Adverse events following administration of vitamin A supplements

The product

Vitamin A supplementation is recommended in countries were vitamin A deficiency (VAD) is a public health problem (WHO, 1996). In such situations, combining the administration of oral vitamin A with immunization services is a safe and effective strategy. Ideally, any programme linking vitamin A supplementation with immunization services should be part of an overall national plan for control of VAD which may include food fortification and dietary approaches.

Preparations of vitamin A can be supplied as oral form of retinyl palmitate, retinyl acetate or retinol, although retinyl palmitate is the form most widely available from commercial sources[1]. As long as the recommended dose is administered, the chemical form is not important. Typically[2], these preparations are diluted with high quality vegetable oil, usually peanut oil, with vitamin E included as an antioxidant and to promote absorption and retention of vitamin A by the body.

When given as a prophylactic with immunization, high-dose[3] vitamin A is usually presented in an oil-based solution (either in soft-gelatin capsules or liquid form) and given at a dosage and frequency according to age[4]:

- Children between 6-11 months: 100,000 IU orally, every 4-6 months;
- Children 12 months and older: 200,000 IU orally, every 4-6 months;
- Women within 6-8 weeks after delivery[5]: 200,000 IU orally, once during safe infertile time

For administration with immunization services, the above are the currently recommended age-specific dosage guidelines. For children, one high-dose supplement is sufficient to fully increase their stores of vitamin A for a period of 4-6 months. Ideally, children at risk of VAD should receive supplements at least twice a year (i.e. every 4-6 months). The minimum interval recommended between doses should not be less than one month.

The interval and frequency of dosage is different when vitamin A supplements are given to prevent VAD in pregnant women, or used for treatment of measles, xerophthalmia, and severe malnutrition (PEM) in the context of the Integrated Management of Child Illness (IMCI) programme (WHO/UNICEF/IVACG Taskforce, 1997).

The administration of excessive amounts of vitamin A can lead to toxicity, known as hypervitaminosis A. The amount required to cause toxicity will vary among individuals. The manifestations of toxicity will depend on the individual's age and hepatic function, and on the dose and duration of administration (Bauernfeind, 1980).

Worldwide, the incidence of hypervitaminosis A, is a very minor problem compared with the incidence and effects of vitamin A deficiency. An estimated 200 cases of hypervitaminosis A occurs annually, whereas an estimated 3 million pre-school children develop clinical vitamin A deficiency each year and are exposed to an increased risk of mortality and morbidity, with 250,000-500,000 of them becoming blind. (Bauernfeind, 1980; Beaton et al., 1994; Glasziou & Mackerras, 1993; WHO, 1995).

Mild adverse events

When the correct age-specific dose of vitamin A is given with immunization, mild side-effects or adverse events may be observed. However, they are rare and transient. Occasionally, some children experience loose stools, headache, irritability, fever, nausea, and vomiting. Depending on age and the dosage given, the excess rate of occurrence of these mild symptoms of intolerance has shown to

[1] Although the International Unit (IU) for vitamin A (which expresses biological activity and not chemical quantity) was official discontinued in 1954, vitamin A preparations are still conveniently labeled in IU with equivalence in mg or µg of retinol or its esters also indicated. A dose of 200,000 IU is equivalent to 110 mg of retinyl palmitate, 69 mg of retinyl acetate or 60 mg of retinol.

[2] Compressed powder tablets also exist but are more rarely used.

[3] For vitamin A supplementation "high dose" refers to amounts greater than 25,000 IU per dose.

[4] Children < 6 months of age, non breast-fed or breast-fed infants whose mothers have not received supplement vitamin a within 6-8 weeks of delivery, 50,000 IU orally.

[5] Vitamin A supplements can be given up to eight weeks after delivery if the mother is breast-feeding, or within six weeks if the mother is not breast-feeding.

be in the range of 1.5-7% (Florentino et al.,1990; West et al., 1992; Agoestina et al., 1994). These side-effects disappear in practically all children within 24-48 hours (Florentino et al.,1990; West et al., 1992; Agoestina et al., 1994).

It is of interest to note, documented beneficial reactions following administration of vitamin A have also been reported by mothers. These positive reactions included improved appetite, more sound sleep, and change in behavior (children became more active and lively) (Florentino et al.,1990).

In neonates and young infants under the age of 6 months, vitamin A supplementation has been associated with an increased incidence of transient bulging fontanelle that resolves itself within 24-72 hours (Florentino et al.,1990; West et al., 1992; Agoestina et al., 1994; Rahman et al., 1995; Baqui et al., 1995). Depending on age and dosage, the excess rate of occurrence has been found to be between 0.5-10% (West et al., 1992; Agoestina et al., 1994; de Francisco et al., 1993; WHO/CHD, 1998). Two studies have investigated the long-term developmental effects and found no long-term developmental abnormalities that result (Agoestina et al., 1994; van Dillen & de Francisco, 1996).

Clinical Toxicity Resulting From Overdose

Hypervitaminosis does not result from public health intervention programmes. Rather toxicity has been associated with the abuse of vitamin A supplements and with diets extremely high in preformed vitamin A (i.e. foods of animal origin). Toxic reactions provoked by large doses of vitamin A are well-known to occur following either intake of liver rich in vitamin A (e.g. polar bear, halibut or whale) or by excessive administration of vitamin A preparations (Miller & Hayes, 1982). It is useful to differentiate between the acute vitamin A-intoxication caused by short-term ingestion of excessive amounts of vitamin A and the chronic hypervitaminosis resulting from long-term intake of more moderate vitamin A doses:

Acute vitamin A toxicity (single ingestion of 25,000 IU per kg or more): Signs and symptoms may be delayed for 8 to 24 hours and include manifestations such as nausea, vomiting, diarrhea, changes in humour (irritability, drowsiness, dizziness, lethargy), increased intracranial pressure (headache, bulging of fontanelle, diplopia, papilloedema), skin changes (erythema, pruritus, desquamation). Peeling of skin around mouth may be observed from 1 to several days after ingestion and may spread to the rest of the body (Miller & Hayes, 1982; Bendich & Langseth, 1989; Hathcock et al., 1990; CPS, 1999; Parfitt, 1999).

