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Acitretin Excretion into Human Breast Milk

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Retinoid transfer into breast milk was studied in a psoriatic woman receiving oral acitretin at a dosage of 40 mg once daily. Concentrations of the parent compound and its main metabolite, 13-*cis* acitretin, were measured in serum and mature milk during the initial nine days of therapy, using reverse-phase high performance liquid chromatography. At steady-state, trace amounts of the drug and metabolite (30–40 ng/ml) appeared in breast milk corresponding to a milk/serum concentration ratio of about 0.18. Acitretin was almost exclusively distributed in the fatty layers of the milk. Although the estimated amount of the drug consumed by a suckling infant would correspond to only 1.5% of the maternal dose, the toxic potential of acitretin justifies its avoidance in breast-feeding women. *Key words: Retinoids; Vitamin A; Etretin; Lactation.*

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Acitretin represents one of the synthetic vitamin A derivatives (retinoids) recently introduced for the oral treatment of severe keratinizing skin disorders. This drug, formerly named etretin, was developed as a result of the clinical and pharmacokinetic experiences with etretinate, the corresponding ethyl ester analogue. Acitretin, which is the predominant and pharmacologically active metabolite of etretinate in man, has the advantage over its precursor of being rapidly eliminated from plasma (1) and of lacking affinity to adipose tissues (2). Nevertheless, both compounds are considered to have a similar toxic potential including liver and lipid alterations, bone toxicity, and severe congenital malformations (3). Acitretin should, therefore, be strictly avoided during pregnancy with a safety margin of 2 months following cessation of the drug. Whether or not acitretin can be used after childbirth by a lactating mother, without risk of adverse effects on a suckling infant, is not known.

This study was aimed at investigating the possible passage of acitretin from maternal blood to mature breast milk.

MATERIALS AND METHODS

Patient

A 31-year-old woman presented 8 months post-partum with extensive plaque psoriasis and acral pustulosis. Her general health was good and laboratory values of kidney and liver functions were normal. Topical antipsoriatic regimens had been used without success and, as the patient did not wish to undergo methotrexate therapy, oral administration of acitretin at a dosage of 0.65 mg/kg/day (4 × 10 mg capsules ingested with water after breakfast) was initiated.

Before starting acitretin therapy the patient discontinued nursing her 8-month-old child and, following informed consent, agreed to collect her breast milk throughout the study period.

Sampling

Milk was collected immediately before acitretin administration and then twice daily for nine days. The breasts were emptied at 9 am (immediately prior to daily dose administration) and 9 pm, using an electrically-operated pump. The volume of milk at each sampling ranged from 40–120 ml with a pH of 6.3 – 6.6.

Venous blood samples were obtained at 0, 0.5, 1, 3, 6, 12, and 24 h following the first acitretin dose. A similar series of samples were taken at the end of the study.

All specimens were handled under dim light and stored at −60°C until analysis.

Retinoid analysis

Acitretin (trimethylmethoxyphenyl retinoic acid, Ro 10–1670), 13-*cis* acitretin (Ro 13–7652) and natural vitamin A (retinol) were measured in hydrolyzed specimens using a previously reported HPLC-technique (4) with small modifications (5). Briefly, 100 µl of the specimen (serum or vigorously mixed whole milk) was added to a centrifuge tube containing a mixture of ethanolic potassium hydroxide and two internal standards; Ro 12–0586 (an aromatic analogue of retinol for quantitation of vitamin A) and all-*trans* retinoic acid (for quantitation of acitretin and its 13-*cis* metabolite). Following heating the mixture to 80°C for 15 min, the neutral retinoids were extracted with hexane and, after adjustment of the aqueous phase to pH 5, the acidic retinoids were subsequently extracted with hexane. The two separate layers were evaporated under nitrogen at 40°C, redissolved in methanol, and then separated at room temperature on a Nucleosil 5µ ODS-column (Macherey-

