The Egyptian Journal of Hospital Medicine (October 2022) Vol. 89, Page 4562- 4565

Possible Side Effects of Isotretinoin Use in Dermatology: Review Article

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ABSTRACT

Background: Isotretinoin is an essential medication for a variety of conditions and uses, including the treatment of severe acne and chemoprevention. Because of the rise in isotretinoin prescriptions, doctors need to be well-versed in the drug's potential side effects, toxicities, and management challenges. The manufacturer has responded to the most pressing problem, congenital abnormalities, by introducing new policies and programmes designed to reduce the likelihood of unplanned pregnancy. Depression in patients using isotretinoin is a new cause for alarm. While mucocutaneous and ocular side effects are the most common, effects on the neurological, musculoskeletal, gastrointestinal, pulmonary, and hematologic systems are also recorded, along with laboratory abnormalities. Additionally, precautions against toxicity, possible drug interactions, and further monitoring are recommended.

Objective: Assessment of side effects of isotretinoin use in dermatology.

Methods: Isotretinoin, dermatology, and side effects were all looked for in PubMed, Google scholar, and Science direct. References from relevant literature were also evaluated by the authors, but only the most recent or complete study from January 2001 to February 2022 was included. Due to the lack of sources for translation, documents in languages other than English have been ruled out. Papers that did not fall under the purview of major scientific investigations, such as unpublished manuscripts, oral presentations, conference abstracts, and dissertations, were omitted.

Conclusion: Isotretinoin is a medicine used all over the world to treat various skin conditions in both sexes and people of all ages. Despite its widespread usage, however, isotretinoin is not without its share of negative side effects. To enhance clinical results and reduce the likelihood of adverse events, it is crucial to obtain thorough informed consent from patients and to counsel and follow them closely.

Keywords: Isotretinoin, Dermatology, Side effects.

INTRODUCTION

During world war 2, researchers learned how vital retinol (vitamin A) was. In 1968, scientists began working on the retinoid drug project, which aimed to chemically modify the molecule of vitamin A in order to manufacture molecules with similar effects and safety profiles. Liver was used to treat endemic night blindness in ancient Egypt, putting this therapeutic use of these compounds back some three thousand years. However, modern retinoids may be traced back to 1909, when vitamin A, a key element in embryo viability, was identified in the fatty extract of the egg yolk. Nearly twenty years ago, retinoids were first used to treat dermatoses like photoaging [(1)].

Retinoids are chemically derived from vitamin A. They influence cellular division and differentiation of stratified structures of epidermis. Natural retinoids such as vitamin A (retinol), beta-carotene, retinal, and all-trans-retinoic acid (ATRA) play crucial roles in a wide range of biological activities, like the processes of seeing, reproducing, vertebrate embryonic morphogenesis and organogenesis, arresting cell development, differentiating cells, triggering cell death, and regulating the immune system [(2)].

Vitamin A (retinol) has a tripartite biological structure, (Figure 1) consisting of a cyclic end group (cyclic ring), a polyene side chain, and a polar end. Synthetic retinoids can be made by tinkering with any one of these three components [(3)].

Isotretinoin is a derivative of retinoic acid (RA) and a derivative of retinol (vitamin A). This substance is a 13-cis retinoic acid in its chemical make-up. As seen, its molecular formula is $C_{20}H_{28}O_2$, and its chemical structure is depicted (Figure 2). Its molecular weight is 300.44 g/mol and it appears as a yellow to orange crystalline powder [(4)].

