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Oral Isotretinoin and Hearing Loss

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Abstract

Isotretinoin is the only available drug that affects all stages of acne pathogenesis and the success of the treatment with oral isotretinoin seems to greatly improve the social functioning of acne patients. Side effects of isotretinoin are well known, but ototoxicity is rarely reported, and its mechanism is not clear. Therefore, this study was designed to address the possible ototoxic effects of oral Isotretinoin on the inner ears of acne patients. Assessment of the selected sample of patients included full history taking as regards hearing loss, tinnitus, vertigo as well as acne vulgaris. General examination, otorhinolaryngological and dermatological examination were performed. Lipid profile, pure-tone audiometry (PTA) as well as auditory brainstem response (ABR) were conducted both prior to and after oral isotretinoin intake. There was significant difference between serum blood lipids, ABR latencies as well as PTA thresholds at 3000Hz before and after treatment with oral isotretinoin and highly significant difference between PTA thresholds at 4000,6000 and 8000Hz before and after treatment. Serum blood lipids seemed to be a good predictor of the adverse effects of oral isotretinoin on human inner ears.

Keywords: Oral Isotretinoin, Hearing Loss

Full length article **Corresponding Author*, e-mail: mustafa.mwm.aud@gmail.com Doi # https://doi.org/10.62877/56-IJCBS-24-25-19-56

1. Introduction

Isotretinoin, 13-cis retinoic acid, is a derivative of vitamin A and falls under the category of retinoids. It is an oral prescription medication primarily utilized to address severe cases of acne. The drug functions by impacting sebaceous glands, aiming to treat severe and resistant forms of acne, particularly nodular acne that has not responded to conventional treatments, including systemic antibiotics. It was approved by the US Food and Drug Administration (FDA) in 1982 for this purpose [1]. The compound 13-cis retinoic acid was initially studied in the 1960s at Roche Laboratories in Switzerland by Werner Bollag as a treatment for skin cancer. Experiments conducted in 1971 indicated that the compound might not be effective for cancer treatment, but surprisingly, it demonstrated potential in managing acne. However, it was also discovered that the compound could result in birth defects. Given the historical context involving thalidomide, which caused birth defects, Roche abandoned the product. In 1979, a study showcased the drug's effectiveness in treating cystic and conglobate acne in fourteen patients, with thirteen experiencing complete clearing of their condition. Clinical trials were meticulously designed to exclude women who were pregnant or might become pregnant. Roche's application for isotretinoin's approval for acne treatment included data demonstrating its potential to cause birth defects in rabbits. The FDA granted approval to the application in 1982 [2].

2. Mechanism of action of isotretinoin

Isotretinoin is the only available drug that affects all stages of acne pathogenesis as it reduces sebum production, causes shrinking of the sebaceous glands, reduces follicular occlusion, inhibits bacterial growth (antimicrobial effect on Cutibacterium acnes) and has anti-inflammatory properties. In neuroblastoma (off-label use), isotretinoin has been demonstrated to decrease cell proliferation and induce differentiation [3].

3. Uses of isotretinoin

Its comprehensive effects on various aspects of acne pathogenesis make it a potent option for treating severe acne and moderate-severe acne that does not respond to conventional treatments. Isotretinoin is also effective for other follicular conditions, such as: Rosacea, Seborrhoea, Hidradenitis suppurativa and Scalp folliculitis. Additionally, It is also prescribed off-label for various other skin diseases, including: Discoid lupus erythematosus, Granuloma

annulare, Grover disease, Sarcoidosis and Extensive actinic keratosis [3, 4]. Isotretinoin's uses extend to the prevention of cutaneous squamous cell carcinoma. It has also been used as an adjuvant in neuroblastoma and cutaneous T-cell lymphomas [5].

