

Prevention of Isotretinoin-Induced Oxidative Stress and Hepatotoxicity

Catherine Xinyue Xu^{*}

¹Jordan High School, 27500 Fulshear Bend Dr, Katy, Texas, United States

Abstract. Isotretinoin, also known as 13-cis-retinoic acid, is one of the most recognized treatments for the skin disease acne vulgaris, which is largely attributed to its high rates of success and overall effectiveness. Isotretinoin treats acne by targeting the skin's sebum production and limiting it through interactions with retinoic acid and retinoid x receptors. However, the usage of isotretinoin has also become increasingly controversial due to its many side effects, ranging from cheilitis and skin dryness to more serious issues, including hepatotoxicity and birth defects. Thus, it has become vital for researchers to identify these effects and find appropriate methods to reduce the risks. A highly concerning side effect of isotretinoin is its effect of increased oxidative stress and the subsequent emergence of hepatotoxicity, which may be due to isotretinoin's effects of reducing antioxidant reserves within the body, for example, vitamin E. Possible solutions, including taurine, selenium, and RSV-isotretinoin-SNEEDS, exert antioxidant effects and minimize and prevent isotretinoin-reduced hepatotoxicity. Further research to study the effects of isotretinoin and possible solutions to combat its adverse effects can be done to allow for the most effective administration of isotretinoin with minimal consequences.

1 Introduction

Isotretinoin is an FDA-approved synthetic vitamin A/retinol analog commonly used to treat severe cases of acne vulgaris unresponsive to alternative treatments [1]. It is a highly effective medication that reduces acne by decreasing the amount of oil and bacteria on the skin, preventing hair follicles from clogging up, and soothing inflammation.

Despite its therapeutic effects, isotretinoin has faced backlash from the public due to its numerous and often severe side effects, including but not limited to hepatotoxicity caused by oxidative stress, inflammatory bowel disease (IBD), increased pressure on the brain leading to possible vision disturbances, and osteoporosis due to a decrease in bone density. Less severe side effects include dryness of the skin and lips (which are the most common issues) [2]. If taken while pregnant, isotretinoin may also lead to miscarriages, stillbirths, and severe birth defects in the baby. Usage of isotretinoin has also been linked with an increased risk of psychosis, depression, and various other mental disorders.

With the worldwide concern of acne in adolescents and young adults alike, the effectiveness of isotretinoin has made it one of the most popular treatments against acne [3].

* Catherine Xu: k1341768@students.katyisd.org

Because of the common usage of isotretinoin, it has become vital to understand the various risks of this medication and search for ways to minimize or eliminate such risks effectively.

This review gives a brief overview of isotretinoin in the context of acne treatment. It mainly focuses on isotretinoin-induced oxidative stress along with the associated hepatotoxic effects of isotretinoin on the human body. Along with this, it also details the effects of taurine and selenium regarding the development of hepatotoxicity and other related liver disorders and touches on the usage of nanotechnology in reducing the toxic effects of isotretinoin.

2 Structure and mechanism of isotretinoin

2.1 Background information

Isotretinoin (PubChem CID 5282379), is a retinoid derivative of vitamin A with a molecular weight of 300.4 g/mol (Figure 1). Isotretinoin, also known as 13-cis-retinoic acid, (CHEBI: 6067), and the brand name Accutane, works to treat acne primarily by targeting and limiting the sebum production that occurs within sebaceous glands as well as having anti-inflammatory and immunoregulatory properties [3]. Isotretinoin limits sebum production through interactions with retinoic acid receptors (RaRs) and retinoid x receptors (RXRs). In the sebaceous glands, isotretinoin is effectively isomerized into all-trans retinoic acid (ATRA) [4]. ATRA binds to nearby RaRs and RXRs, and this interaction between the retinoic compound and its receptor triggers an expression of the forkhead box transcription factor (FoxO). FoxO is essential in preventing the formation of acne and has thus been found to be unresponsive in patients with severe acne. FoxO allows for tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) to be expressed, which causes sebocyte apoptosis and thus limits production of acne-causing sebum.

The recommended dose of isotretinoin for safe and effective use is 1 mg/kg a day, and most of the negative side effects that present themselves with the usage of isotretinoin is dose-dependent, including risk of IBD, hepatotoxicity, and cheilitis [2]. Teratogenicity, however, is seen as the most severe and dose-independent adverse effect of the medication and is one of the biggest factors in why much of the public is cautious about the usage of isotretinoin.

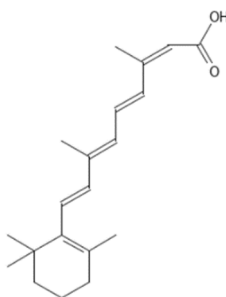


Fig. 1. The chemical structure of isotretinoin.

2.2 Isotretinoin-induced oxidative stress and hepatotoxicity

Oxidative stress is the result of a higher level of free radicals, specifically those of the reactive oxygen species (ROS). This oxidant-antioxidant imbalance within the body can lead to inflammation, tissue damage, and various other issues [5]. Free radicals, also called prooxidants or oxidants, are molecules that have an unpaired electron within their valence

orbital [6]. Most free radicals do not pose a significant danger to organisms, but those of the ROS group, which mainly include superoxide anion and hydroxyl radicals, are reactive enough to be considered dangerous [5]. If molecules of this nature are rapidly produced under oxidative stress, it can lead to the damage of all kinds of cellular biomolecules [7].