Received: 18/05/2022
Accepted: 25/07/2022

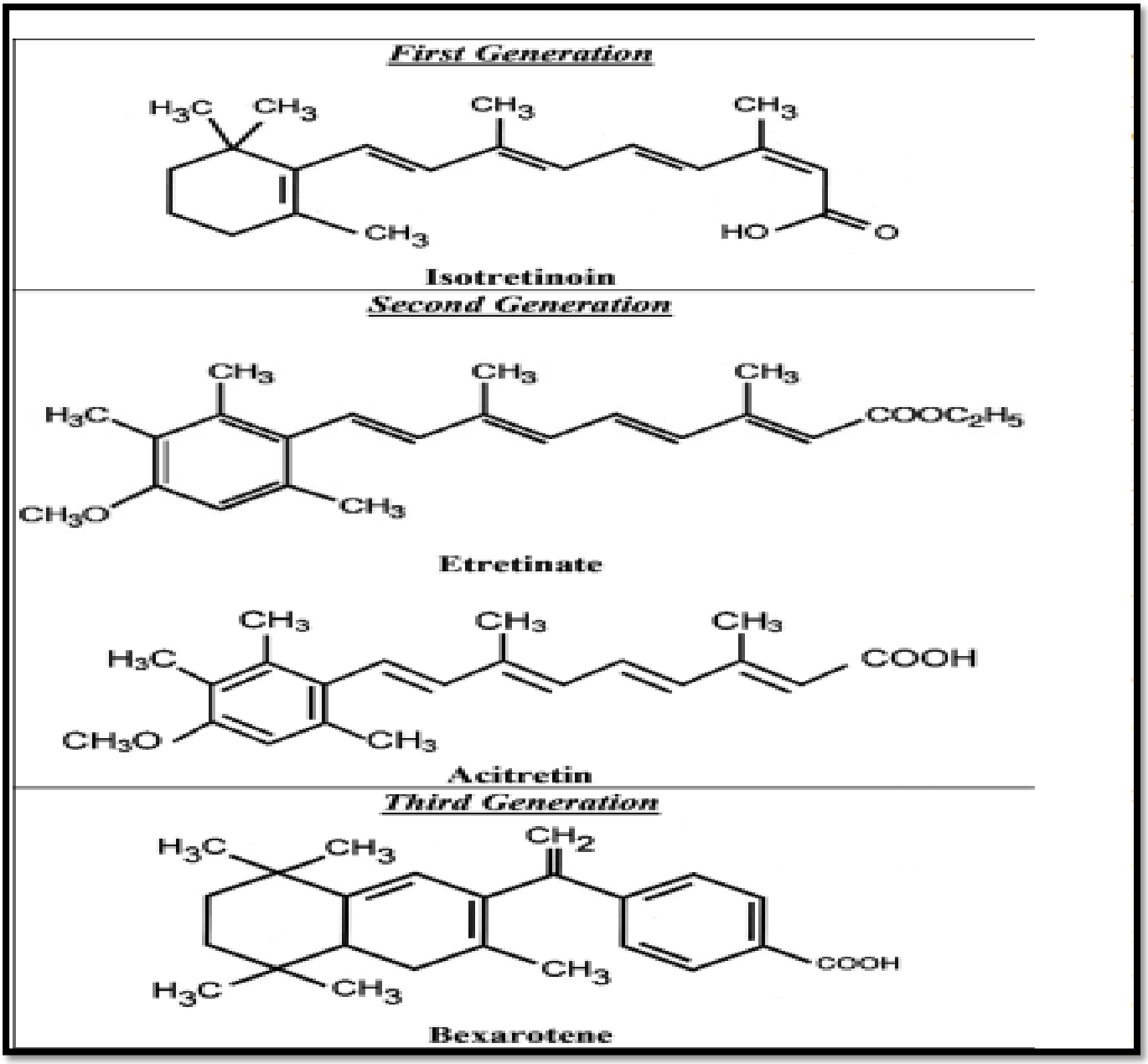

Figure (1): Chemical structure of retinoids [3].

