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A Brief Review on Isotretinoin

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***Abstract*: The aim of this review article is to bring awareness about the isotretinoin [B-cis-retinoic acid] which is the teratogenic medication used in the treatment of nodular acne and other skin related problems, this article focuses on the composition, mechanism of action, abnormalities, adverse effects, contradictions and its teratogenic effect. This review article concludes that isotrtinoin should not be taken or prescribed to avoid the reproductive toxicity or fetal anomalies, because this shows its action on cell proliferation and apoptosis.**

***Keywords*: teratogenic, fetal anomalies, isotretinoin, nodular acne.**

1. Introduction

Isotretinoin is an oral prescription medicine that treats severe acne by affecting the sebaceous glands.

The medicine was licensed by the US Food and Drug Administration (FDA) in 1982 for the treatment of severe, resistant, nodular acne that has failed to respond to standard treatment, including systemic antibiotics [4].

During the last few decades, it has been clear that medicines given to mothers during pregnancy may have negative consequences for the fetus's physical development. Medication usage during pregnancy and lactation is sometimes unavoidable, but patient and healthcare provider understanding on fetus and breastfed infant safety is inadequate. Drug treatment during pregnancy is especially dangerous because of the risk of teratogenic consequences and physiologic changes in the mother as a result of the pregnancy.

The pharmacokinetics of drugs taken is affected by pregnant physiology, and certain pharmaceuticals can reach the fetus and cause harm. [1]-[3]

2. Isotretinoin

Isotretinoin is only prescribed when other acne treatments have failed. It's also used to treat a variety of other skin problems and cancers. Moderate acne, cutaneous T-cell lymphomas, neuroblastoma, and the prevention of squamous cell carcinoma in high-risk patients are among the non-FDA-approved indications. Rosacea, folliculitis, and pyoderma faciale have all been treated with isotretinoin. Isotretinoin is an oral retinoid, which is a type of medication. Retinoid is a synthetic version of vitamin A that is used to treat a variety of skin problems. Also, malignancies of the blood

No previous acne treatment targeted all four pathogenesis variables (hyperkeratinization, sebum production, Cutibacterium acnes growth, and inflammation) before isotretinoin. [5,6] Other acne therapies that aren't isotretinoin are frequently used in conjunction to target many components of acne aetiology at the same time. Isotretinoin is an oral retinoid that has been prescribed as a first-line treatment for severe nodular acne in the United States for nearly four decades.

Oral isotretinoin is used for the treatment of moderate acne that is resistant to other treatments, as well as the management of acne that causes physical scars, psychosocial discomfort, or both. When isotretinoin is taken without a high-fat meal, the efficiency of the treatment is reduced. Although it is recommended that patients take traditional oral isotretinoin with a meal, many do not. Adolescents and young adults, who make up the majority of acne patients, have inconsistencies in their eating habits. Variability in gastrointestinal absorption following oral isotretinoin administration can be caused by this irregular diet. Furthermore, during the 15- to 20-

week course of therapy, very few patients consume a high-fat, high-calorie meal with each dose of isotretinoin twice a day. [7]-[12]

3. Qualitative and Quantitative Composition

Capsules of ISOTROIN-10
Each soft gelatin capsule contains the following ingredients:
IP Isotretinoin (10 mg)
Capsule shell colour that has been approved (-)
Capsules of ISOTROIN-20
Each soft gelatin capsule contains the following ingredients:
IP Isotretinoin (20 mg)
Capsule shell colour that has been approved (-)[13]

4. Clinical Benefit of Oral Isotretinoin

Depending on the amount given, most people who receive oral isotretinoin will be acne-free within 4–6 months of treatment.

According to recent clinical data, the long-term cure rate may be lower than previously anticipated. [14]-[15]

Isotretinoin is increasingly used to treat people with less severe acne, which could explain this. The initial cohorts of patients had severe disease and were less concerned about the

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reappearance of a few spots, but these cases respond exceedingly well and hope to remain clear. Furthermore, some of the early reported 'cures' could have been due to people growing out of their acne after receiving initial treatments much later in the course of their disease. Younger people are more likely to relapse than older patients, according to data. Isotretinoin is now approved to treat severe acne as a second-line treatment in cases where other treatments, such as antibiotics, have failed. [16] Isotretinoin has been administered as a first-line treatment for severe acne, acne with poor prognostic characteristics, and some acne-related disorders by skilled clinicians for many years.

Isotretinoin prescribing has recently been regulated by a European directive. The directive's goals were to,

1) Ensure that generic prescribing was coordinated and administered effectively across the European Union, and
2) Reduce the risk of adverse effects, such as pregnancy.

5. Pharmacokinetics

A. Absorption

Isotretinoin's oral absorption is improved when administered with a high-fat meal due to its high lipophilicity. Food increased the time to peak concentration (Tmax), which could be due to a longer absorption phase. As a result, ISOTROIN should be taken with food at all times. There is no change in the pharmacokinetics of isotretinoin between patients with nodular acne and healthy people with normal skin, according to clinical investigations.

B. Distribution

Isotretinoin binds to plasma proteins, chiefly albumin, to the tune of 99.9%.

C. Metabolism

At least three metabolites of isotretinoin have been discovered in human plasma after oral administration: 4-oxo-isotretinoin, retinoic acid (tretinoin), and 4-oxo-retinoic acid (4-oxo-tretinoin). Retinoic acid and 13-cis-retinoic acid are geometric isomers that can interconvert in a reversible manner. When one isomer is administered, the other is produced. Isotretinoin can also be oxidised irreversibly to 4-oxo-isotretinoin, which is the geometric isomer of 4-oxo-tretinoin.

