

Review Article

Acitretin in dermatology – A review

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Introduction

Acitretin is a weak acid ($pka = 5$) and is highly lipophilic, with a partition coefficient ($\log p$) of approximately 6. Acitretin is normally administered by oral route with food.¹ Following administration in this way, the compound is relatively rapidly and extensively absorbed from the intestinal tract. The half-life of absorption is 0.2-1.7h. At least 93% of a dose is absorbed over 18 days, the majority fairly rapidly. Taking acitretin with food results in increased and more consistent absorption. As it is highly lipophilic and penetrates readily into body tissues. Protein binding of acitretin exceeds 99%. In animal studies, acitretin passed the placental barrier in quantities sufficient to produce fetal malformation.²⁻⁴ Due to its lipophilic nature, it can be assumed that acitretin passes into breast milk in considerable quantities.

Chemistry

Acitretin is a yellow-to greenish crystalline powder which may have faint odor. It is made by chemical synthesis. It is only very slightly soluble in water but at pH 7.5 (the pH of intestinal contents), it is slightly soluble. Chemical name is (4- Methoxy-2, 3, 6-trimethyl phenyl)-3, 7- dimethyl-2, 4, 6, 8-nonatetraenoic acid (Figure-1)

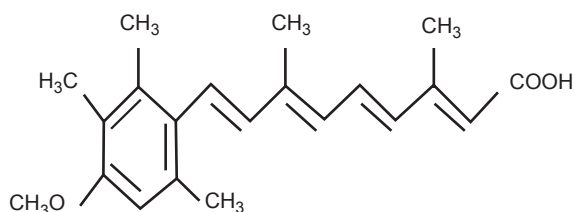


Figure-1: Chemical composition of Acitretin

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Pharmacology

Retinoids by acting upon nuclear receptor affect epidermal cell growth and differentiation as well as sebaceous gland activity, and also have anti-inflammatory properties. Retinoid X receptor(RXR) and retinoic receptor(RAR) activate gene transcription by binding to DNA as homodimers or as heterodimers with Vitamin D, thyroid hormone or peroxisome- proliferator-activated receptors etc. Skin mainly expresses RAR gamma and RXR alpha receptors. There are many consequences including repression of Interleukin-2 formation as a result of these nuclear events.

Clinical Pharmacology

Acitretin has been much less studied than its esterified parent compound etretinate but as the latter is rapidly hydrolyzed in vivo to acitretin it is highly likely that the data relating to etretinate are also valid for acitretin. In Psoriasis; Where epidermopoiesis is accelerated and Keratinocyte maturation is down regulated retinoids produce a normalizing effect. The suppression of terminal differentiation is probably of prime importance in the therapeutic effect of retinoids in psoriasis. Clinical studies have confirmed that in psoriasis and dyskeratosis, acitretin brings about a normalization of epidermal cell proliferation, differentiation and keratinization in doses at which the side effects are generally tolerable. The effect of Acitretin is purely symptomatic; the mechanism of action is still largely unknown.

Metabolism

Acitretin is extensively metabolized, presumably in the liver. No unchanged acitretin or 13-cis-metabolite is excreted in urine. The metabolites of acitretin are excreted to approximately equal extents in the urine feces. A small amount of acitretin is converted by esterification into etretinate(the ethyl ester) which is much more lipid soluble than the parent compound and persists for much longer in the body, particularly in fatty tissue.⁵⁻⁷

Indications of Acitretine

1. Psoriasis
2. Disorders of Keratinization e.g. Ichthyosis, Keratodermas, Darier's disease
3. Prevention of cutaneous malignancy in solar damage
4. Genetic Syndromes predisposing to skin Cancer

5. Other dermatoses, e.g. DLE, Lichen Sclerosus, Granuloma anulare

Contraindications of Acitretin

Acitretin is absolutely contraindicated in pregnancy. Pregnancy is also contraindicated in the two year period after stopping therapy with Acitretin. Relative contraindications include hepatitis and liver disease concomitant other diseases e.g. serious retinal disorder, diabetes, hyperlipidemia, pancreatitis, inflammatory bowel disease.

Adverse events during clinical trials

Very common: Over 80% of patients experienced hypervitaminosis A e.g. dry lips. 40-80% of patients experienced dry mucous membranes of mouth and nose. 10-40% of patients experienced nose bleed, erythema, pruritus, dermatitis, hair loss.⁸⁻¹⁰

Common: Up to 10% of patients experienced development of rhagades, blistering of the skin, and change in hair structure.

Rare: Conjunctivitis, ulcer of the Cornea, myalgia, nausea, vomiting, diarrhea, hepatitis and jaundice.

Investigations

In addition to a possible increase in liver function values, an elevation of blood lipids has also been observed during treatment with Acitretin.¹¹

The following changes in laboratory values occurred in patients during clinical trials - elevation of triglycerides, total cholesterol, SGPT, creatine phosphokinase, SGOT, alkaline phosphatase, direct bilirubin, lactate dehydrogenase and uric acid; and lowering of HDL cholesterol.

Drug Interactions

Potential hazardous interactions have been found with the following drugs.

1. Oral Contraceptives
2. Glyburide
3. Alcohol
4. Dexamethasone
5. Methotrexate
6. Tetracyclines
7. Vitamin A
8. Warferinin
9. Cyclosporine

Discussion

Acitretin is highly teratogenic and hence contraindicated in Women of Childbearing potentials unless pregnancy is reliably prevented 4 weeks before, during and 2 years after the completion of therapy.¹² Clinical evidence has shown that etretinate can be formed with concurrent ingestion of acitretin and alcohol. Women of childbearing age must therefore not consume alcohol (in drink, food or medicine) during treatment with acitretine and for 2 months after cessation of therapy.¹³ Contraceptive measures and pregnancy tests must also be taken for 2 years after completion of acitretin treatment.

In view of possible effects on Liver function this must be monitored regularly during treatment. Hepatic function should be checked before starting treatment with Acitretin every 1-2wks for the first 2 months after commencement and then every 3 months during treatment.¹⁴ If abnormal results are obtained wkly checks should be monitored. Serum cholesterol and Serum triglycerides (fasting values) must be monitored, especially if high risk patients (disturbance of lipid metabolism, diabetes mellitus, obesity, alcoholism) and during long-term treatment. The effect of UV light is enhanced by retinoid therapy, therefore patients should avoid excessive exposure to Sunlight and unsupervised use of Sun Lamps.

Acitretin has moderate influence on the ability to drive and use Machines.¹⁵ Decreased night vision has been reported with acitretin therapy. The high risk groups of Acitretin therapy are as: Neonates, Children, pregnant women, elderly.

Retinol (vitamin A) is known to be essential for normal epitheliating growth and differentiation, through the mode of this effect is not yet established. Both retinol and retinoic acid are capable of reversing hyperkeratotic Skin changes.

However, these effects are generally only obtained at dosages associated with considerable local or systemic toxicity. Acitretin the active ingredient of Acitretin, is a systemic analogue of retinoic acid and the main metabolite of etretinate, which has been used with success for a number of years in the treatment of Psoriasis and disorders of Keratinisation.

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