Original Article

Evaluation and Monitoring of Isotretinoin use in Iran

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Abstract

Background: Isotretinoin (13-cis retinoic acid) is used for treatment of nodular cystic acne unresponsive to conventional therapy. It is an expensive, potent teratogenic drug with serious adverse drug reaction (ADRs). Recently, use of this drug has increased in Iran. To date, there are no published data about the use of isotretinoin in Iran; therefore, this study aims to assess its use in this country.

Methods: This was a prospective, drug utilization evaluation (DUE) study conducted in an institutional community pharmacy affiliated with Tehran University of Medical Sciences (TUMS). Drug prescription, administration, and evaluation of appropriateness were recorded and compared with standard protocols. Collected data were analyzed by SPSS software.

Results: A total of 274 outpatients treated with isotretinoin enrolled in the study. Of these, 51.3% were prescribed isotretinoin under the usual recommended daily doses of 0.5mg/kg/day. Data also indicated that 33.5% of the patients were given total doses of less than 100 mg/kg (72.4 ± 17.2 mg/kg) and 12.2% received more than 150 mg/kg. With regards to the teratogenic effects of isotretinoin, only 6.8% of couples simultaneously used two methods of contraception (P = 0.001). In addition, we detected improper use of isotretinoin for mild and moderate acne in about 20% of cases.

Conclusion: The most important finding of this study is that the doses of isotretinoin are incorrect in many cases. Incorrect dosages would decrease drug efficacy and increase the risk of relapse. In addition, patients have not been adequately counseled about isotretinoin's teratogenicity and the seriousness of its adverse effects.

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Introduction

Acne vulgaris, generally termed as acne, is the most common skin disease that affects about 80% – 90% of all adolescents.[1,2] It can cause skin deformities and permanent scarring, resulting in psychological distress, low self-esteem, social withdrawal, and depression, all of which affect quality of life.[3–6]

Isotretinoin (13-cis retinoic acid) is approved for the treatment of nodular cystic acne unresponsive to conventional acne therapy. It is one of the most effective therapeutic agents for acne with a long-term remission rate.[7–9] However, isotretinoin is a potential teratogenic drug with serious adverse effects such as depression, suicidal thoughts, and pancreatitis. Therefore, utilization evaluation and monitoring of this medication is an important issue for improving treatment outcomes and lowering treatment cost and complications.[10–14]

According to data from the Health Ministry of Iran, there was a rapid increase in isotretinoin use from 2000 to 2007 in Iran.[15] At the time of writing this study there were no surveillance and published data about its use in Iran. Therefore, this study evaluated the utilization and monitoring of isotretinoin in Iran.

Materials and Methods

This was a prospective, drug utilization evaluation (DUE) study conducted from July 2007 to January 2008, in an institutional community pharmacy service affiliated with the College of Pharmacy, Tehran University of Medical Sciences (TUMS). At the time of this study, this institutional community pharmacy was the only center authorized to dispense isotretinoin in Tehran. The criteria for dispensing and social security coverage for isotretinoin included completion of a consent form about the teratogenic and adverse effects of isotretinoin by patients and completion of patients' medical records by dermatologists. Patients were referred on a monthly basis to this pharmacy to obtain their medication; their medical files were maintained in the pharmacy.

All patients with indications for isotretinoin who completed consent forms, had medical records, and were visited by the authors at least twice during the study period were enrolled. Sampling size was determined by simple randomization from the patients who met our study criteria for a period of six months. We excluded patients from the study who were pregnant or breast-feeding, those with incomplete consent forms and medical records, and those who had any contraindications to isotretinoin as confirmed by dermatologists.

The appropriateness of isotretinoin prescription, administration, and utilization was evaluated according to the designed protocol, which was approved in ethics committee of university.

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Table 1. Patient demographic data

Sex (n)	
Male	52 (19%)
Female	222 (81%)
Marital status (n)	
Single	219 (80%)
Married	56 (20%)
Married males	12 (21%)
Married females	44 (79%)
Age (year)	
Mean±SD	24.5±5.8
Median	24
Range	15–54
Weight (Kilograms)	
Mean±SD	60.3±10.3
Median	59
Range	31–92

Table 2. Distribution of patients according to sex and age.

Female (n=222)	Male (n=52)	Total patients (n=274)	Age (years)
0	0	0	0–10
48 (21.5%)	16 (31.3%)	64 (23.3%)	11–20
155 (70%)	27 (51%)	182 (66.6%)	21–30
17 (7.6%)	7 (13.7%)	24 (8.7%)	31–40
0	2 (4%)	2 (0.7%)	41–50
2 (0.9%)	0	2 (0.7%)	over 50

Table 3. Methods of contraception in study participants.