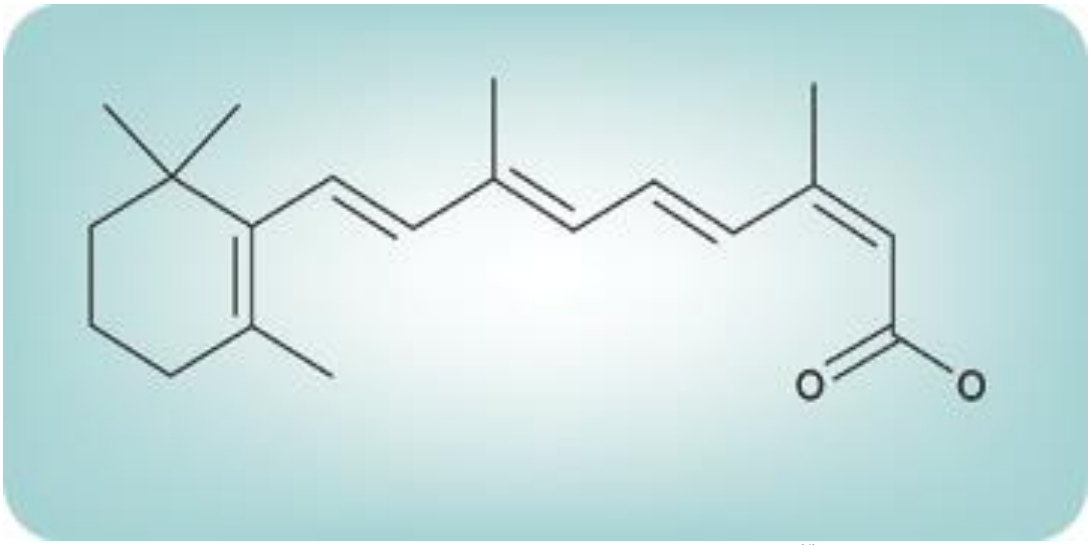

Figure (2): Chemical structure of isotretinoin [4].

Pharmacokinetics:

Isotretinoin, also known as 13-cis-retinoic acid, is a derivative of vitamin A that occurs in trace amounts in human blood and tissues. It is mostly processed by the cytochrome p450 system in the liver and is hence relatively water-soluble. Isotretinoin undergoes isomerization and oxidation in the liver, where it becomes 4-oxo-isotretinoin and other metabolites like tretinoin. When taken orally, isotretinoin reaches its peak concentration in the blood sometime between 1 and 4 hours later. Optimal plasma concentrations of 4-oxo-isotretinoin are reached between 6 and 20 hours. After stopping oral isotretinoin for a month, retinoids levels go back to normal. Metabolites of the medication are eliminated mostly by feces (53-74%), with just trace amounts passing into the urine [(5)].

Because of its high lipophilicity, oral isotretinoin is most effectively absorbed when taken with a high-fat meal. Isotretinoin is twice as effective when given after a high-fat meal as when taken on an empty stomach. Because of its close molecular connection to vitamin A, isotretinoin should not be used with vitamin A supplements [(6)].

Adverse effect of isotretinoin:

Skin:

Common and often dose-dependent adverse effects involving the mucosal and/or cutaneous systems. As many as 98% of patients will experience cheilitis at some point. Noncompliance with treatment may be indicated by the absence of cheilitis. Up to 50% of people get cheilitis, xerosis, and occasional pruritus when using isotretinoin, and those with an atopic diathesis are more likely to experience these side effects at higher doses. Acral desquamation, face erythema, and eczema are all examples of mucocutaneous adverse effects that may call for corticosteroid treatment if they persist [(5)].

Extreme photosensitivity is another major side effect of isotretinoin. Patients should be educated about the importance of using sun protection, moisturizing, and protecting their skin before beginning treatment. Patients should also wait at least six months after treatment before undergoing any sort of skin resurfacing procedure (waxing, dermabrasion, laser therapy) due to the increased risk of skin irritation and scarring [(7)].

Ocular:

It's common knowledge that isotretinoin and other retinoids can cause vision problems. Since isotretinoin has an apoptotic effect on the meibomian glands, dry eyes are a common side effect of therapy. As a result, some people are unable to wear contact lenses. These alterations may be permanent or terminal in certain individuals. Common side effects of meibomian gland dysfunction (MGD) on the eyes include red eyes from conjunctivitis, blepharitis, and discomfort. Visual disturbances such as impaired vision, poor night vision (which may be permanent), colour blindness, inflammation of cornea (keratitis), incidence of corneal opacities, photophobia, and other visual disturbances are rare but possible ocular adverse effects [(8)].

Gastrointestinal:

Nausea, vomiting, constipation, diarrhoea, and stomach pain are some of the moderate, typical side effects of isotretinoin. The medicine is linked to ulcerative colitis but not Crohn's disease as a form of IBD. Isotretinoin has been shown to not increase the risk of Crohn's disease or ulcerative colitis in recent major case-control and cohort studies [(9)].

