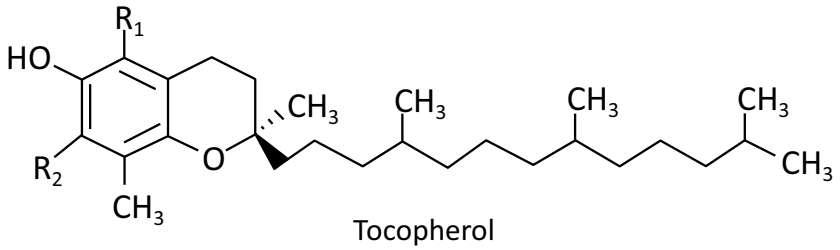
-tocopherol as the only form that meets human vitamin E requirements because only α-tocopherol has been shown to reverse human vitamin E deficiency symptoms although, *alpha*-tocotrienol, *gamma*-tocopherol, and *delt*a-tocotrienol have emerged as vitamin E molecules with functions in health and disease that are clearly distinct from that of *alpha*-tocopherol [1]. For instance, *gamma*-tocopherol exhibits only 10–30% of the biological activity of *alpha*-tocopherol [1]. The vitamin E is generally ingested along with fat-containing foods and good sources are vegetable oils, nuts and nut oil seeds, margarine, soya beans, wheat germ, oatmeal, avocados, olives, green leaf vegetables, *etc* [1]. Tocopherols are predominant in olive, sunflower, corn, soya beans oils, and tocotrienols are the major vitamin E components of palm oil, barley and rice bran. The tocopherols are viscous oils at room temperature, insoluble in water but soluble in ethanol and other solvents like benzene, toluene and acetone. Vitamin E is a slightly yellow to amber, nearly odorless, clear, viscous oil, which darkensupon exposure to air or light by oxidation. It is stable at ambient temperature, but it is readily oxidized at high temperature, under light or in an alkaline medium [1]. α-Tocopherol has a molecular weight of 430 and it can be found in dextrorotatory [*d*] and [*l*] levorotatory forms [2]. In nature, α-tocopherol occurs as a single stereoisomer *RRR*-α-tocopherol, while synthetic vitamin E is a mixture of eight stereochemical isomers different in the three chiral centers in the phytyl side chain [RRR, RSR, RRS, RSS, SRR, SSR, SRS, SSS]. [all-*racemic*, all-*rac*], usually in equal proportions and with different biopotency.Interestingly, natural vitamin E has approximately twice the systemic availability of synthetic tocopherol [*all-rac*-tocopherol]. For that reason, chemically synthesized *alpha*-tocopherol is not identical to the naturally occurring form [1]. Since the poor water solubility of vitamin E has greatly limited its application, other formulations of α-tocopherol have been synthetized as esters to increase their solubility as shown in Table **1** [2]. Moreover, being free vitamin E much more sensitive to oxidative degradation compared to the acetate form or other derivatives; vitamin E is available in commercial cosmetic formulations as the free alcohol or its esters. Vitamin E is widely used as a dietary supplement, by itself or together with other micronutrients and minerals and the forms of vitamin E in most supplements are the synthetic all-*rac*-*alpha*-tocopheryl acetate or all-*rac*-a-tocopheryl succinate, or nicotinate, however in the organism, they are quickly hydrolyzed in the gut and are absorbed as a-tocopherol [1]. On the contrary, it has been demonstrated the acetate ester of tocopherol, when applied topically on the skin, showed no evidence of conversion to the biologically active form, alpha-tocopherol, despite its adequate absorption into the epidermal layers [3]. The absorption of vitamin E is also dependent on the fat content of the meal,absorption being relatively poor when it is consumed without fat, or when vitamin E pills are consumed without food. The dietary reference intake of a-tocopherol is 15 mg/day [22,4 IU] for