Methods	n=44
Condom	17 (38.7%)
OCPs[1]	11 (25%)
IUD[2]	7 (16%)
OCPs and condom	3 (6.8%)
Withdrawal method	2 (4.5%)
No answer	4 (9%)

[1]Oral contraceptive pills; [2]Intra-uterinedevice

Demographics that included age, sex, marital status, weight, estimated treatment period, past medical history and presence of systemic illness, indication for isotretinoin, dose, concurrent drug use, contraception methods, previous use of isotretinoin, location of acne on patient's body, telephone and address that confirmed and completed by dermatologists were also recorded by pharmacist.

After six months of isotretinoin use, collected data were analyzed by SPSS 16 software. For assessment of two independent observational samples, we used student's t-test and Mann-Whitney test. To evaluate the correlation between frequencies of categorical variables we conducted the chi-square test. *P* values less than 0.05 were considered statistically significant.

Results

A total of 274 outpatients who received isotretinoin entered the study. Patients consisted of 52 males (19%) and 222 females (81%; $P < 0.001$). The mean ± SD age of patients was 24.5 ± 5.8 years. Demographic data is shown in Table 1. The mean weight ± SD of patients was 60.3 ± 10.3 kilograms. Most patients (51% males, 70% females) were between the ages of 21 – 30 years (Table 2; $P < 0.001$).

The contraception methods of sexually active females are also shown in Table 3. Only 6.8% of the couples used two contraception methods that included oral contraceptive pills (OCP) and condoms ($P < 0.001$).

In the present study, the most common indication for isotretinoin was recalcitrant acne that had not responded to other therapies such as systemic antibiotics, whereas about 20% of prescriptions were for mild and moderate acne. In addition, 2.9% of dermatologists prescribed isotretinoin for non-acne indications such as acne rosacea, hidradenitis suppurativa and acne scars ($P < 0.001$).

Among the study population, face and trunk of patients were the most commonly affected body areas. In 58.2% of cases, acne was located only on the face, whereas 39.9% of cases had acne in both the face and trunk areas. The number of isotretinoin prescriptions

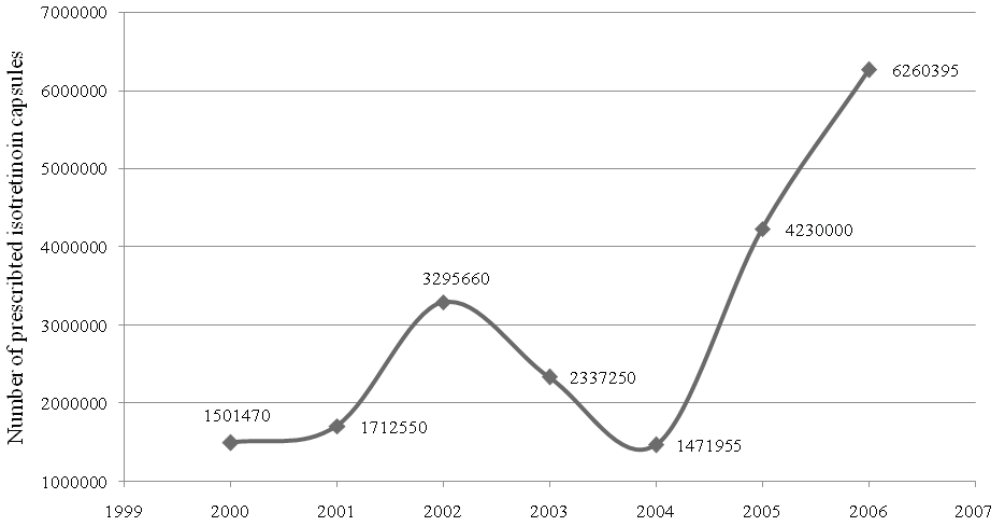

Figure 1. Prescription pattern of isotretinoin in Iran from 2000 – 2006.

Table 4. Isotretinoin daily doses, total doses, dosage and treatment period.

Variable	Daily dose (mg/day)	Dosage (mg/kg/day)	Total dose (mg/kg)	Treatment period (months)
Mean±SD	31.5±9.2	0.5±0.2	117.1±45.5	7.5±2.4
Median	30	0.5	120	6
Range	10–60	0.16–1	30.7–360	4–16
N	274	274	274	274

correlated with the location of the acne ($P < 0.001$).

Seventeen (6.2%) patients reported previous use of isotretinoin. In these patients, only 8 (47%) completed one course of treatment (total dose: 120 – 150mg/kg in 5 – 6 months).[6–9] Patients' past drug histories for acne were topical erythromycin and clindamycin, oral doxycycline, erythromycin and tetracycline, which had been taken by 88% of patients prior to isotretinoin.

The mean dose of isotretinoin was 0.53 ± 0.2 mg/kg/day; the mean total dose of isotretinoin was 117.145.5± mg/kg.