To combat this dangerous increase in ROS molecules, defense systems including both enzymatic and nonenzymatic antioxidants (found in foods or naturally produced within the body) have been set up in an attempt to prevent oxidative stress and damage, working by donating some of their own electrons to deactivate these free radicals [7]. Thus, levels of antioxidants have been used as a means of measuring the presence of oxidative stress, where a decrease in antioxidant levels within the body may indicate the presence of oxidative stress. Molecules resulting from damage of biomolecules due to oxidative stress have also been used as indicators [2]. Increases in the presence of these product molecules propose that there has been an increase in the damage of biomolecules, suggesting oxidative stress within the body.

A possible reason why isotretinoin causes oxidative stress is its proven effect of reducing vitamin E [8]. Vitamin E is a very important intracellular antioxidant reserve, and as mentioned previously, antioxidants are vital to the prevention of oxidative stress. Since isotretinoin reduces the amounts of antioxidants within the body, it makes the individual taking the medication more vulnerable to oxidative stress due to their weakened antioxidant defense system. Oxidative stress has been directly correlated with the appearance of hepatotoxicity, which is a liver inflammation condition that is acquired through certain drug exposure. Thus, this increased risk of oxidative stress is responsible for the increased risk of hepatotoxicity associated with isotretinoin [8].

An experiment was conducted to study the relation between isotretinoin and oxidative stress/damage in blood, muscle tissue, and liver tissue by observing isotretinoin's effect on albino rats [2]. Three groups of rats were each given isotretinoin, at a dosage of 7.5 mg/kg, daily over the span of 1-3 months, with a control group of rats being given soy oil for 2 months. Rats from all four groups were later dissected once the experiment was concluded to evaluate the concentration of different antioxidant defense markers present in liver tissue samples. Results of the study show that levels of the oxidative stress indicators malondialdehyde (MDA), glutathione (GSH), protein carbonyl (PC), and nitric oxide (NO) in liver tissue were noticeably increased in the treatment groups, whereas superoxide dismutase (SOD) and glutathione peroxidase (GPX) levels had minimal important variation between any of the three treatment groups as well as the control group. Levels of 8-hydroxy-deoxyguanosine (8-OHDG), while showing no significant differences among all groups, did have a higher average in the control group. The level of MDA and PC, had a positive correlation with the duration of time the rats were administered isotretinoin, meaning the longer the duration of their isotretinoin treatment, the higher the levels of the oxidative stress markers [2].

3 Prevention of isotretinoin-induced hepatotoxicity

The methods used to prevent isotretinoin-induced hepatotoxicity discussed in this paper are taurine, selenium, and RSV-isotretinoin-SNEEDS (Table 1).

3.1 Usage of taurine

Taurine (2-aminoethane-sulfonic acid) is an amino acid commonly residing within tissue around the body and is a proven protectant against oxidative stress and hepatotoxicity [9]. Taurine can increase GSH levels, decrease the levels of MDA, and act as an indirect antioxidant through its radical scavenger effect and ability to stabilize cellular membranes [8].

One study observing the effects of taurine against isotretinoin-induced hepatotoxicity has proven taurine's potent effects against preventing isotretinoin-induced hepatotoxicity [8]. In this study, four groups of male rats were utilized (2 treatment groups, 2 control groups) with each group receiving different combinations of saline solution, olive oil, isotretinoin, and taurine for 30 days. Between the two control groups, Group 1 was treated with 1ml/kg or saline daily while Group 2 was treated with 0.75 mg/100g isotretinoin in olive oil daily. Among the treatment groups, Group 3 was given 1 ml/kg of taurine mixed with saline solution along with 0.75 mg/100 g of the isotretinoin-olive oil mixture while Group 4 was given 1 ml/kg of taurine along with 0.75 mg/100 g of the isotretinoin-olive oil mixture. These dosages were based on the hepatotoxic dose and antioxidant dose of isotretinoin and taurine [8].

Samples of liver tissue were later extracted from rats in all groups, and levels of SOD, GSH, and catalase (CAT) activity were evaluated to determine the effectiveness of taurine as a hepatoprotective drug [8]. There was little difference between all four groups regarding the SOD levels in the liver tissue, suggesting that both drugs did not affect the amount of this biomolecule. The levels of GSH notably increased between the isotretinoin-taurine treated groups when compared to the isotretinoin treated group (which has lower levels of GSH when compared to control groups), with a positive relationship between GSH levels and taurine dose. Analysis of CAT activity in the liver tissue samples shows taurine negating isotretinoin's effects of reducing CAT activity, also with a positive correlation between the levels of CAT activity and dose of taurine. These results, which reveal taurine's ability to reverse any significant damage isotretinoin causes on GSH and CAT activity levels, provide evidence that taurine is an effective hepatoprotective medication against isotretinoin-induced hepatotoxicity [8].