adults [1]. The richest dietary sources of vitamin E are edible vegetable oils, because only plants may synthesize vitamin E [1]. It has been estimated that, about 35.000 tons of vitamin E is manufactured per year worldwide because of its large applications in the food, cosmetic and pharmaceutical industries [4], although industrial processing influences the content of tocopherols and 15–40% losses occur during refining depending on the process [4]. The international market for vitamin E in 1995 was about US dollar 1 billion, of which the share of synthetic and natural vitamins represented 85% and 15%, respectively and vitamin E supplements are taken daily by more than 35 million people only in the United States [1]. However, in Europe the following E-numbers are approved by the EU as food additives: natural tocopherol- extract [E306], synthetic d,l-*alpha*-tocopherol [E307], synthetic d,l-*beta*-tocopherol [E308], and synthetic d,l-*delta* -tocopherol [E309] [2]. Beyond as a dietary supplement, vitamin E is largely used in cosmetics for its antioxidant and antiaging properties. Hence, it is present in creams, ointments, anti sunlight preparations, deodorants and moisturizers [2] and it is indicated to treat either topically orsystemically some skin disorders [3] as Hailey–Hailey disease, epidermolysis bullosa, psoriasis, scleroderma, atopic dermatitis and others, although vitamin E has never been used extensively to treat epidermal pathologic conditions, but always in few randomized studies [3]. Although some experimental models and observational studies have suggested that vitamin E supplementation may prevent cardiovascular disease, Alzheimer disease and cancer, these data were not confirmed by several trials in which high-dosage vitamin E supplementation showed non-statistically differences in total mortality; indeed a careful meta-analysis evidenced a relationship between vitamin E high dosage daily intake [> 150-400I.U.] and increased rates, low but statistically significant, of all-cause mortality [5].



Tocopherol

Fig. 1 cont.....

CHAPTER 14

Vitamin K (Phytomenadione)

Abstract: Vitamin K is a fat soluble vitamin used to treat or prevent certain coagulation disorders, because it is strongly required by the human organism for the production of the coagulation factors II, VII and X, and the dietary intake of the daily doses are strongly recommended to avoid the onset of bleeding and haemostasis disorders. However, Vitamin K is surely the vitamin for which majority of hypersensitivity reactions have been described for, either immediate or delayed-type, and sometimes the clinical manifestations do not allow the certain identification of the immune pathomechanism. Furthermore, the excipient like Cremophor EL *i.e*., polyoxyl 35-hydrogenated castor oil, plays a role in eliciting immediate type reactions, which can be pseudo allergic or IgE mediated even. Crempopor EL is in fact used as a suspending agent in many hydrophobic drugs like cyclosporine, tacrolimus, paclitaxel, teniposide and many others. On the other hand, vitamin K-induced delayed type reactions exhibit a wide range of morphological clinical pictures, mainly cutaneous. Patch tests and intradermal tests are very useful in delayed type reactions to diagnose such a hypersensitivity, while immediate reading skin tests have resulted doubtful or poorly helpful in the diagnosis of the immediate type reactions.

Keywords: Allergic Contact Dermatitis, Anaphylaxis, Cremophor EL, Delayed Type Reactions, Eczema, Immediate-type Reactions, Patch Tests, Phylloquinone, Phytonadione, Preservative Scleroderma, Skin Tests, Texier Disease, Urticaria, Vitamin K, Vitamin K1, Vitamin K3.

INTRODUCTION

Vitamin K [from the Danish word “Koagulation”] was isolated in 1930 by the Danish Dam and it is an essential factor required for post-translational modification of coagulation factors II, VII, IX, and X; thus the term Vitamin K is used to indicate some compounds which possess a common 2-methyl-1,4 naftoquinone core, called menadione, and a phytyl chain ide at the 3-position. That side chain is an isoprenoid structure, varying in lengths and degrees of saturation and exhibiting anti-hemorrhagic properties [1].

There are seven molecules which have been designated as vitamin K as shown in Table **1**.

Table 1. The seven forms of vitamin K by Fiore *et al*. [3] (modified).

Vitamin K1	2-methyl-3-phythyl-1,4-naphthoquinone	Phylloquinone – phytonadione - phytomenadione
Vitamin K2	2-methyl-3-difarneasyl-1,4-naphthoquinone	menaquinone –menatetrenone
Vitamin K3	2-methyl-1,4-naphthoquinone	menadione – menadione Na-bisulfite
Vitamin K4	2-methyl-naphthalene-1,4-diol	menadiol and its esters (diacetate, dibutyrate)
Vitamin K5	4-amino-2-methyl-1-naphthol	-
Vitamin K6	2-methyl-1,4-2-naphthaelendiamine	-
Vitamin K7	4-amino-3-methyl-1-naphthol	-

Vitamin K occurs naturally in two forms only, *i.e*., vitamin K1 and K2, whereas vitamins K3 to K7 are synthetic compounds. Vitamin K1 can be found in plants and vitamin K2 is synthesized by Gram positive, above all anaerobic *Bacterioides* species, found in normal flora of the large intestine [1]. Vitamin K1 is also known as phylloquinone and vitamin K2 is also designated as menaquinone [1]. The chemical structure of vitamin K1 consists of a basal 2-methyl-1,4-naphthoquinone molecule, indicated as menadione in which the two methyl groups are functionally important, and an isoprenoid side chain containing 20-30 carbon atoms at the C3 position [1]. That side chain may change in length and degree of saturation. Vitamin K1 is the predominant form of vitamin K present in the diet and it is also the most widely used preparation for intravenous administration, although vitamin K1 (phytonadione) is a fat-soluble synthetic derivative identical to the naturally occurring vitamin K1.