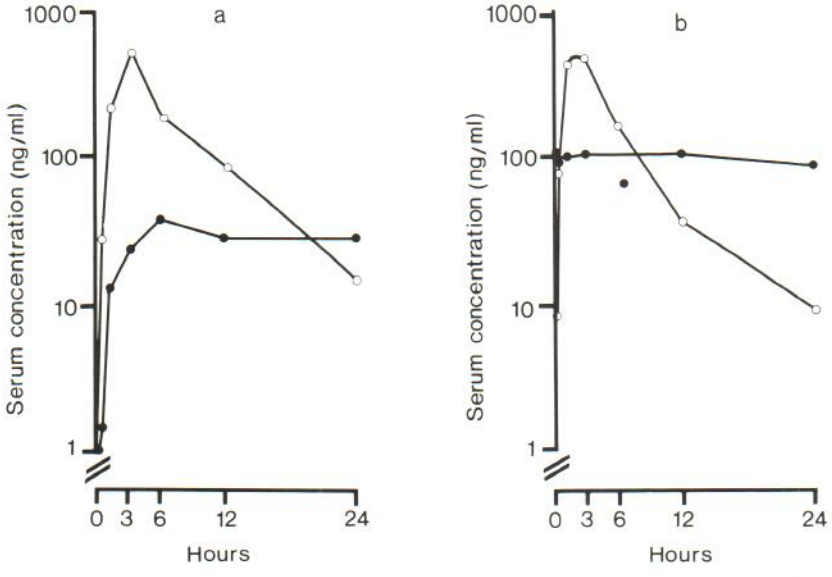

Fig. 1. Serum concentrations of acitretin (○) and its 13-*cis* metabolite (●) following (a): the initial oral dose and, (b): nine days' therapy of 40 mg acitretin daily.

Nagel & Co, Düren, West Germany) using acetonitrile: water:acetic acid (82:18:0.05, v/v) as eluent (1.2 ml/min).

Peak identification was based on retention time and peak absorbance ratio at two fixed wavelengths (326 and 360 nm). Quantitation was performed by measuring the peak height ratio (the sum of all-*trans* and 13-*cis* isomer) versus the mass ratio for the retinoid of interest relative to the internal standard. Linear calibration curves were obtained by analyzing 1-ml aliquots of pretherapy milk samples (depleted of vitamin A by UV-exposure) supplemented with known amounts of retinoids.

This method gives a high recovery (85–90% extraction efficiency of spiked retinoids) but produces 15–25% artificial *cis-trans* isomerizations of the acidic retinoids. Hence, sample hydrolysis was applied only for quantitation of vitamin A and the total amount of the drug (e.g. acitretin plus 13-*cis* acitretin).

The proportion of all-*trans* to 13-*cis* isomers of acitretin were determined from unhydrolyzed, non-heated samples (250–500 µl) extracted with methyl-butyl ether/ethanol instead of using hexane/water (5). The relative abundance of acitretin and its 13-*cis* metabolite was calculated from the chromatograms by measuring the relative height ratios of the two compounds. The artificial *cis-trans* interconversions of acitretin by using this technique were 3% or less.

The distribution of the synthetic retinoids in milk was determined following separation of fat from skim milk by centrifugation at 4000 × g for 30 min.

RESULTS

The time course for the appearance of acitretin in serum after the initial oral dose, and following multiple doses for nine days, respectively, are shown in Fig. 1. In both instances peak acitretin concentrations of 0.5–0.6 µg/ml were attained in 1.5–3 h and

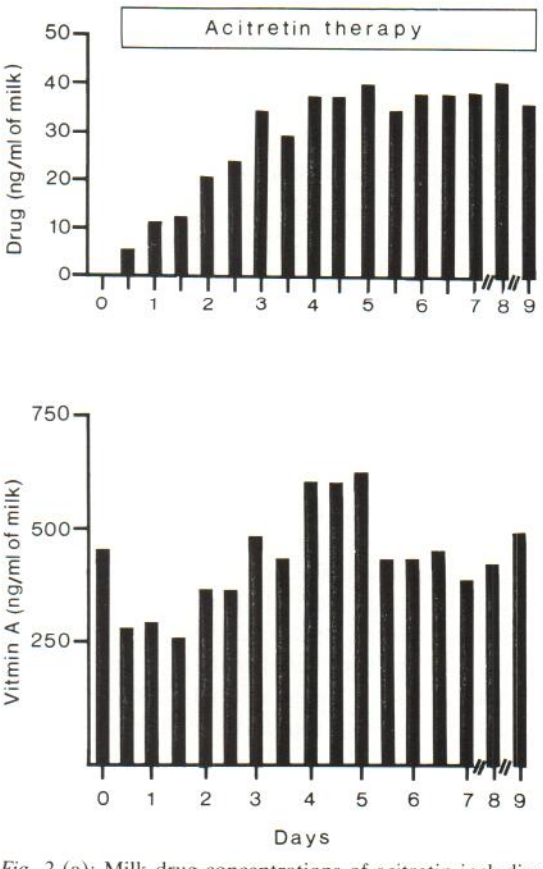

Fig. 2 (a): Milk drug concentrations of acitretin including its 13-*cis* metabolite during the first nine days of acitretin therapy, and (b): the corresponding concentrations of vitamin A (retinol plus its esters).

the areas under the concentration-time curves (AUC) were 1.1–1.2 $\mu g \cdot ml^{-1} \cdot h$. The apparent terminal half-time of the unchanged drug after the initial drug administration ($t_{1/2}\beta$ 4.6 h) was somewhat prolonged during repetetive dosing.

