Washout Period for Pregnancy Post Isotretinoin Therapy

Abstract

Introduction and Background: Isotretinoin is an oral medication used for the treatment of severe acne unresponsive to other medications. This drug is teratogenic and should be prescribed with appropriate caution in selected group of patients. The washout period for pregnancy post isotrenoin therapy has always been a topic of controversy. Several guidelines have recommended a wash out period of one month if pregnancy is planned in a patient being administered with the drug. **Objective:** This article discusses the available evidence for different recommended wash out periods and addresses important clinical questions that arise. **Methods:** Pubmed research was carried out to collect relevant data using the keywords isotretinoin, pregnancy, contraception, pharmacokinetics and guidelines. **Conclusion:** Our research based on the published data concludes that a wash out period of 35 days post isotretinoin therapy is adequate in routine clinical practice.

Keywords: *Contraception, India, isotretinoin, new guidelines, pregnancy*

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Introduction

Isotretinoin is an oral derivative of vitamin A. Oral isotretinoin (13-cis-retinoic acid) was first approved by the US Food and Drug Administration (FDA) for treatment for severe acne in 1982.[1] Isotretinoin is a pro-drug that is converted intracellularly to metabolites that are agonists for Retinoic acid receptor (RAR) and retinoid X receptor (RXR) nuclear receptors.[2-5] Isotretinoin influences all of the major etiological factors implicated in acne by affecting the cellular differentiation, cell-cycle progression, cell survival, and apoptosis.[2-8] As a consequence there is a remarkable reduction in sebum production, comedogenesis, surface and ductal Propionibacterium acnes population, and inflammation. A dose of 0.5-1.0 mg/kg/day dramatically reduces sebum excretion by 90% within a period of 6 weeks. The average course of treatment is 4-6 months.[1] Isotretinoin is category X drug and one of the most well established and potential serious adverse effect of isotretinoin is teratogenic if not taken under proper guidance.[9] If used in first trimester, it may lead to increased fetal loss and specific malformations like cleft palate, stenosis of the external ear canal, microtia, and hydrocephalus. Cardiac outflow tract defects may occur when consumed later in pregnancy.[10] Therefore, is it contraindicated during pregnancy or in patients who are trying to conceive.[11]

For this reason, strict contraception is advised to all the sexually active female patients. The routinely followed recommendation for contraception is for 1 month prior to initiation of isotretinoin therapy, during the treatment period, and 1 month after discontinuation of the treatment.[1] However, the recommendation regarding contraception period post isotretinoin therapy is a topic of debate. This issue is further discussed in detail.

Methods

PubMed research was executed to gather the relevant data needed using the keywords - isotretinoin, pregnancy, contraception, pharmacokinetics, and guidelines. Suitable information regarding isotretinoin was taken from all the publications and guidelines available as well as from the dermatological textbooks. A total of 23 publications could be found on PubMed on the subject and were analysed.

Analysis of data

In the US, isotretinoin-based drugs are sold through a special restricted distribution programme approved by the US Food and Drug Administration (FDA). In 2005

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the FDA introduced 'iPLEDGE', a risk management distributed program. The program was initiated to prevent pregnant women from being prescribed or exposed to the medication.It mandated that both male and female users of oral isotretinoin would have to enrol into the National Registry. If this is not achieved, patients will no longer be able to receive the drug. Women of childbearing age have to provide two negative pregnancy tests before their initial prescription, show evidence of another negative pregnancy test before each monthly repeat prescription. Unless continuously abstinent, patient has to comply with the iPLEDGE necessity to use two forms of contraception 1 month before, during, and for 1 month after completion of treatment.[1,12]

The European Directive concerned with the prescribing of oral isotretinoin and the European FDA have also implemented a pregnancy prevention programme for females on isotretinoin. According to this programme, female patients are advised to use at least one but ideally TWO methods of contraception for 1 month before starting treatment, including a barrier method, and to continue to use effective contraception throughout the treatment period and for at least 1 month after cessation of treatment. Mandatory pregnancy testing is performed pre-therapy, during and 5 weeks post-therapy.[13]

Kanelleas *et al*. suggest that patients should agree to at least one and preferably two complementary methods of contraception, including a barrier method, before the initiation of therapy, during treatment and for 5 weeks after the conclusion of it.[14]

Boucher and Beaulac-Baillargeon conclude that patients should be advised to begin using two effective contraceptive methods 1 month before starting isotretinoin and continue using the same during the treatment and 1 month after the last dose.[15]

According to Abroms *et al*., pregnancy prevention is needed for 1month interval after the isotretinoin therapy ends as 32% of isotretinoin exposed pregnancies occurred during this post-therapy period.[16,17]

