CONTINUING MEDICAL EDUCATION

ORAL RETINOIDS IN DERMATOLOGY

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Oral retinoids are the natural or synthetic analogues of vitamin A acid. These represent one of the major dermatologic achievements in recent years, next only to corticosteroids. The concept of dermatologic therapy has undergone a revolutionary change with their spectacular success in a number of chronic dermatoses for which the treatment till now had been either empirical or totally unsatisfactory. These are valuable in the management of congenital disorders of keratinisation such as ichthyoses, Darier's disease, PRP and porokeratoses; intractable pustular psoriasis, nodulo-cystic acne, erosive mucosal lichen planus and several other diseases. Their role in the prevention of epithelial malignancy is of special importance. No wonder, these drugs may constitute an effective substitution therapy for oral corticosteroids and cytostatics in the near future.

Several excellent reviews, symposia, reports and comments have been published on oral retinoids in the Western literature.[1-6] However, this subject has not received much attention in our country, in spite of the fact that these drugs are likely to invade the Indian pharmaceutical market in the near future.

Historical :

Vitamin A, the parent compound of retinoids, was first discovered in 1909 as an essential fat-soluble vitamin from egg yolk.[7] Despite its widespread use over the past four decades, this drug has not proved of much success in skin disorders. Three major forms of vitamin A, viz, vitamin A aldehyde (retinal), vitamin A alcohol (retinol) and vitamin A acid (retinoic acid or tretinoin), represent its biological activity in the body. Tretinoin, the fore-runner of modern oral retinoids, was first synthesized in 1946, and because of serious systemic toxicity, its use is restricted to topical application only in some skin disorders. Further screening efforts to discover more effective and safer compounds have so far led to three clinically important retinoids, isotretinoin (Ro 4-3780), etretinate (Ro 10-9359) and arotinoid (Ro 13-6298). At present, none of these three drugs are available in India.

Isotretinoin : This first generation oral retinoid was first synthesized in 1955, and has undergone extensive clinical trials between 1972 and 1979. Chemically, it is 13-cis isomer of tretinoin. Currently, it is available commercially for the treatment of nodulo-cystic acne in USA under the trade name Accutane(R).

Etretinate : This synthetic oral aromatic retinoid represents the second generation retinoids. It is available under the trade name Tigason(R) in Europe since 1981, for the treatment of disorders of keratinisation. Chemically, it is trimethoxyphenyl analogue of retinoic acid ethyl ester.

Arotinoid : It is a third generation synthetic oral aromatic retinoid and also the most recent in the series. It differs considerably in its chemical structure from etretinate, and is still under experimental clinical evaluation, although it is presumed to be the most effective and least toxic retinoids tested so far.[3,8,9]

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Pharmacology of oral retinoids

Isotretinoin and etretinate are administered orally in the dose of 0.5 to 2 mg/kg/day in two divided doses. These are readily absorbed from the gut and undergo extensive enterohepatic cycling before entering into the systemic circulation.[10] Peak blood levels with etretinate occur in 4 hours. Its metabolic products, retinoyl-beta-glucuronide and retino-taurine, are excreted in the bile and urine respectively. The drug is stored in the body tissues to the toxic proportions during long term therapy mainly in the liver and to a lesser extent in the skin.[11] Traces of this drug could be detected in the body even 110 days after cessation of therapy.[7] Peak blood levels with isotretinoin occur in two to three hours after ingestion, followed by a sharp decrease later. The half-life period was estimated to be 10 to 20 hours. Unlike etretinate, this drug is not much stored in the body. Both these retinoids are transported to the skin by binding to the plasma proteins, especially the albumin and lipoproteins.

Clinical Indications of Oral Retinoids

Oral retinoids were found extremely useful in the management of several disorders hitherto unresponsive to conventional therapy, because of their broad spectrum activity such as anti-inflammatory, antikeratinising, antineoplastic, hormonomimetic and immunomodulatory effects. Their efficacy is being further evaluated in a large number of clinical conditions with encouraging results.