4. Administration and dosage of isotretinoin

Isotretinoin is administered orally in a capsule form. The drug is characterized by low bioavailability and high lipophilicity. To enhance oral absorption, it is advisable to take the drug with a meal. It should be taken with a full glass of water to avoid esophageal irritation. Initial dosing of isotretinoin often starts at 0.5 mg/kg per day, and the dose can be gradually increased to a dose of 1.0 mg/kg per day based on the patient's tolerance. Typical therapy requires a 12- to 20-week course of daily isotretinoin administration to achieve complete prolonged remission of the disease. Some prescribers have targeted a total cumulative dose of 120–140 mg/kg, with the aim of reducing relapse, but the evidence for this remains controversial [6]. The individual dose prescribed by the dermatologist is influenced by : prescriber preference , patient body weight, the specific condition being treated, the severity of the skin condition ,response to treatment , other treatment used at the same time and side effects experienced [5].

5. Precautions when taking isotretinoin

There are several important considerations and precautions associated with the use of isotretinoin: Isotretinoin should not be used during pregnancy or breastfeeding due to the risk of severe birth defects. Commercial pilots may be subject to flying restrictions if they take isotretinoin , due to the potential side effects. High dose isotretinoin in very young children has been linked to premature epiphyseal closure, resulting in shorter stature (this is not seen in the low dose used for the treatment of acne) [4]. Prior to prescribing isotretinoin , screening for depression, suicidal ideation, past suicide attempts, and aggressive and/or violent behaviors is important. Instances of depression and psychosis have been reported in patients taking isotretinoin [6].

6. Contraindications to isotretinoin

- Isotretinoin is contraindicated in pregnancy (category X drug under the previous FDA system) .To prescribe and receive isotretinoin, the Food and Drug Administration requires prescribers and patients to register with the iPLEDGE program. iPLEDGE ensures the fulfillment of appropriate requirements before dispensing isotretinoin to prevent the use of this medication during pregnancy. These requirements include negative pregnancy tests and the use of birth control before and while taking isotretinoin [7].
- Blood donation is prohibited for both males and females while on isotretinoin treatment and for one month after discontinuing treatment due to the risk of embryo-fetal toxicity.
- liver or kidney disease.
- high blood fats and diabetes.
- hypersensitivity to any of its components, including vitamin A and preservatives within the gel capsule [8].

7. Drug interactions with isotretinoin

Care should be taken with the following medications [9]:

Vitamin-A (retinoic acid): There is a cumulative effect of vitamin A and its derivatives, which could lead to severe side effects. Beta-carotene (provitamin-A) is permitted.

Tetracyclines (including doxycycline, minocycline): the use of tetracycline antibiotics alongside isotretinoin may increase the risk of headaches and blurred vision due to increased intracranial pressure.

Warfarin: careful monitoring of INR (International Normalized Ratio) is necessary when using warfarin in conjunction with isotretinoin.

8. Side effects and risks of isotretinoin

The side effects of isotretinoin are influenced by the dose used; at 1 mg/kg/day, nearly all patients will have some side effects. On the other hand, at 0.1 mg/kg/day, most patients are less likely to experience side effects . The range and severity of the side effects also depend on personal factors and the disease being treated. Patients with significant liver or kidney disease, high blood fats, diabetes and depression may be advised not to take isotretinoin or to be on a lower dose than usual and to have regular follow-up visits [8].

8.1. Cutaneous and mucocutaneous side effects

Most of the common side effects due to isotretinoin are cutaneous or mucocutaneous which are related to the mode of action of the drug. When side effects are troublesome, isotretinoin may need to be stopped or the dose reduced. The most common side effects are listed here:

Dry lips, cheilitis: sore, cracked or scaly lips are common side effects, occurring in 100% of patients on 1 mg/kg/day.

- Acne flare-up particularly if the initial dose is > 0.5 mg/kg/day.
- Dry skin, fragile skin, eczema/dermatitis (itchy, red patches of skin).
- Increased sweating may be noticed.
- Dry nostrils, epistaxis .
- Dry, watery or irritable eyes : especially in contact lens wearers , conjunctivitis, keratitis
- Dry anal mucosa, bleeding at the time of a bowel motion
- Dry genitals, dyspareunia (discomfort during intercourse)
- Facial erythema.

Sunburn: increased sensitivity to the sun can lead to sunburn upon exposure.

- Temporary hair loss
- Brittle nails

- Pyogenic granuloma
- Skin infections: impetigo, acute paronychia [9-10].