Thus most recommendations are for 1 month period after stopping the drug. However, there is one paper by Choi *et al.*,[18] which suggested for contraception longer than one month, taking into account the variability in the pharmacokinetics of isotretinoin. It recommends a 3-month window for the use of contraception post isotretinoin therapy to provide an adequate safety margin to prevent fetal exposure, based on more than five elimination half-lives of the drug.[19] There was also a report of suspected isotretinoin-induced ear malformations in a newborn whose mother had taken isotretinoin for 2 years until one month prior to the time when she became pregnant.[20]

As stated by several pharmacokinetics studies of isotretinoin and its metabolites, the harmonic mean elimination half-life of isotretinoin and 4-oxo-isotretinoin following the oral administration of isotretinoin range from 10 to 20 hours and 24 to 29 hours, respectively.[21-23] There is thus evidence of variability in isotretinoin elimination half-life (from 5.3 hours to 7 days) and such variability in the pharmacokinetics may also lead to exposure during pregnancy. Hence, 1 month may not be sufficient for clearing of the drug in all women.[24] According to a study by Nulman *et al*., the $t_{1/2}$ of isotretinoin and its metabolite 4-oxo-isotretinoin is generally short, but they observed a prolonged $t_{1/2}$ in two female patients. This may have happened because of hepatic recirculation. Therefore, in the worst case scenario with $t_{1/2}$ of approximately 1 week, 5 half-lives will be needed to allow levels to return to baseline.[24]

In the United Kingdom, the Pharmacovigilance Risk Assessment Committee of European medicines agency has adopted recommendations for isotretinoin based on the pharmacovigilance data. It suggests the requirement for two forms of contraception during the treatment and 1 month following the end of treatment, which is determined based on the metabolism of the product.[25]

Another paper on pharmacokinetics of oral isotretinoin by Wiegandand Chou stated that the metabolite of isotretinoin with the longest elimination half-life (oxoisotretinoin), returns nonteratogenic plasma (endogenous) retinoid concentrations within 2 weeks after the end of isotretinoin treatment. Also, retinoic acid, which is thought to be partly responsible for the teratogenic effect ofisotretinoin, takes only 2 days to return to physiologic levels. Hence, the post-therapy contraceptive period of 1 month has been experimentally verified as an adequate safety margin for isotretinoin.[19]

Dai *et al*. have done an analysis of 88 case reports from pregnant patients in whom conception occurred after discontinuing isotretinoin treatment. Among these, 90% pregnancies occurred within 2 months and 64% occurred within 1 month of discontinuing isotretinoin. Moreover, three women obtained their last dose of isotretinoin within 2 days before the estimated date of conception and eventually delivered normal full-term infants. In these 88 case reports, it was found that there was no increased risk of congenital malformations or spontaneous abortions among these women who completed or discontinued isotretinoin therapy before conception. Also, the incidence rates of congenital malformations and spontaneous or missed abortions in these patients did not show variation from the incidence rates reported in normal females of reproductive age group who had not been exposed to isotretinoin.[26]

Discussion

As it can be seen from the above analysis, that isotretinoin should be prescribed with caution to women of child bearing age and patients should be provided with detailed

information regarding the teratogenic effects of isotretinoin on fetus and contraception while prescribing the drug. Prescribers should counsel sexually active women to select and use two forms of effective contraception simultaneously for at least 1 month prior to initiation of isotretinoin therapy, during therapy, and for 1 month following discontinuation of therapy. Effective contraception should consist of concurrently using both a primary (tubal ligation, partner's vasectomy, intrauterine device, estrogen-containing birth control pills, or topical, injectable, implantable, or insertable hormonal birth control products) and a secondary method of birth control (diaphragm, latex condom, or cervical cap, each to be used with spermicide).[27]

Recently the Central Drugs Standard Control Organisation (CDSCO) from India has issued safety guidelines and labelling rules for isotretinoin, citing the harmful side effects and adverse reactions. These guidelines advocate to avoid pregnancy in patients for 6 months after stopping the treatment.[28]

However, all the recommendations quoted above and the standard dermatological text book suggest only 1month's period of contraception post isotretinoin therapy,[29-31] with European guidelines recommending a 35 day period.[13] No textbook, guideline or publication has mentioned contraception for more than 3 months after conclusion of treatment. In view of the above-stated studies, we feel the Indian recommendation is not justified.

Conclusion

Considering the variability of isotretinoin pharmacokinetics and taking into account a maximum t1/2 of approximately 1 week, elimination period (five times of t1/2) would be a maximum period of 35 days. This means that the time needed to allow levels to return to baseline would be a 35-day period before safe conception.[20,25] We therefore feel a 35 day recommendation as stated in recommendation by European directive and Kamellan would be suitable.[13,14]

Thus based on pharmacokinetic studies of isotretinoin, recommendation for a wash out period of 35 days post isotretinoin therapy would be adequate and appropriate.

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Conflicts of interest

There are no conflicts of interest.

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