The results of this study showed that 51.3% of patients were given isotretinoin under the usual recommended daily doses of 0.5 – 1 mg/kg/day (0.36 ± 0.1 mg/kg/day; $P < 0.001$).[6–9]

The total doses of isotretinoin for a treatment period of six months were also evaluated. The results showed that 33.5% of patients were given less than 100 mg/kg (72.4 ± 17.2 mg/kg), whereas 12.2% received more than 150 mg/kg. Only 28.75% of patients received the standard total doses of 121-150 mg/kg[6–9] ($P < 0.001$). Data for daily doses, total doses, dosage and treatment periods for patients are shown in Table 4.

In this study, the mean recommended treatment period of isotretinoin by dermatologists was 7.5 ± 2.4 months. Only 50% of patients used isotretinoin for the standard treatment period of 5 – 6 months ($P < 0.001$). In 3% (n = 8) of prescriptions, dermatologists prescribed isotretinoin concurrently with multivitamins and topical vitamin A+D preparations.

Discussion

This was a DUE study of isotretinoin undertaken for the first time in Iran. The authors conducted this study because of the increased use of isotretinoin in Iran, high cost, seriousness of side effects, and potential teratogenic issues of this medication. In addition, according to the authors' knowledge and experience during the study period, cosmetic issues other than the true indication for isotretinoin played a role in prescribing this medication. Therefore, the aim of this research was to assess isotretinoin use in Iran.

According to a study by Wysowski et al. there was a rapid increase in isotretinoin use (250%) in the United States from 1992 through 2000.[16] We have also seen this increasing pattern of use in our study (Figure 1).[15] In addition, we have detected mislabeled use of isotretinoin for mild and moderate acne in 20% of cases. This finding is consistent with findings by Wysowski et al.[16] Therefore, it appears that isotretinoin has been prescribed for cosmetic purposes. This fact warrants concern about the use of this drug because of its serious adverse effects, teratogenicity, and cost.

In the Wysowski et al. study the sex distribution of patients was nearly even, which was not the case in our study.[16] Studies and clinical experiences have indicated that women seek more medical care for the treatment of acne.[17,18] We also reported a significant difference between the proportion of females and males treated for acne.

In this study, there was a significant difference in the use of isotretinoin among different age groups; most patients who took isotretinoin were young. This was due to the increased prevalence of acne in this age group.

The most serious adverse events associated with isotretinoin use are teratogenic. In fact, the risk of serious teratogenic effects during exposure to isotretinoin is at least as high as the risk of a con-

genital defect after exposure to thalidomide.[19] Therefore, sexually active females who use this medication must simultaneously use two safe methods of contraception.[10,11,19] However in this study, only a few sexually active females used two contraception methods; most used only one contraception. A possible explanation was that patients were not properly counseled about the seriousness of isotretinoin's adverse effects. Therefore, serious consideration and warning must be given to prevent this problem.

According to our study, about half of the patients received a lower daily dose of isotretinoin; over half received a lower total dose.[6–9] This can increase the risk of relapse, decrease treatment efficacy, and increase the cost of therapy. In addition, 12% of patients received higher than the recommended total doses. This would not increase therapy efficacy but could cause severe and serious adverse reactions.[18–21]

In this investigation men received lower doses compared to women. This was because isotretinoin cannot be prescribed based on a patient's weight due to the availability of only one single dosage (20 mg capsule) in Iran.

In this study, there was a significant relation between the site of acne and the number of prescriptions for isotretinoin. Patients with more acne on their faces visited dermatologists more frequently, which possibly was due to the high prevalence of acne on their faces and/or cosmetic issues.[6]

In addition, 6.2% of the patients reported a history of previous isotretinoin use; only half completed their treatment, which could increase the risk of relapse.[18–21]

In agreement with the standard indication for isotretinoin, recalcitrant and severe nodulocystic acne is the major reasons for prescribing isotretinoin. We have also reported that 3% of dermatologists prescribed vitamin A preparations with isotretinoin. This can result in an agonist increase in toxicity.[18,19] Therefore, it is necessary to be aware of this interaction and notice that multivitamin preparations usually include vitamin A.

Our limitations in this study are poor patient compliance and time constraints. We suggest that large, well-designed studies be undertaken throughout Iran, not only for assessment of this drug use but also for any critical drugs to improve public health care, decrease cost and lessen treatment complications.

In conclusion, the most important findings of this study are the lack of correct doses of isotretinoin that have been prescribed in many cases. This would decrease drug efficacy and increase the risk of relapse. In addition, patients have not been properly counseled about isotretinoin's teratogenicity and the seriousness of its side effects. Therefore, there is a need for monitoring of drug use in the health system with the intent to reduce adverse drug reactions (ADRs), therapy costs, and to improve both the efficacy and safety profile of medications.

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