Review Article

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Hypervitaminosis A

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Abstract

Vitamin A is essential for life and is the first found vitamin. It has many effects on growth, reproduction, vision and immune system. Nowadays, there is a risk of intoxication following the increase in intake of vitamin A ,taken with foods, with additional supplementary drugs Many studies have been conducted on the deficiency of vitamin A and although adequate measures have been taken in developed and developing countries, it is difficult to estimate the health risks to be created in the future due to the lack of adequate studies in terms of vitamin A intoxication and failure to take necessary measures on the subject.

Acute intoxication has been reported rarely, especially in young adults, as vitamin A is highly tolerated by the body in the acute phase. Intoxication, which mostly develops after chronic exposure to high-dose vitamin A, affects many organs.

Further epidemiological studies are needed to be able to understand how serious public health problem vitamin A intoxication without specific treatment is.

Key words: Retinoic asid, Toxication, Vitamin A

Özet

A Vitamini yaşam için esastır ve ilk bulunan vitamindir. Büyüme, üreme, görme ve bağışıklık sistemi üzerinde birçok etkisi vardır. Son zamanlarda, gıdalarla ve ek ilaçlarla artmış A vitamini alımına bağlı zehirlenmelerle karşılaşılmaktadır. A vitamini eksikliği konusunda birçok çalışma yapılmış bu konuda gelişmiş ve gelişmekte olan ülkelerde yeterli önlemler alınmıştır. Ancak A vitamini zehirlenmesi konusunda yeterli araştırma yapılmaması ve konuyla ilgili gerekli önlemlerin alınmaması nedeniyle gelecekte ortaya çıkacak sağlık risklerini tahmin etmek zordur.

Özellikle genç erişkinlerde akut zehirlenme nadiren bildirilmiştir, çünkü A vitamini akut fazda vücut tarafından oldukça tolere edilir. Çoğunlukla yüksek dozda A vitaminine kronik maruz kalmadan sonra gelişen zehirlenme birçok organı etkiler.

A vitamini zehirlenmesinin, spesifik tedavisinin yapılmadığında ne kadar ciddi bir halk sağlığı problem haline gelebileceğini anlamak için ileri epidemiyolojik çalışmalara ihtiyaç vardır.

Anahtar kelimeler: A vitamini, Retinoik asit, Zehirlenme

Short History

Vitamin A (retinoic acid) is a fat-soluble substance necessary for growth, reproduction, immunity and vision. Although it is not known exactly when vitamin A was discovered, it was observed in a study conducted in 1881 that the growth and development of the subjects regressed, the immune system weakened and severe eye inflammation developed after the removal of natural fats in the nutrients of animals. Then, with the addition of natural fats to their diets, it was possible to say that a fat-soluble substance is essential for life after rapid recovery of animals[1]. After its chemical structure was first discovered in 1931 many studies on the biological process of vitamin A and its derivatives on metabolism have revealed that vitamin A is essential for life [2]. After the discovery of its antioxidant properties, it has started to be used in the treatment of oncological patients and regression of skin aging[3,4].

Although vitamin A has been discovered and its importance has been understood in the last centuries, its toxicity has been known for thousands of years. In the studies on human fossils from ancient times, bone anomalies are thought to be caused by hypervitaminosis A[5,6].

Studies on vitamin A toxicity were primarily conducted to investigate the short-term acute effects in animals[7-9]. Intramuscular and intravenous forms of vitamin A were used in these studies. No significant data could be obtained from these studies since the gastrointestinal effects were bypassed[10,11].

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Increased nutritional and vitamin supplements in foods and increased interest in multivitamin supplements in developed countries have led to an increase in the level of vitamin A in the majority of the population[12]. Observational studies have shown that 75% of people receive vitamin A above the recommended daily intake[12]. Although vitamin A deficiency is a major health problem, particularly in developing countries, and public health entrepreneurs have drawn much attention to this problem, hypervitaminosis A, which has persisted throughout human history, may be an increasing but ignored problem.