Moreover, synthetically prepared vitamins K1, K3, K4, and K5 have been used in clinical practice, and vitamins K3 and K4 are available as water-soluble salts [1]. However, vitamin K1 remains the preferred molecule being the K vitamer available for oral, intramuscular, subcutaneous, and intravenous administration, although oral preparations are not well absorbed [2]. Vitamin K1 is used as an antidote to contrast warfarin overdose [1].

Interestingly, vitamin K1 molecule has two geometrical isomers (cis-trans or (Z)-(E)-isomers) plus two asymmetric carbon atoms (C7 and C11), each generating two enantiomers (R or S). Thus, there are eight diastereoisomers (four in the trans- and four in the cis- configuration). For that reason, in truth, Vitamin K1 is a mixture of 2-methyl-3-[(2E)-(7R,11R)-3,7,11,15-tetramethylhexadec-2-enyl] naphthalene-1,4-dione (trans-phytomenadione), 2-methyl-3-[(2Z)-(7R,11R)-3, 7,11,15-tetra-methylhexadec-2-enyl]naphthalene-1,4-dione [cis-phytomenadione], and 2,3-epoxy-2-methyl-3-[[2E]-[7R,11R]-3,7,11,15-tetramethylhexadec-2-enyl]-2,3-di hydronaphthalene-1,4-dione (trans-epoxy-phyto-menadione), where, the name Vitamin K1 and its pharmacological properties fits appropriately only for

the 2'-Trans-7R, 11R-stereoisomer (the others are not vitamins because the cis-isomer is inactive) [2], and the 2'-Trans-7R, 11R-stereoisomer represents the 75-90% of the mixture, whose chemical formula is shown in Fig. (**1**).

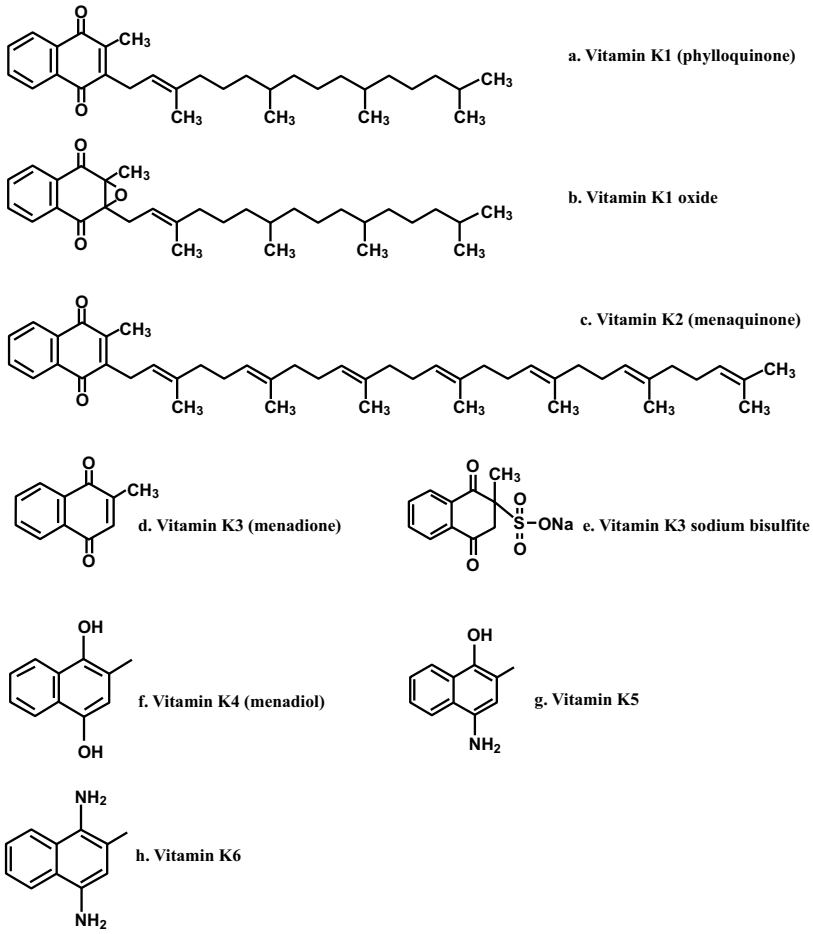


Fig. (1). The vitamin K vitamers and the main derivatives.

