Absorption, distribution, metabolism and excretion - Statement on the effects of excess Vitamin A on maternal health

In this guide

Absorption, distribution, metabolism and excretion

28 EFSA (2015) state that preformed vitamin A is efficiently absorbed in humans (70 – 90 % in children). The absorption of β-carotene appears to be highly variable (5 – 65 %), depending on food- and diet-related factors, genetic characteristics and the health status of the subject. Carazo et al. (2021), in their review of retinoid kinetics, found that all-trans RA had low bioavailability after oral administration and its high affinity to plasma proteins led to it being transported in the blood bound to albumin. Isotretinoin had a bioavailability of around 20 % and was also extensively bound to albumin in plasma. Tissue concentrations were usually lower than that in plasma. Etretinate and acitretin (etretin) had a bioavailability of approximately 50%.

29 Goodman et al. (1984) studied the human plasma kinetics of both retinol and its metabolites, retinyl palmitate and retinyl stearate, following oral administration of retinol. Retinoid plasma kinetics were studied on the first day of treatment, at weeks 2 and 4, and every 2-3 months thereafter as long as the patient remained on therapy. Plasma retinol concentration did not change significantly up to 24 hours after a single oral dose of retinol ($p > 0.05$). The plasma concentration of retinyl palmitate and retinyl stearate markedly increased with a mean time to peak plasma concentration of 4.3 ± 0.7 hours. Retinyl palmitate disappearance from the plasma had an initial phase half-life of 2.2 ± 0.9 hours. The terminal phase half-life appeared prolonged and could not be accurately determined. Retinyl stearate was detected in the plasma of all patients with plasma concentrations paralleling and ranging from 20 % to 40 % of those of retinyl palmitate. With prolonged retinol administration, peak plasma retinyl palmitate concentrations increased with both increasing retinol dose (p 0.001) and increasing duration of treatment ($p = 0.001$).

30 Buss et al. (1994) dosed 10 healthy female volunteers with 5 different doses of vitamin A and studied the effects on plasma vitamin A and its metabolites. The single supplements were provided as either retinyl palmitate (15,000 and 45,000 mg RE) or an equivalent dose in fried calf liver. Blood was collected at intervals over the first 12 hours of dosing and thereafter for 6 days. The results showed substantial increases in plasma retinyl palmitate, 13-cis- and all-trans-RA, and 13-cis and all-trans-4-oxo RA. Women who received the supplement had significantly higher concentrations of retinoids than those who

received the liver, possibly because the food matrix had ameliorated the absorption rate or altered the circulating forms of vitamin A. However, plasma retinol changed only slightly, which supported the view that this method was not an appropriate means by which to evaluate a vitamin A supplementation trial.

31 Hartmann et al. (2005) evaluated plasma concentration-time curves of retinyl esters, retinol and their metabolites at increasing doses of vitamin A in 3 groups (12 per group) of non-pregnant women aged 18 - 40 years. received once daily oral doses of vitamin A palmitate up to 30,000 IU (9,000 mg RE)/day over 21 days. The area under the plasma concentration-time curve (AUC (24 hours)) served as indicator for exposure. The AUC (24 hours) of retinyl esters increased linearly with dose. Retinol concentrations were unaffected. All-trans RA exhibited a diurnal-like concentration-time profile (maximum blood concentration (Cmax) at 3 hours; minimum blood concentration (Cmin) at 8 hours), concentrations decreasing below pre-dose levels at 5 hours and regaining pre-dose levels at 16 hours. The maximum temporary increase in exposure was 33 % (single dose) and 19 % (repeated doses) above baseline, but the AUC (24h) remained unaltered. The AUC (24h) increased linearly with dose for 13-cis RA and 13-cis-4-oxo RA. Repeated doses caused a 25 % increase in exposure with the highest vitamin A intake. Accumulation of 13-cis-4-oxo RA at 30,000 IU (9,000 mg RE)/day doubled compared to the 4,000 IU (1,200 mgRE)/day intake.