Musculoskeletal:

The anti-inflammatory drug isotretinoin has several impacts on the skeletal system. Symptoms of muscle and joint discomfort (myalgia) (joint pain). Sacroiliitis is an uncommon side effect of isotretinoin, but nonspecific inflammatory back pain is seen often; these musculoskeletal complaints are dose-related and often disappear after one month of anti-inflammatory medication treatment [(10)].

Long-term usage of isotretinoin has been connected to a variety of skeletal abnormalities, such as diffuse idiopathic skeletal hyperostosis (DISH) syndrome, ligament calcification, osteoporosis, premature fusing of epiphyses, and long bone modelling anomalies (longer than 4 years). Keratinization disorders (like palmoplantar keratoderma, ichthyoses, as well as Darier's disease) are known to affect bone mineral density. Hyperostosis of the cervical and thoracic spine were among the skeletal abnormalities detected by radiography. However, there is no evidence that shows that short-term therapy affects bone mineral density [(5)].

Teratogenicity:

Taken by pregnant women, isotretinoin is a known teratogen that can cause severe birth abnormalities. Hydrocephalus, microcephaly, cardiac septal defects, microphthalmia, thymus gland abnormalities, hearing and visual impairment, missing or deformed earlobes, facial dysmorphism, and abnormalities in brain function are some of the most prevalent birth problems associated with this medicine [(9)].

CNS and Psychological effects:

Rarely will you have central nervous system (CNS) related adverse effects. It is unusual to see the full syndrome of papilledema and hazy vision caused by elevated intracranial pressure, while isolated symptoms such as headache, nausea, and vomiting are occasionally noted. Pseudotumor cerebri is far more likely to develop when other medicines (such tetracycline, doxycycline, or minocycline) that are linked to intracranial hypertension are also used [(4)].

A small number of patients on isotretinoin have suffered mood changes, including despair, suicidal ideation, and suicide. There are no conclusive studies

linking isotretinoin to suicidal thinking or behaviour, depression, anxiety, or mood swings at this time. Isotretinoin has not been found in population studies to cause depression. Quite the opposite, isotretinoin has been proven in the vast majority of trials to either improve mental health or have no negative impact on mental health at all [(11)].

Menstrual irregularities:

Isotretinoin has been linked to many cases of amenorrhea in women of reproductive age who were not using an oral contraceptive pill (OCP). One of the negative effects of having periods. After stopping the medicine, amenorrhea resolved on its own in all cases reported. The recommended use of other contraceptives in conjunction with isotretinoin further shows that cases of amenorrhea are underreported [(12)].

Toxicity:

Isotretinoin overdose has no standard treatment. Acute intoxication has been linked to a worsening of isotretinoin's well-known side effects, like cheilitis as well as xerosis [(7)].

Laboratory disturbances:

Very low-density lipoprotein (VLDL) triglyceride and alanine aminotransferase (ALT) and aspartate aminotransferase (AST) blood levels are commonly elevated in patients using isotretinoin. Isotretinoin-mediated FoxO1 signalling may also account for isotretinoin-induced hypertriglyceridemia, and hepatocyte death may account for the increased blood transaminase concentrations [(13)].

Hematological abnormalities, such as agranulocytosis, neutropenia, thrombocytopenia, and thrombocytosis, leukopenia, have been linked to oral isotretinoin use. Changes in hematological parameters are not often common or severe. Patients with a clinical suspicion of an abnormality should have their white blood cell count, hemoglobin level, and platelet count routinely monitored during isotretinoin medication [(14)].

CONCLUSION

Isotretinoin is a medicine used all over the world to treat various skin conditions in both sexes and people of all ages. Despite its widespread usage, however, isotretinoin is not without its share of negative side effects. To better therapeutic results and reduce the likelihood of adverse events, it is crucial to obtain thorough informed consent from patients, provide comprehensive counselling, and conduct close monitoring.

Financial support and sponsorship: Nil.
Conflict of interest: Nil.

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