Metabolism

People cannot synthesize vitamin A and therefore, meet their needs from the carotene in plants or foods of animal origin or supplements[13].

After its oral intake, vitamin A is absorbed by the epithelial cells in the small intestine, esterified and chylomicrons are formed with different fatty acids. Intestinal epithelial cells process chylomicrons or release them into circulation. Finally, chylomicron residues are either transported to target tissues or hydrolyzed in the liver and stored as retinol[14]. Retinol is then released into the circulation, binds to retinol-binding proteins, and enters the cell through the retinol-binding protein receptor in the target tissues[15]. Retinol is then processed to form palmitate and other retinyl esters in the cell or hydrolyzed with alcohol dehydrogenases in all tissues to form retinaldehyde. Retinaldehyde that is only present in the target cells is re-hydrolyzed through the enzyme dehydrogenase and retinoic acid is formed [16]. Retinoic acid shows its efficacy by interacting with the retinoic acid receptor (RAR) and retinoid X receptor (RXR) which are the members of the nuclear receptor family[17].

Toxicology

Daily vitamin A requirement is met from plants (provitamin A), meat and dairy products and medicines (preformed vitamin A). Seventy-five percent of the population in Europe, America, and other industrialized countries meet their daily vitamin A requirement from milk, butter, margarine, fish oil, or multivitamins that contain preformed vitamin A. Preformed vitamin A is absorbed by the intestines at the rates of 70–90%[18,19]. Developing countries meet their daily vitamin A requirements from plants in the form of provitamin A. The absorption rate of provitamin A by the intestines is 20–50% [20,21]. Vitamin A of plant origin (preformed vitamin A) toxicity is almost impossible due to the low absorption rate and difficult conversion into vitamin A[22-24].

Even if adults are exposed to vitamin A up to 100 times the recommended daily intake and children are exposed to vitamin A up to 20 times the recommended daily intake within hours or days, this exposure is not as problematic as a chronic toxicity. For this reason, acute vitamin A toxicity is quite uncommon[18,25].

Acute retinoid toxicity presents with mucocutaneous symptoms and laboratory findings. The most common mucocutaneous symptoms are dryness of the lips, cheilitis, and dryness of the oral, ophthalmic and nasal mucosa. Drying of mucous membranes is assumed to be due to reduced sebum production, thinning of epidermal thickness, and alteration of the epidermal barrier. Other cutaneous effects include general skin dryness, itching, peeling of palms and soles, and fissuring of fingertips. A significant amount of hair loss can be seen[26].

The most common side effect of topical retinoids is epidermal irritation. Temporary hypopigmentation, hyperpigmentation, psoriasis Koebner phenomenon, ectropion, and allergic contact dermatitis are among other side effects [26]. The peeling from topical retinoids is due to the hyperproliferation of the epidermis mediated by retinoic acid receptor stimulation[27].

Chronic toxicity develops after exposure to a large amount of preformed vitamin A for months or years. Daily intake of more than 25,000 IU for six years or more than 100,000 IU for six months is considered to be toxic. However, the lowest dose required to elicit toxicity cannot be calculated precisely because it varies from person to person[28-30]. The daily dose of 15,000 IU used in the treatment of degenerative eye diseases has been reported to be well tolerated after 12 years of treatment[31].

Children are more sensitive to vitamin A than adults. Daily intake of 1,500 IU/kg is reported to cause toxicity[28,29,32]. Similarly, elderly people are at risk for vitamin A toxicity compared to adults. Although the underlying cause of this increased risk is unknown, it is thought to be due to the increased intestinal absorption and chylomicron clearance of vitamin A[33,34].

The effect of genetic factors on intoxication is not known since the individual tolerances of vitamin A derivatives have not been adequately studied[18,29,35].