Congenital Disorders of Keratinisation : Several studies around the world have confirmed the effectiveness of oral retinoids in almost all types of ichthyoses including the lamellar, x-linked, and epidermolytic hyperkeratosis for which the treatment available at present is thoroughly disappointing.[1,12,13] Etretinate was found to be superior to isotretinoin in this regard. Initially, a dose of 1-2 mg/kg/day orally of either of these drugs is needed to produce clinical resolution of the lesions, followed by a long term maintenance therapy with a smaller dose to avoid relapse. In spite of the fact that satisfactory clinical improvement occurs after retinoid therapy, characteristic histopathologic abnormalities still persist. A small percentage of these patients may actually discontinue the drug because of marked shedding of the horny material leaving behind extensive painful raw areas on the skin.[14] Similar gratifying results were obtained with etretinate in other congenital keratotic disorders such as Darier's disease, PRP, erythrokeratoderma variabilis, all types of porokeratoses especially the linear varient, pachyonychia congenita, verrucous epidermal nevus, etc.[2] The exact mechanism as to how the defective keratinisation is taken care of by oral retinoids is not clear, though it is believed that these drugs inhibit or regulate the proliferation and differentiation of the keratinocytes.[9]

Psoriasis : Undoubtedly, the retinoids constitute an effective new therapeutic modality in the management of recalcitrant psoriasis. Many studies are available proving their efficacy, especially of the aromatic compound etretinate in generalised pustular psoriasis, psoriatic erythroderma and arthropathy.[9,15,16] Further, these were found to be useful adjuvants to potentiate the effect of other agents such as UVA, UVB, PUVA, dithranol and topical corticosteroids in patients who are not responding to either treatment alone.[2] The dose and mode of administration is similar to that used for congenital keratotic disorders.

Nodulo-cystic Acne : Multicentric clinical trials conducted in USA, West Germany and England revealed that isotretinoin is extremely useful in severe uncontrollable inflammatory nodulo-cystic acne that failed to respond to conventional therapy.[17-19] The drug is administered in the dose of 0.5 to 1.5 mg/kg/day for a period of atleast 3 to 4 months. A second course of the drug in a few patients with residual lesions cleared the picture with no further

evidence of relapses during the period of two years under observation. Although surprising, the exact reason for the apparent lack of beneficial effect in acne with etretinate is not clear.

The effectiveness of isotretinoin in acne appears to be due mainly to its effect on the physiology of sebaceous gland resulting in a decrease of the sebum excretion rate and ductal hyperkeratinisation. Nevertheless, the antiinflammatory and immunomodulatory effects of the drug also contribute to a certain extent. Efforts to produce an effective topical retinoid including the latest motretinid (methyl methoxy analogue of retinoic acid, Ro 11-1430) in acne have not yet been successful.

Miscellaneous Disorders : The efficacy of oral retinoids is currently under investigation in a number of other chronic dermatoses including rosacea, Gram negative folliculitis, mucosal and disseminated lichen planus, multiple plantar warts, Reiter's disease, subcorneal pustular dermatosis, chronic bullous disorders, scleroderma, LSA, DLE, Kyrle's disease and sarcoidosis etc.[1,2,4]

Oral Retinoids and Tumor Prevention

The value of vitamin A and synthetic retinoids for the prevention of epithelial cancer was suggested by the epidemiologic and laboratory data. Several clinical studies are under progress, and the available evidence[20-23] points out that these drugs in combination with BCG afford protection against some premalignant and malignant conditions such as basal cell epithelioma, multiple solar keratoses, epidermodysplasia verruciformis, keratoacanthoma, T-cell lymphoma, mycosis fungoides and malignant melanoma. The antineoplastic effect of these drugs appears to be due to the inhibition of ornithine decarboxylase induction which is an essential prerequisite for the initiation of complex events concerned in carcinogenesis.[24]

Mode of Action of Oral Retinoids

Oral retinoids exert their beneficial effect through more than one mechanism, somewhat similar to the oral corticosteroids. Their ability to regulate or inhibit the keratinocyte proliferation and differentiation is responsible for their beneficial effect in disorders of keratinisation, although the exact mechanism how this occurs is not clear.[2,9]