8.2. Other dose-related side effects of isotretinoin

- Headache.
- Myalgia (muscle aches) and arthralgia (joint aches), especially after exercise and in pediatric population (back pain).
- Tiredness (lethargy and drowsiness).
- Disturbed night vision and slow adaptation to the dark. Drivers may experience increased glare from car headlights at night.
- Laboratory Abnormalities: it causes decreased high-density lipoproteins (HDLs), increased triglycrides, increased liver function tests (LFTs), increased creatinine phosphokinase (CPK), decreased hemoglobin and hematocrit, increased erythrocyte sedimentation rate, decreased leukocyte counts, and increased platelet counts. In the rare event that neutropenia or agranulocytosis should occur, isotretinoin should be discontinued [11].
- Irregular or heavy menstrual periods.
- Birth defects due to in-utero exposure: because the drug molecule closely resemble to retinoic acid, a natural vitamin A derivative that controls normal embryonic development(hearing and visual impairment, missing or malformed earlobes, facial dysmorphism, and abnormalities in brain function) [10].

8.3. Rare side effects of isotretinoin

The causality of some of these side effects may not have been confirmed. The following are some additional potential side effects of isotretinoin:

- Severe headache with blurred vision due to increased intracranial pressure.
- Mood changes and depression : While depression can be associated with isotretinoin use, it's often linked to the underlying skin condition or other health and psychosocial. Antidepressant medications may be helpful.
- Sexual dysfunction: such as erectile dysfunction and decreased libido.
- Corneal opacities and cataracts.
- Hearing loss: ototoxicity is rarely reported, and its mechanism is not clear. it could induce nerve conduction alteration . sudden sensorineural hearing loss with tinnitus developed in some patients after one week of treatment. In other patients, increased hearing thresholds developed after one, two, and three weeks of treatment this improved when the drug was discontinued, and there were no other causes of hearing loss. On the other hand ,some authors claimed that systemic isotretinoin does not have permanent ototoxic effects.
- Accelerated diffuse interstitial skeletal hyperostosis (bony change).
- Abnormal liver function tests or symptomatic hepatitis.
- Diarrhoea or bleeding from the bowel.
- -Pancreatitis.
- Allergy to isotretinoin causing liver disease and a febrile illness [11-12].

9. Treatment of mucocutaneous side effects

- Dosage Reduction: to 5–10 mg/day.
- Emollients, lip balm, petroleum jelly, sunscreen, eye drops and lubricants should be applied frequently and liberally when needed.
- Dermatitis can be treated with topical steroids.
- Take short, cool showers without using soap.
- Use mild or diluted shampoo.
- Do not start wearing contact lenses for the first time.
- Avoid having elective eye surgery while on isotretinoin or for 6 months afterwards.
- Do not have mechanical dermabrasion or ablative laser treatments (CO_2 resurfacing) while on isotretinoin or for 6 months afterwards. Other laser and light treatments may be performed with care.
- For hair removal: Shaving is preferred than wax.
- Topical and/or oral antibiotics may be prescribed for impetigo [13-14].

10. Monitoring during isotretinoin therapy

10.1. Females of Child-Bearing Potential (FCBP)

Two negative pregnancy tests are necessary before the start of therapy with isotretinoin. The first pregnancy test is done up to 30 days before medication initiation. The second pregnancy test must occur at least 19 days after the first negative pregnancy test and within the first five days of the patient's menstrual cycle. Each subsequent month the patient must have a recorded negative pregnancy test to continue therapy. After discontinuation of therapy, a final pregnancy test should be done 30 days following therapy completion. Females of child-bearing potential (FCBP) must use two effective forms of birth control or complete abstinence while receiving isotretinoin therapy [10].

10.2. Pretreatment Monitoring (All Patients)

Liver function tests (LFTs), fasting lipid profile (including triglycerides), blood glucose, creatinine phosphokinase (CPK), and complete blood counts (CBC) with differential should be done before start of therapy with isotretinoin. Screening for mood alteration, psychosis, aggression, suicidal ideation, skin changes, and visual changes should also be conducted before starting therapy [14].

10.3. Ongoing monitoring (All Patients)

Regular monitoring of liver function tests (LFTs) and lipid profile is required at a biweekly interval until establishing a response to isotretinoin [15].

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