32 Spiegler et al. (2012) reviewed the disposition of vitamin A in animals. Nearly all retinyl esters in the diet are hydrolysed to retinol in the intestinal lumen. Retinol is absorbed by intestinal epithelial cells, where it is re-esterified to long-chain fatty acids, primarily by the enzyme lecithin:retinol acyltransferase (LRAT), which is widely expressed in tissues, and is incorporated into chylomicra, which circulate in the intestinal lymph before moving into the general circulation. Once in the general circulation, lipoprotein lipase (LPL), which is bound to the luminal surface of the vascular endothelium, catalyses the lipolysis of triglycerides to generate free fatty acids and chylomicron remnants. Chylomicron remnants are cleared mainly by the liver, but extrahepatic uptake of the remnants may be important in the delivery of vitamin A to some tissues such as the mammary tissue, bone marrow, adipose tissue, and spleen. Retinyl esters in serum are normally below 0.2 mmol/l in the fasting state but they increase significantly after a large influx of vitamin A, such as occurs after a vitamin A–rich meal.

33 In the liver, retinyl esters are again hydrolysed to retinol to be transferred to hepatic stellate cells and then re-esterified by LRAT for storage.

Alternatively, retinol can bind to retinol-binding protein (RBP) and be secreted into the bloodstream as a 1:1 molar complex with the serum protein transthyretin. RBP thus functions to mobilise hepatic retinoid stores and deliver retinol to peripheral tissues and developing embryos. In fasting conditions, retinol-RBP accounts for approximately 95 – 99 % of all serum retinoids. Upon vitamin A intake, the concentration of retinoids in chylomicrons and chylomicron remnants can greatly exceed that of plasma retinol. Blood levels of retinol-RBP in both humans and animals are tightly controlled, except in extreme cases of insufficient intake of vitamin A, protein, calories and zinc; or in response to hormonal factors, stress; and in certain disease states.

34 Spiegler et al. (2012) also stated that the mechanisms that regulate the secretion of the complex retinol-RBP from the liver have yet to be fully elucidated. Even in the fasting state there are low concentrations of RE that are associated with circulating lipoproteins (in VLDL and LDL) and small amounts of circulating RA bound to albumin. Within cells, retinol is reversibly oxidized to retinal by members of the alcohol dehydrogenases, medium-chain dehydrogenase/reductases, retinol dehydrogenases and short-chain dehydrogenase/reductases. Retinal is further oxidized to RA by retinal dehydrogenases. Several intracellular binding proteins for retinol, retinal and RA have been identified and characterised, including cellular retinol-binding proteins I, II and III, cellular retinaldehyde binding protein and cellular RA-binding proteins I and II. Each of these retinoid-binding proteins has a distinct expression pattern and plays a specific role in vitamin A transport and metabolism.

35 The metabolism of pre-formed vitamin A in well-nourished people has been studied by several research groups. To control vitamin A deficiency in developing countries, large therapeutic doses are administered to women and children, who are often undernourished. Nevertheless, little attention has been given to the short-term kinetics (i.e., after absorption but before storage) of a large dose of vitamin A or to the short- and long-term effects of such a dose given to lactating women on serum and breast milk concentrations of retinol and its metabolites. Moreover, appropriate dosing regimens have not been systematically evaluated to ascertain the quantitative improvement in vitamin A status of the women and children who receive these supplements. The authors concluded that further research was needed to ascertain the areas of the world in which subclinical toxicity exists and to evaluate the effects on overall health and well-being (Spiegler et al, 2012).