Many organs can be affected by chronic retinoid toxicity. Formation of bone spurs and bone resorption leading to calcinosis and hypercalcemia can be listed among its effects on bone[36]. Long-term consumption of high levels of vitamin A can stimulate bone resorption and may result in osteoporosis and hip fractures[37]. Central nervous system effects include

headache, nausea, and vomiting. Despite being rare, pseudotumor cerebri syndrome developed secondary to vitamin A has been reported[38]. Studies in which bexarotene was used in the treatment of cutaneous T-cell lymphoma have reported that reversible hypothyroidism has occurred upon discontinuation of treatment[39]. Furthermore, impairment was observed in reversible renal function tests during etretinate treatment[40].

Teratogenicity

Teratogenicity is the most worrying side effect in systemic retinoid use. Excessive intake of vitamin A has been associated with teratogenicity in both human and animal studies. Congenital malformation has been reported in 1 out of 57 pregnant women who were exposed to vitamin A intake greater than 10,000 IU/day via supplements[41]. Teratogenic findings include craniofacial (cleft lips/palates), cardiac (transposition of the great vessels), thymic and central nervous system (microcephaly, hydrocephalus) abnormalities[42]. Isotretinoin is estimated to increase the risk of malformation 25-fold. Vitamin A is thought to have a toxic effect on neural crest cells, possibly affecting the axial pattern regulation in the embryo through the Hoxb1 expression of the homeobox gene[43]. Animal and human studies have shown that the risk of teratogenicity from topical retinoids is quite low[44]. No minimum retinoid dose to be taken during pregnancy has been established yet.

Laboratory

The most common systemic effect of retinoids is hypertriglyceridemia. Both triglyceride and cholesterol levels have been shown to increase in patients taking bexarotene, isotretinoin, etretinate, and acitretin[45,46]. Acute hemorrhagic pancreatitis and eruptive xanthoma may develop secondary to hypertriglyceridemia.

High triglyceride and cholesterol levels are the most common laboratory abnormalities in patients receiving isotretinoin. These levels, therefore, should be checked periodically in patients receiving isotretinoin[47].

Although liver enzyme elevations are typically mild and reversible, alanine aminotransferase and aspartate aminotransferase enzymes are recommended to be monitored on a periodic basis in patients receiving treatment[26].

Furthermore, both urine and serum pregnancy (beta-hCG) tests are recommended in female patients twice 30 days before the initiation of isotretinoin treatment. Pregnancy should be monitored during treatment and up to 30 days after treatment[26].

Radiological imaging may be considered for hyperostosis in patients taking high-dose isotretinoin for a long time.

The presence of pseudotumor cerebri should be examined if the patient has a continuous complaint of headache during treatment.

Thyroid function tests should be monitored for hypothyroidism in patients taking bexarotene[48].

If the use of etretinate is required in patients with kidney disease, renal functions should be monitored during the course of treatment[40].

Treatment

For the reduction of skin irritation developed due to topical retinoid use, it is necessary to reduce the volume and frequency of the drug used and to use emollients.

Eye drops containing artificial tears and methylcellulose may be used for dryness of the eyes.

In cases where the triglyceride levels increase due to oral retinoid use, dose reduction or discontinuation of the drug may be considered due to the risk of pancreatitis if the triglyceride level is above 800 mg/dL. In cases where there is less increase, treatment can be continued by monitoring the course of triglyceride levels[26].

The combined use of a statin or fibrate is recommended due to the risk of pancreatitis after retinoid-induced hyperlipidemia in patients receiving bexarotene[49].

In cases where pseudotumor cerebri syndrome develops, discontinuation of vitamin A-containing medication and acetazolamide treatment have been found to be effective in reducing intracranial pressure[39].

Conclusion

Since vitamin A is essential for life, it has been added to most of the convenience foods in developed countries. Just as the harmful effects of vitamin A deficiency are known and necessary steps are taken with food and medicine supplements to eliminate this deficiency, so the presence of toxicity, as well as health and well-being, should be monitored in individuals exposed to high doses of vitamin A. Furthermore, the distribution and storage of vitamin A should be examined and genetic studies should be performed to determine individual tolerances in the face of increased hypervitaminosis A problem.

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