These promote synthesis of extracellular glycosaminoglycans which are important for the cohesive property of epidermal cells, accounting for their efficacy in bullous disorders.[6] Oral retinoids exert cytostatic effect also due to their inhibitory effect on ornithine decarboxylase activity and hence promote tumor prevention.[24] The anti-inflammatory activity of these drugs is obvious from their clinical effect on severe inflammatory nodulo-cystic acne and the early disappearance of neutrophils (the main component in the inflammatory process) in the histopathologic sections of psoriatic patients after retinoid therapy. Further proof in this direction is evident from the fact that these drugs, except etretinate, markedly inhibit the production of superoxide anion and lysozyme release. Several disorders that show improvement with oral retinoid therapy such as nodulo-cystic acne, exfoliative psoriasis, epithelial malignancy etc are known to have an immunologic component, lending support to the concept of immunomodulatory effect of oral retinoids.

Toxicology of Oral Retinoids

Systemic side effects with oral retinoids are much less serious in comparison to vitamin A. Both isotretinoin and etretinate exhibit similar adverse effects although their relative frequency and severity differs. These may be classified under minor and major effects. The minor effects are more frequently encountered, and include predominantly, in the order of frequency, cheilitis, desquamation of palms and soles and central face, dryness of the nose and mouth, ocular irritation, blepharo-conjunctivitis, transient thinning of hair, paronychia, skin rashes such as urticaria, petechiae, photosensitivity,

hypo or hyper pigmentation and exuberant granulation tissue formation over the healing lesions of acne. In addition, there may be mild gastro-intestinal disturbances, headache, irritability and loss of weight. Children on etretinate therapy have been noted to have skeletal abnormalities such as calcification of spinal ligaments, hyperostosis of the vertebrae frequently referred to as diffuse idiopathic skeletal hyperostosis (DISH syndrome).[26] Similar changes have been noted in the epiphyses of long bones resulting in growth abnormalities.

Specific laboratory abnormalities while the patient is on long term retinoid therapy include, dose-dependent and reversible elevation of liver enzymes, mainly SGOT, SGPT and alkaline phosphatase and serum lipids especially triglycerides.

More serious but less common side effects which definitely need cessation of retinoid therapy include pseudomotor cerebri (benign intracranial hypertension), corneal opacities, inflammatory bowel disease and teratological abnormalities (hydrocephaly, microcephaly, anomalies of the pinna and micro-ophthalmia). No definite evidence of carcinogenicity or mutagenicity in humans is available after treatment with oral retinoids.[27]

Contraindications to Oral Retinoid Therapy

In view of their potential teratogenicity, these drugs should be avoided in pregnancy as well as those intending to become pregnant during therapy, and also in lactating mothers since its excretion in the breast milk is not known. Patients with obesity, alcoholism, history of coronary disease and abnormalities of the lipid metabolism should better not receive oral retinoids since elevation of serum triglycerides and cholesterol fractions have been noted during prolonged retinoid therapy. Similarly, these drugs should not be given in patients with a previous episode of pseudomotor cerebri, corneal opacities, inflammatory bowel disease and hyperostosis of the bones.

Precautions Necessary during Retinoid Therapy

Females in the child-bearing age group should be strongly advised strict contraception while on treatment with retinoids, atleast a month prior to therapy and 3 months (isotretinoin) and 6 months (etretinate) after discontinuation of therapy. Adequate clinical evaluation of the ocular, skeletal and neurologic systems is important before starting retinoids. Similarly, laboratory studies comprising complete haemogram, urinalysis, LFT, serum lipid profiles, radiologic skeletal survey, pregnancy tests in females should be undertaken before treatment and during follow-up. Patients receiving oral retinoids should not be given vitamin A to avoid addition of the toxic effects. The efficacy of retinoids is altered if given in concurrence with other drugs like beta-blockers, chloroquine, aspirin or high doses of tetracycline.