The liver is the site of synthesis of vitamin K dependent coagulation factors, but the concentration of vitamin K in the hepatic tissue is extremely variable [1]. Furthermore, phylloquinone is a minor component of hepatic vitamin K, being only 10%, whereas menaquinones represent 90% of the liver storage [1] and, although the liver is reputed to be the main catchment area of vitamin K, other tissues as kidney, lung, bone and skin work like reservoire for vitamin K [2]

Vitamin K1 has a molecular weight of 450.68 g/mol and it looks like a clear or golden yellow viscous liquid, insoluble in water, slightly soluble in ethanol, and

CHAPTER 15

Unusual Clinical Aspects of Vitamin Hypersensitivity

Abstract: Although immediate-type hypersensitivity and allergic contact dermatitis have been mainly reported following vitamins or multivitamins intake and exposure respectively, more rarely unusual immune-mediated adverse reactions such as fixed drug eruption and other more serious hypersensitivity syndrome are described in the literature, but their diagnostic approach is more difficult because skin tests in severe cutaneous adverse reactions are validated for few drugs as anti-convulsivant agents.

Keywords: DRESS Syndrome, Drug Hypersensitivity Syndrome Fixed Drug Eruption, Drug-induced Aseptic Meningitis, Hemolysis, Multivitamin, Thrombocytopenia, Vitamins.

INTRODUCTION

Immediate-type hypersensitivity reactions to vitamins are represented by urticaria angioedema, bronchospasm and anaphylaxis involving an IgE mediated pathomechanism or a non-immunologic hypersensitivity, whereas delayed type reactions are T cell-mediated and are represented mainly by an allergic or photoallergic contact dermatitis. However, other delayed type reactions to vitamins involving a T cell response have been reported more rarely in the literature. Given the exceptionality of these case reports, the diagnostic and management strategies are more difficult than an allergic reaction or allergic contact dermatitis, even because skin tests are not fully validated in case of severe hypersensitivity [1]. Then, it is very hazardous to perform skin tests or an oral challenge with every component of the compound, including excipients, and once more, these tests are not validated, poorly described and they could induce a relapse of the severe reaction. Moreover, in most of these cases, the patient was consuming multivitamins or compounds with multiple ingredients; thus the identification of the culprit agent was a true riddle for the clinicians. In literature, unusual hypersensitivity reactions as fixed drug eruption, drug hypersensitivity reaction, drug-induced aseptic meningitis attributed to vitamins are exceptionally reported. Hereby, it is a short review of literature.

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Fixed Drug Eruption (FDE)

The term Fixed drug eruption (FDE) is used to describe an annular erythematous violaceous patchy and sharply demarcated lesion of the skin or genital or oral mucus membranes that occurs few hours (from 6 to 12 hours) following the administration of a drug and it subsides when the drug is withdrawn, with the tendency to recur at the same location when the drug is reintroduced, the patient being sensitized to that particular drug or its metabolites. Pruritis and burning usually precede the appearance of the lesion. A lesion can be isolated or, less frequently multiple. The clinical resolution usually yields post-inflammatory pigmentation. The most involved sites are the hands, feet, lips, genital, oral and perineal areas. The FDE has been seen to be a form of delayed-type hypersensitivity, mediated by intraepidermal CD8+ T cells, found in the perilesional area at skin biopsy [2]. The diagnosis usually is confirmed by an oral challenge test, also used to identify the culprit drug. Patch tests gave a positive response only when performed on the lesion [2]. The first case of FDE induced by vitamins was reported in 1955 [3]. The author described a 37-year-old Caucasian woman developing a bullous FDE on the left wrist. An oral challenge test with nicotinic acid 50 mg four times in a day led to the recurrence of the eruption. However, the patient tolerated 25 mg four times daily [3], then the reaction subsided progressively, although the patient continued to take the drug [3]. Various Indian authors reported patients developing FDE after the repeated consumption of multivitamin compounds [4 - 7]. Usually, an isolated FDE was described [4 - 6], but also multiple bullous FDE has been also reported [7]. In some cases, the components were not reported [4, 5], whereas other authors investigated the composition of different multivitamins, looking for common components [6, 7]. No author performed perilesional patch tests, given the complexity of the compounds and the careful clinical history avoided to carry out a challenge test with the multivitamin. In all the cases, patients had frequently assumed various multivitamin compounds from different brands and, at first, the multivitamin formulations were not thought to be the culprit agent responsible for the skin eruption [4 - 7]. The comparison of the different compounds identified folic acid, niacinamide, calcium pantothenate, vitamin C, and biotin as recurrent components in a case [6] and methylcobalamine, vitamin C, folic acid, riboflavin, and calcium pantothenate in another one [7]. Recently, Italian researchers found a 40-year-old woman with an FDE of the left iliac spine appearing after 15 days of folic acid therapy. Patch tests with folic acid at unknown concentrations on healthy and affected skin gave a negative response at 24 hours reading. An oral challenge test performed a month after stopping folic acid therapy was positive with the reappearance of the lesion in the same area [8].