Serum concentrations of the *cis*-metabolite following the first acitretin dose were just above the limit of assay (5 ng/ml), but significantly higher levels were attained after multiple drug administrations (Fig. 1b). Hence the observed concentration-time profile of the drug in our case was comparable to the pharmacokinetic behaviour of oral acitretin reported previously in patients with severe psoriasis (6,7).

Traces of the drug were detected in the first milk sample collected 12 h after the initial acitretin dose. In the next 4–5 days increasing amounts of the retinoid (parent compound plus main metabolite) were found in the milk attaining steady-state levels of 30–40 ng/ml whole milk (Fig. 2a).

The parent compound formed a major part (55–80%) of the total drug content in the evening milk (collected 10–12 h after a previous dose), whereas in pre-dose morning milk (22–24 h after a previous dose) the 13-*cis* metabolite was the predominant (56–85%) drug component.

Like natural vitamin A, acitretin was mainly distributed in milk fat. At steady-state the lipid fraction contained 96.5 % of the total drug (and 87.0% of total vitamin A e.g. retinol plus retinyl ester), corresponding to a drug concentration of about 750 ng/g milk fat and 1.3 ng/ml skim milk.

The vitamin A concentrations in the serum (data not shown) and in the milk (Fig. 2b) did not change significantly during acitretin therapy.

DISCUSSION

The transfer from blood to breast milk of acitretin and its main metabolite is not an unexpected finding considering the lipid-soluble nature and relatively low molecular weight of these compounds. When administered at an ordinary dosage level the proportion of the drug excreted into the milk, however, was fairly low. Assuming an average drug concentration in milk of 35 ng/ml, the milk:serum concentration ratio of the drug (acitretin plus 13-*cis* acitretin) was approximately 0.18. The restricted passage of the drug into milk is presumably due to its strong binding to plasma albumin and lipoproteins (8), and to "ion-trapping" since acitretin is a weak acid and hence more ionized at pH 7.4 in serum than in milk at pH 6.3 – 6.6.

As a result of their lipophilicity the retinoid compounds were almost exclusively distributed in the fatty layers of the milk. Because the lipid content and the fat composition of human milk varies considerably from woman to woman and at different times during lactation (9) major variations in drug excretion are likely to occur due to these factors.

Comparative pharmacokinetic data on the possible passage into human milk of etretinate, the precursor of acitretin and the aromatic retinoid most extensively prescribed in clinical practise, are not available. However, because of its relatively higher lipid-solubility as compared to acitretin, it seems probable that etretinate would pass more readily into the mammary gland.

Several drugs modify the composition of human breast milk. Bearing in mind the structural similarities between acitretin and retinol it might be anticipated that acitretin therapy would affect the physiological mechanism of the transfer of vitamin A into breast milk. The results obtained in this patient, however, indicate that no such interaction takes place. This might be explained by separate routes of entry of the two compounds into the milk. Retinol, circulating in plasma bound to a specific retinol-binding protein (RBP), presumably enters the milk by a carrier-mediated transport via cell-surface receptors for RBP (10). In contrast, acitretin is non-specifically bound to plasma albumin and lipoproteins, and hence more likely to gain access to milk by passive diffusion through the membranes that separate blood from milk.

In general, breast-feeding the infant before drug administration to the mother will minimize drug transfer to the infant. In this study, however, the total drug level did not appear to display any diurnal variations although the relative abundance of the two components differed significantly. The latter feature probably reflects the concentration-time profile in serum of the parent drug and its main metabolite (Fig. 1).

Although the dose of acitretin delivered by way of breast milk would be small, adverse effects to a suckling infant cannot be discounted. The maximum quantity of the drug be ingested in 800 ml of milk a day would be about 32 μg, e.g. 8 μg/kg/day for a 4-kg infant, or 1.5% of the maternal dose level. Whether or not this exposure of a newborn to acitretin may cause adverse effects cannot be estimated since the

oral bioavailability and clearance of the drug in infants are not known. In general, the pharmacokinetic handling differs markedly between adults and neonates, with the latter having a generally lower drug clearance. Immature renal and hepatic systems for drug elimination and metabolism may lead to relatively high serum drug levels while, in contrast, poor absorption from the neonate's gastrointestinal tract may have the opposite effect. However, because of the theoretical risk of undesirable effects on a suckling infant it seems advisable to recommend that the administration of acitretin to a mother is a contraindication to breast-feeding.

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