Concurrent administration of food increased the extent of development of all metabolites in plasma after a single 80 mg oral dosage of isotretinoin to 74 healthy adult volunteers as compared to the extent of formation under fasted conditions.

All of these metabolites have retinoid activity that is higher than the parent isotretinoin in various in vitro models. The clinical importance of these models, however, remains unknown. The steady state exposure of patients to 4-oxo-isotretinoin under fasting and fed settings was approximately 3.4 times higher than that of isotretinoin after multiple oral dosage administration of isotretinoin to adult cystic acne patients (age 18).

The principal cytochrome (CY) P450 isoforms implicated in isotretinoin metabolism, according to in vitro studies, are 2C8, 2C9, 3A4, and 2B6. Isotretinoin and its metabolites are then converted into conjugates, which are eliminated in the urine and faeces.

D. Elimination

The half-life of 14C-activity in blood was 90 hours after oral administration of an 80 mg dose of 14C-isotretinoin as a liquid suspension. Isotretinoin and its metabolites, as well as any conjugates, are eliminated in nearly equal proportions in the faeces and urine (total of 65 percent to 83 percent).

Under fed settings, the mean S.D. elimination half-lives (T1/2) of isotretinoin and 4-oxo-isotretinoin were 18 hours and 38 hours, respectively, after a single 80 mg oral dosage of isotretinoin to 74 healthy adult participants. The half-lives of 4-oxo-isotretinoin and 4-oxo-isotretinoin were 21.0 8.2 hours and 24.0 5.3 hours, respectively. In patients with cystic acne, the observed accumulation ratios of isotretinoin ranged from 0.90 to 5.43 after single and multiple doses. [13]

6. Mechanism of Action

Isotretinoin is a systemic retinoid that is taken by mouth. Isotretinoin is an effective acne treatment at a pharmacologic dose of 0.5 to 1.0 mg/kg per day. Isotretinoin reduces sebaceous gland function and keratinization at pharmacologic levels, while the exact mechanism of action is uncertain. Isotretinoin has been proven to reduce cell proliferation and induce differentiation in neuroblastoma (off-label use). [17], [18]

Isotretinoin is the only therapy that impacts on all of the major aetiological factors implicated in acne. It achieves this remarkable efficacy by influencing cell-cycle progression, cellular differentiation, cell survival and apoptosis. Unlike tretinoin (all-trans retinoic acid), isotretinoin has little or no ability to bind to cellular retinol-binding proteins or retinoic acid nuclear receptors (RARs and RXRs) but may act as a pro-drug that is converted intracellularly to metabolites that are agonists for RAR and RXR nuclear receptors. Isotretinoin induces apoptosis in sebocytes and these effects are independent of RAR receptor activation suggesting that it is sebaceous gland involution resulting from oral isotretinoin which leads to reduced sebum production. [19]

7. Adverse Effects

The most prevalent dose-dependent side effect found in roughly 90% of people receiving isotretinoin is cheilitis or dry lips. Patients who take isotretinoin frequently experience dry skin (xerosis), dry mouth (xerostomia), dry nose, and sun sensitivity. Before starting the drug, patients should learn about sun protection, skin moisturisers, and barriers. To avoid skin irritation and scarring, patients should avoid any skin resurfacing operations (waxing, dermabrasion, laser therapy) during treatment and for at least six months after treatment.

Isotretinoin medication can potentially cause hypertriglyceridemia and an increase in the erythrocyte sedimentation rate. To monitor these common side effects, frequent laboratory monitoring is recommended during the induction period and during isotretinoin treatment. [20]

8. Contradictions

Lactating women: This medication is not known to be excreted in human milk. ISOTROIN should not be given to nursing mothers because of the risk of side effects.

Paediatricpatients: The use of isotretinoin in children under the age of 12 has not been researched. The use of ISOTROIN for the treatment of severe recalcitrant nodular acne in children aged 12 to 17 years should be carefully considered, particularly in those with a known metabolic or structural bone problem.

Geriatric patients: Isotretinoin clinical trials did not involve a large enough number of patients aged 65 and up to assess whether they respond differently than younger subjects. Although no variations in responses have been found in recorded clinical experience between elderly and younger patients, the effects of ageing may be predicted to exacerbate some of the dangers associated with isotretinoin medication.

Effects on ability to drive and use medicine: Isotretinoin has the potential to impair one's ability to drive and operate machinery.

A number of cases of reduced night vision have been reported after isotretinoin therapy, with some cases persisting following treatment. Because the onset was sudden in some individuals, patients should be informed of the risk and encouraged to use caution when driving or operating machinery.

Very rarely, drowsiness, dizziness, and vision abnormalities have been reported. Patients should be advised that if they have these symptoms, they should not drive, operate machinery, or engage in any other activity that could put them or others in danger. [13]

9. Conclusion

The adaptability of isotretinoin can be vividly visualized through this conversation. Apart from controlling nodular acne, isotrtinoin has been shown to be beneficial in a variety of other dermatological disorders. I, like any other medicine, has a toxicity profile attached to it. As a result, if a patient is administered isotrtinoin, it is obligatory for all practitioners to follow the monitoring recommendations. It also used for the treatment of cancer and other skin disorders.

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