3.2 Usage of selenium

The trace element selenium (Se) is vital to the protection of cellular membranes and prevents oxidative stress/damage by increasing GSH levels in the body, which allows for more free radical scavenging [10]. However, the slim window between selenium's therapeutic and toxic dosages has made its effective use to combat oxidative stress an important topic of study [11].

A recently conducted experiment was run to determine selenium's therapeutic effects in combating isotretinoin-induced hepatotoxicity in rats [2]. 4 groups were created between 48 Wister rats all in the same weight range. Group 1 acted as the control group and was administered a water-olive oil mixture. Group 2 was treated with selenium, Group 3 with isotretinoin, and Group 4 with both selenium and isotretinoin. All selenium was given at a dosage of 50 μ g /100 g daily while all isotretinoin was given at a dosage of 0.75 mg/100 g a day. All rats were treated for 28 days. Half of the rats in each group were euthanized after those 28 days of treatment while the remaining rats were euthanized 15 days after the end of treatment, and liver and blood samples were then taken. Levels of Thiobarbituric acid reactive substance (TBARS), GSH, and NO, and activity of SOD and CAT were examined in collected liver samples. Serum enzymes (enzymes in the blood that indicate organ damage) aspartate aminotransferase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), tetrahydrocannabinol (TCH), transglutaminase (TG), and high-density lipoprotein (HDL) were tested in blood samples [2].

Examination of serum enzymes revealed that levels of AST, ALT, TG, TCH, and ALP significantly increased in rats treated with solely isotretinoin was decreased to normal control levels in rats that were treated with both isotretinoin and selenium, suggesting selenium's ability to lower the activity of these serum enzymes [2]. Levels of the serum enzyme HDL, depleted by the usage of isotretinoin, were also restored to original levels with the usage of selenium. Furthermore, the increased levels of TBARS and NO in liver samples of

isotretinoin-intoxicated rats were shown to be mitigated by the effects of selenium, which brought levels of TBARS and NO back down in isotretinoin-selenium treated rats. GSH levels and CAT and SOD activity decreased by isotretinoin, were similarly restored by selenium. All these results were shared in both samples of rats euthanized both after the experiment and after 15 days. These results thus prove the therapeutic effect selenium has on isotretinoin-induced oxidative stress and hepatotoxicity [2].

3.3 Usage of resveratrol and nanotechnology

A common pharmaceutical option used to treat oxidative stress and liver disease is that of resveratrol (RSV) [12]. RVS is a natural phenolic compound derived from berries and other food sources and is renowned for its anti-inflammatory, antioxidant, and hepatoprotective effects through its regulation of liver lipid metabolism. However, complications regarding RSV’s photosensitivity and partial intestinal absorption have led researchers to search for other routes of administration.

Self-nano emulsifying delivery systems (SNEDDS) are a widely considered topical medium to deposit insoluble/partially soluble therapeutic agents into the body [12]. It has been seen as a potential method to allow for a quicker and more effective way to administer isotretinoin.

A study testing RSV-loaded isotretinoin-SNEEDS on rats was used to compare the hepatoprotective effects of RSV-loaded isotretinoin-SNEEDS compared to other commercially marketed drugs [12]. *In vivo* study results revealed a noticeable improvement in antioxidant properties as well as a reduction in oxidative stress (through decreases in lipid peroxidation) with the usage of the RSV-isotretinoin formulation. These findings have proven RSV-isotretinoin-SNEEDS as a promising new nanopatform that could be used in the future to administer isotretinoin with minimal side effects.

Table 1. Approaches to prevent isotretinoin-induced hepatotoxicity

Approaches	Mechanism	Effects	References
Taurine	Acts as an indirect antioxidant through radical scavenger effects & cellular membrane stabilization	Increase in GSH levels Increase in CAT activity	[5]
Selenium	Increases antioxidant levels in the body to protect cellular membranes & prevent oxidative stress/damage; Decreases serum enzyme levels	Decrease in AST, ALT, TG, TCH, HDL, & ALP serum enzyme levels Decrease in TBARS & NO levels Increase in GSH levels Increase in Cat & SOD activity	[2]
RSV-isotretinoin-SNEEDS	Effective permeation of isotretinoin; Regulation of liver lipid metabolism that provides anti-inflammatory, antioxidant, & hepatoprotective effects	Increase in antioxidant properties Decrease in lipid peroxidation that reduces oxidative stress	[12]

4 Conclusion

Research conducted regarding the effects of isotretinoin has proven to be monumental in identifying and developing new technology to combat the adverse effects of isotretinoin, such

as taurine, selenium, and RSV-isotretinoin-SNEEDS. These new technologies have been proven to help with the effective and safe administration of isotretinoin through their antioxidant properties and antioxidant-boosting effects. Nonetheless, many adverse effects of isotretinoin still have yet to be closely examined and properly prevented, thus making it vital for further research to be conducted. With this increase in the understanding of isotretinoin, its side effects, and effective reduction/treatment methods, reassurances over the usage of isotretinoin will allow for a shift in the fears and doubts much of the public has and thus boost its overall popularity and public usage.

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