Drug Rash, Eosinophilia, Systemic Symptoms (DRESS) Syndrome/Drug Hypersensitivity Syndrome (DHS)

Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome is a life-threatening condition characterized by the presence of at least three of the following findings: fever, skin rash, usually a severe maculopapular or morbilliform exanthema, eosinophilia, atypical circulating lymphocytes, lymphadenopathy. The visceral involvement can be asymptomatic, or it may include hepatitis, renal insufficiency, pneumonitis, polyserositis, myocarditis and blood cells or bone marrow dyscrasia [9]. DHS usually begins with the skin rash and fever > 38° 2 or 3 weeks after starting the culprit drug [9]. The syndrome is difficult to diagnose, as many of its clinical features mimic those found with other serious systemic disorders [10]. Such an idiosyncratic reaction occurs most commonly after exposure to drugs like allopurinol, minocycline, sulfonamides, dapsone, aromatic anti-convulsants such as phenytoin, phenobarbital and carbamazepine, but also lamotrigine, and certain antiviral agents as abacavir and nevirapine [9]. Furthermore, the clinical manifestations of the syndrome are linked to the drugs; thus each drug may cause clinical pictures slightly different from the classical DHS/DRESS syndrome [11]. The syndrome is often associated with a herpes virus reactivation [9].

The pathogenesis of DHS/DRESS syndrome remains unclear, although it is generally regarded as a T-cell mediated hypersensitivity reaction, as in other severe drug eruptions [10]. Moreover, even the circulating specific IgG to the drug may play a role in pathogenesis, evolution and prognosis of the syndrome [12]. Actually, in the literature, three case reports describe drug hypersensitivity syndrome that occurred during the administration of multivitamin formulations. In all the cases the causative agent was not certainly identified because the compound included various ingredients and two or more vitamins.

Debordeau *et al*. found a 76-year-old woman taking vitamin H [biotin] 10 mg and vitamin B5 [panthotenic acid] 300 daily to treat alopecia [13]. After two months of therapy, the patient went to the hospital for sudden dyspnea and chest pain. Chest radiography evidenced pleural effusion with myocardial enlargement, due to pericardial tamponade confirmed by an echocardiogram [13]

The patient underwent pericardiotomy that showed a sterile exudate with high eosinophilia (1500 cells/ mm^3). The histologic examination of the pericardial biopsy evidenced infiltration of eosinophils too. The pleural effusion relapsed, although various thoracenteses were performed, leading lastly to a thoracotomy. Even pleural fluid revealed the presence of hypereosinophilia, while serologic tests were negative for autoimmune diseases and viral, bacterial and parasi-

Conclusion

Actually, hypersensitivity reactions to vitamins are rare, and surely underestimated too. However, given the importance of vitamins for human health, the onset of an allergy to a vitamin represents a great problem for the patient and a challenge for the clinicians and the nutritionists. Although lipid-soluble vitamins seem to be more likely to induce delayed type reactions, *i.e*. allergic contact dermatitis mainly, the widespread use of new synthetic hydro-soluble vitamin derivatives in cosmetics and dairy consumer products, is rapidly gaining the gap, causing allergic contact dermatitis to these compounds, which may involve the original vitamin molecule even. Furthermore, since hydro-soluble vitamins are perceived less hazardous than fat-soluble vitamins, being less toxic, the large consumption of hydro-soluble vitamins in multivitamins, energy drinks and dietary supplements might cause a potential switch or patent an occult sensitization, from a "simple" allergic contact dermatitis to a serious anaphylaxis, when the vitamin is taken orally or parenterally. Surely, further studies are required to increase the actual knowledges about hypersensitivity to vitamins, so it would be desirable clinicians had a more investigative approach when they meet a patient with hypersensitivity to a vitamin, performing skin tests, challenge tests or *in vitro* tests, if available, and publishing their case report, because even a single case report is a little piece added to the vitamins allergy puzzle, useful to help other doctors in future.

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