References

1. Ruiz-Maldonado R and Tamayo L : Retinoids in keratinizing diseases and acne, Paed Clin N Amer, 1983; 30 : 721-734.
2. Orfanos CE : Oral retinoids—Present status, Brit J Dermatol, 1980; 103 : 473-481.
3. Jones DH : Retinoids for skin disorders, Practitioner, 1984; 228 : 1043-1048.
4. Retinoid symposium (September 20-22nd, 1984, Geneva), Dermatologica, 1984; 169 : 217-260.
5. Marks R : Synthetic retinoids, in : Recent Advances in Dermatology, No. 6, Editors, Rook A and Maibach HI : Churchill Livinstone, Edinburgh, 1983; p 237-264.
6. Pochi PE : Oral retinoids in dermatology (Special report), Arch Dermatol, 1982; 118 : 57-61.
7. Paravicini U, Camenzind M, Gower M et al : Multiple-dose pharmacokinetics of Ro 10-1670, the main metabolite of Tigason, Dermatologica, 1984; 169 : 240 (abstract).
8. Fritsch P, Rauschmeir W and Zussner G : Arotinoid in the treatment of psoriatic arthropathy, Dermatologica, 1984; 169 : 250 (abstract).

9. Staaler R, Marcelo CL, Voorhees JJ et al : Effect of a new retinoid, Arotinoid (Ro 13-6298) on in vitro keratinocyte proliferation and differentiation, Acta Dermato-Venereol, 1984; 64 : 405-411.
10. Brazzel RK and Collburn WA : Pharmacokinetics of the retinoids; isotretinoin and etretinate, J Amer Acad Dermatol, 1982; 6 : 643-651.
11. Vahlquist A : Distribution of natural and synthetic retinoids in the skin, Dermatologica, 1984; 169 : 230 (abstract).
12. Windhorst DB : The use of isotretinoin in disorders of keratinization, J Amer Acad Dermatol, 1982; 6 : 708-770.
13. Baden HP, Buxman MM, Weinstein GD et al : Treatment of ichthyosis with isotretinoin, J Amer Acad Dermatol, 1982; 6 : 716-720.
14. Marks R, Finlay A and Holt PJA : Severe disorders of keratinization—Effects of treatment with Tigason (etretinate), Brit J Dermatol, 1980; 104 : 667-673.
15. Gorez G and Orfanos CE : Systemic treatment of psoriasis with a new aromatic compound, Dermatologica, 1978; 187 : 38-44.
16. Ehmann CW and Voorhees JJ : International studies of the efficacy of etretinate in the treatment of psoriasis, J Amer Acad Dermatol, 1981; 6 : 692-696.
17. Peck GL, olse TG, Noder FW et al : Prolonged remissions of cystic and conglobate acne with 13-cis-retinoic acid, N Eng J Med, 1979; 300 : 329-333.
18. Plewig G, Gollnick H, Meigel W et al : (Quoted by reference 17).
19. Jones H, Blanc D and Cunliffe WJ : 13-cis-retinoic acid and acne, Lancet, 1980; 2 : 1048-1049.
20. Peck GL, Gross EG, Butkus D et al : Chemoprevention of basal cell carcinoma with isotretinoin, J Amer Acad Dermatol, 1982; 6 : 815-823.
21. Moriarty M, Dunn J, Darragh A et al : Etretinate in treatment of actinic keratosis, Lancet, 1982; 1 : 364-365.
22. Haydey RR, Reed ML and Dzubav LM : Treatment of keratoacanthomas with oral 13-cis-retinoic acid, N Eng J Med, 1980; 303 : 560-564.
23. Meyskens FL : Studies of retinoids in the prevention and treatment of cancer, J Amer Acad Dermatol, 1982; 6 : 824-827.
24. Boutwell RK : Retinoids and inhibition of ornithine decarboxylase, J Amer Acad Dermatol, 1982; 6 : 796-798.
25. Windhorst DB and Nigra T : General toxicology of oral retinoids, J Amer Acad Dermatol, 1982; 6 : 675-682.
26. Sillevis Smith JH and De Mari FR : A serious side effect of etretinate (Tigason), Clin Exp J Dermatol, 1984; 9 : 554-556.
27. Kamm JK : Toxicology, carcinogenicity and teratogenicity of some orally administered retinoids, J Amer Acad Dermatol, 1982; 6 : 652-659.