36 Nau (1995), in review, found that activation (oxidation of RAs: hydrolysis of glycoconjugates) and deactivation reactions (isomerisation from trans- into cis- configuration; b-glucuronidation) appeared to relate to retinoid-induced teratogenesis. The b-glucuronides of RAs showed poor placental transfer and prolonged presence in maternal animals. The observed low teratogenic potency of 13-cis-RA in the rat and mouse may be explained by limited placental transfer, rapid plasma clearance and extensive metabolic detoxification; conversely, the high teratogenic activity of this retinoid in the monkey (and possibly humans) could be the result of more extensive placental transfer, slower plasma clearance and extensive metabolism to the active 4-oxo-metabolite. There is evidence that non-retinoid compounds such as antiepileptic agents may exert some of their teratogenicity via alteration of endogenous retinoid levels.

37 Söderlund et al. (2005) measured serum concentrations of all-trans RA and 13-cis RA in newborns and their mothers and in women in the first trimester of pregnancy. The newborns had significantly lower retinol concentrations (1.0 m mol/L) than did their mothers (1.7 mmol/L; p = 0.013). Serum all-trans RA was also significantly lower in the newborns (3.4 nmol/L) than in their mothers (5.8 nmol/L; p = 0.008). Serum concentrations of 13-cis RA were significantly lower in the newborns (2.0 nmol/L) than in their mothers (2.6 nmol/L; p = 0.005). The serum concentrations of retinol did not accurately reflect the concentrations of the biologically active derivative all-trans RA. Pregnant women and those in childbirth had significantly lower serum concentrations of retinol than control subjects. The concentration of all-trans RA was higher in the parturient mothers than in the control subjects, but concentrations of 13-cis RA were lower than in the controls or pregnant women. No difference was observed in the concentrations of all-trans and 13-cis RA between pregnant women and control women.

38 Brazzell and Colburn (1982) studied the pharmacokinetics of orally administered isotretinoin and etretinate. The pharmacokinetic profile of isotretinoin exhibited linear pharmacokinetics. The drug was rapidly absorbed, highly bound to plasma protein, and metabolized to 4-oxo-isotretinoin. The apparent half-lives of elimination of isotretinoin and 4-oxo-isotretinoin following the oral administration of isotretinoin were 10 to 20 hours and 24 to 29 hours, respectively. Steady-state pharmacokinetic profiles in patients were consistent with the single-dose pharmacokinetics in healthy subjects. Oral etretinate underwent first-pass biodegradation to its corresponding carboxylic acid, which appeared rapidly in the circulation, often earlier than the parent drug, and its plasma concentration was usually comparable to, or greater than, that of the

parent drug. The apparent elimination rates of drug and metabolite were similar (6 to 13 hours) following a single dose, suggesting that metabolite elimination may be formation-rate limited. During multiple dosing of etretinate, a very slow terminal elimination phase was observed which was not seen after single-dose administration. The prolonged half-life of this phase suggested accumulation in a deep tissue compartment. Differences between the two retinoids were thought to reflect their differing physicochemical properties.

39 In addition to retinoid intake via the oral route, women of childbearing age may also be exposed via dermal application of medication for the treatment of skin conditions such as acne. Although not dietary, topical treatments have the potential to contribute to overall exposure to vitamin A and its derivatives, therefore, topical absorption data are provided below.

40 Willhite et al. (1990) found that a single application of 17 µg/kg or 8.7 mg/kg of radiolabelled all-trans-[10,11-^{3}H2]-RA dissolved in acetone to shaved dorsal hamster skin was rapidly absorbed and showed a dose-dependent rate of elimination. An equation describing a two-compartment open model with a very brief lag time and first-order uptake and elimination was used to describe the central plasma compartment kinetics. Unchanged all-trans-RA represented up to 4 % of the total circulating radioactivity. Peak circulating concentrations of parent all-trans-RA were less than those observed after an equivalent oral dose, but prolonged absorption from the skin contributed to high total bioavailability of retinoid applied topically.