Chronic vitamin A toxicity (excessive ingestion of 4,000 IU/kg daily for 6 to 15 months) may produce low-grade fever, headache, fatigue, irritability, anorexia and loss of weight, vomiting and other gastro-intestinal disturbances, hepatosplenomegaly, skin changes (yellowing, dryness, sensitivity to sunlight, alopecia cracking and bleeding lips, brittle nails, hair loss), anaemia, hypercalcemia, subcutaneous swelling, nocturia and pains in the bones and joints. Symptoms of chronic toxicity may also include raised intracranial pressure (papilloedema mimicking brain tumors, tinnitus, visual disturbances which may be severe), blindness and painful swelling of the long bones. Increased plasma concentrations of vitamin A occur but do not necessarily correlate with toxicity (Miller & Hayes, 1982; Bendich & Langseth, 1989; Hathcock et al., 1990; CPS, 1999; Parfitt, 1999).

Harmful Effects During Pregnancy: Excessive or high-dose vitamin A should be avoided during pregnancy because of potential teratogenic effects to the fetus (birth abnormalities or birth defects). Where vitamin A deficiency is endemic, current recommendations advise that the safe vitamin A supplementation of pregnant women should not exceed 10,000 IU per day, or 25,000 IU per week (WHO, 1998). During the safe infertile period 6-8 weeks post-partum[5] depending on breastfeeding status, it is safe to give women one high-dose supplement of vitamin A. This raises the content of vitamin A in the breastmilk and benefits the breastfeeding infant under the age of 6 months.

Prevention: Avoid overdoses by following the recommended age-specific dosage schedule as appropriate for prevention or treatment .

Treatment: For an acute overdose, refer to hospital, preferably the intensive care unit. For chronic ingestions, discontinue vitamin A and refer to a health unit for examination. Toxicity is slowly reversible but may persist for several weeks.

References

Agoestina T, Humphrey JH, Taylor GA, et al. Safety of one 52 µmol (50000 IU) oral dose of vitamin A administered to neonates. *Bull WHO* 1994; 72;859-68.

Baqui AH, de Francisco A, Arifeen SE, Siddique AK, Sack RB. Bulging fontanelle after supplementation with 25 000 IU of vitamin A in infancy using immunization contacts. *Acta Paediatr* 1995; 84:863-6.

Bauernfeind JC. The safe use of vitamin A: a report of the International Vitamin A Consultative Group (IVACG). Washington DC: The Nutrition Foundation. 1980.

Beaton GH et al. Vitamin A supplementation and child morbidity and mortality in developing countries. *Food and Nutrition Bull* 1994;15(4):282-9.

Bendich A, Langseth L. Safety of vitamin A. *Am J Clin Nutr* 1989;49:358-71.

Compendium of Pharmaceuticals and Specialities (CPS), 34ed Canadian Pharmacists Association. 1999: Toronto.

Florentino RF, Tanchoco CC, Ramos AC et al. Tolerance of preschoolers to two dosage strengths of vitamin A preparation. *Am J Clin Nutr* 1990;52:694-700.

de Francisco A, Chakhaborty J, Chowdhury HR, et al . Acute toxicity of vitamin A given with vaccines in infancy. *Lancet* 1993;342:526-7.

Glasziou PP Mackenas DEM. Vitamin supplementation in infectious disease: a meta-analysis. *Brit Med J* 1993;306:366-70.

Hathcock JN et al. Evaluation of vitamin A toxicity. *Am J Clin Nutr* 1990;52:183-202.

Miller DR, Hayes KC “Vitamin excess and toxicity” in Hathcock JN (ed). Nutritional Toxicology. Vol. 1 New York: Academic Press 1982:81-133.

Parfitt K (ed) Martindale: the complete drug reference. Pharmaceutical Press. 1999. London.

Rahman MM et al. Administration of 25,000 IU vitamin A doses at routine immunization in young infants. *Eur J Clin Nutr* 1995;49:439-45.

Van Dillen J, de Francisco A. Long-term effect of vitamin A with vaccines. *Lancet* 1996;347:1705.

West KP, Khatry SK, LeClerq SC, et al. Tolerance of young infants to a single, large dose of vitamin A: a randomized community trial in Nepal. *Bull WHO* 1992;70:733-9.

WHO. Indicators for assessing vitamin A deficiency and their application in monitoring and evaluating intervention programmes. WHO/NUT/96.10. WHO. Geneva. 1996.
WHO. Global Prevalence of Vitamin A Deficiency: MDIS Working Paper #2. WHO:Geneva.1995.

WHO/CHD Immunization-linked vitamin A supplementation study group. Randomized trial to assess benefits and safety of vitamin A supplementation linked to immunization in early infancy. *Lancet* 1998;352:1257-63.

WHO/UNICEF/IVACG Taskforce. Vitamin A supplements: A guide to their use in the treatment and prevention of vitamin A deficiency and xerophthalmia (2nd ed). World Health Organization, Geneva: 1997.