41 Latriano et al. (1997) dosed 28 subjects in four treatment groups with a single dermal dose of tritiated tretinoin (all-trans RA) in a 0.05 % formulation of emollient cream or cream alone or with 28 days of repeated nonradioactive doses. In a second study, subjects received single topical doses of tritiated tretinoin cream alone (n = 5) or after 1 year of nonradioactive applications (n = 4). Plasma, urine, and faecal samples were analysed to determine absorption. Plasma samples in the first study were also analysed for concentrations of tretinoin and its metabolites. Percutaneous absorption of tretinoin was approximately 2 % after a single dose and after 28 days of daily application. In patients receiving long-term therapy (>1 year), absorption averaged 1.1 %. Mean plasma concentrations of tretinoin after 28 days of treatment with either tretinoin emollient cream or tretinoin cream were not significantly changed when compared with the corresponding endogenous concentrations before treatment. Neither single dose nor long-term treatment with topical tretinoin formulations appeared to affect the endogenous levels of tretinoin or its metabolites.

42 Nohynek et al. (2005) investigated the effect of topical vitamin A on human endogenous plasma levels of Vitamin A and its metabolites. Two groups of 14 female volunteers of child-bearing age were kept on a vitamin A-poor diet and treated topically for 21 days with creams containing 0.30 % retinol or 0.55 % retinyl palmitate on approximately 3,000 cm^2 of their body surface area. This gave a total dose of approximately 30,000 IU (9,000 mg RE) vitamin A/subject/day. After a 12-day wash-out period, the study groups received single oral doses of 5,600 or 16,800 mg retinyl palmitate (RP), (corresponding to 3,000 or 9,000 mg RE), the maximal EU allowance during pregnancy or three-times higher, respectively. Blood samples were collected over 24 hours on study days -3 (pre-study), 1, 21 (first and last days of topical treatment) and 34 (oral administration) at 0, 1, 2, 4, 6, 8, 12, 14-16 hours and 24 hours after treatment. Plasma concentrations of retinol, retinyl palmitate, retinol oleate and retinol stearate , 9-cis-, 13-cis-, all-trans- (AT), 13-cis-4-oxo- or AT-4-oxo-RAs were analysed. With the exception of transient mild (retinyl palmitate-group) to moderate (retinol-group) local irritation at the treatment sites, no adverse local or systemic effects were noted. On days 1 or 21 of topical treatment, no changes were observed in individual, or group mean plasma Cmax, AUC (0 - 24 hours) or other pharmacokinetic parameters of retinol, retinyl esters or RAs relative to pre-study data. In contrast, single oral doses of retinyl palmitate at 3,000 or 9,000 mg RE produced dose-related and sustained increases in Cmax and AUC (0 - 24 hours) values of plasma retinyl palmitate, retinol oleate, retinal stearate, 13-cis- and 13-cis-4-oxo-RAs, as well as a transient increase in all-trans-RA. Topical exposure to retinol- or retinyl ester-containing cosmetic creams at 9,000 mg RE /day and maximal use concentrations were therefore found to not affect plasma levels of retinol, retinyl esters or RAs, whereas single oral doses at 3,000 or 9,000 mg RE produced significant increases in plasma concentrations of retinyl esters and RAs.

43 Retinol metabolites are excreted mainly in the urine (38 to 60 %), but also in faeces (18 to 37 %) and breath (18 to 30 %) in humans after 400 days on a vitamin A-deficient diet. Retinol is metabolised in the liver to numerous products, some of which are conjugated with glucuronic acid or taurine for excretion in bile and the amount of retinol metabolites excreted in bile increases as the liver retinol exceeds a critical concentration. Excretion of labelled retinol metabolites in bile of rats fed increasing amounts of retinol traced by [^{3}H]-retinyl acetate was constant when hepatic retinol concentrations were low (≤ 32 µg/g (112 nmol/g)) and increased rapidly (by eight-fold) as liver retinol concentration increased, up to a plateau at hepatic retinol concentration ≥ 140 µg/g (490 nmol/g) This increased biliary excretion may serve as a protective mechanism for reducing the risk of

excess storage of vitamin A. (EFSA, 2015)