ACUTE MUCOCUTANEOUS AND SYSTEMIC ADVERSE EFFECTS OF ETRETINATE

H. Mortazavi[1], B. Shariati[2] and N. Zarrinpour[1]

1) Department of Dermatology, Razi Skin Hospital, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

2) Department of Social Medicine, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

Abstract- This cross sectional study was carried out between 1993 to 1998 at Razi Skin Hospital, the affiliated Dermatology Department of Tehran University of Medical Sciences. Eight hundred patients receiving etretinate for various skin diseases took part in this study. Among them, 457 patients with first admission to dermatologic clinic who had at least four regular sequential visits and responding to our questionnaire were selected to enter the study for evaluating acute toxicity of etretinate. Cheilitis with a frequency of 88 percent was the most frequent side effect. Hair loss (22.97%), dry mouth with thirst (15.09%), dryness of mucous membranes (13.12%), xerosis with pruritus (11.15%), nose bleeding (8.31%), paronychia (5.47%), facial dermatitis (3.06%), conjunctivitis (2.84%) and in addition to mucocutaneous ones, chills (2.63%), headache (2.19%), mental depression (2.19%), urinary frequency (1.53%) and papilledema (0.44%) were among the other observed toxicities. The relationship between mucocutaneous side effects with dosage of etretinate, sex and, age of the patients was evaluated. The association between mucocutaneous toxicities and sex was significant ($P < 0.05$). We observed four rare side effects in the patients including hair color lightening appearing as whitening or blondness, hair waving, dyspareunia and gynecomastia. In conclusion, females were more prone to acute mucocutaneous toxicities of etretinate.

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Key words: Etretinate, retinoids, adverse effect, side effect, toxicity, acitretin

INTRODUCTION

Retinoids are classified into three generations (1,2). First-generation retinoids are non-aromatic and natural metabolites of vitamin A. The well-known oral synthetic drug of this group is isotretinoin, which is mainly used systemically for treatment of acne (3). Second-generation retinoids are synthetic aromatic compounds of retinoids including etretinate and acitretin. Terminal elimination half-life of etretinate in plasma is suggested to be 100 days (4), moreover; it can be detected in trace amounts 2.9 years after discontinuation of therapy (5). In order to reduce the long terminal half-life of etretinate, acitretin, a carboxylic acid metabolite of etretinate, with terminal half-life of 55 to 60 hours, was produced. Unfortunately, the conversion of acitretin to etretinate in patients consuming alcohol has been confirmed (6,7,8). The main indications of this generation include psoriasis and its variants, disorders of keratinization and cancer prevention (6). Third-generation retinoids are polyaromatic retinoids, which include bexarotene.

It is an approved oral retinoid for the treatment of cutaneous T-cell lymphoma (5,6).

Retinoid toxicities or adverse effects are divided to acute and chronic (9). Acute adverse effects of retinoids are also divided to mucocutaneous, systemic and laboratory adverse effects (9). Adverse effects of retinoids, due to potential teratogenicity and long half-life, have attracted the attention of dermatologists and other health workers (1,10). Except for teratogenicity, all other adverse effects are controllable (2). Because most of the researches on adverse effects of retinoids have been performed in the United States and European countries (11, 12) we decided to study the adverse effects of etretinate in Iranian patients.

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Corresponding Author:
H. Mortazavi, Department of Dermatology, Razi Skin Hospital, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
Tel: +98 21 2066052
Fax: +98 21 5618989
E-mail: mortazave_ho@yahoo.com

MATERIALS AND METHODS

This cross sectional study was carried out from 1993 to 1998 in outpatient department of retinoid (O.P.D of retinoid) at Razi Skin Hospital of Tehran. During the study period the pharmacy of Razi Hospital

was the sole distributor of etretinate in Iran. Therefore, all the Iranian outpatients receiving etretinate for the first time, took part in this study.

The O.P.D. of retinoid was established to study adverse effects of oral etretinate and to monitor the patients receiving the drug. The first object was to determine acute adverse effects of etretinate.

At the first step, we created a questionnaire for nearly all adverse effects of etretinate based on Peck and DiGiovanna's classification of retinoid toxicities (9). The questionnaire also included a section for following up the patients. The unusual findings including non mentioned adverse effects in the questionnaire and new and unreported adverse effects in the literature were also reported in the follow up section. In this study, according to the diagnoses of the diseases that were treated with etretinate, the dosage of the drug ranged from 0.5 mg to 1 mg/kg/day.

The patients, who participated in this study, signed a consent form written in Persian.

Inclusion criteria:

A: First course of etretinate therapy with no history of use of this drug previously. B: An indication for etretinate therapy, such as the following diagnoses:

1- Variant of psoriasis resistant to other therapies
2- Pustular psoriasis
3- Mycoses lungoides
4- Ichtyosiform dermatosis including Darier disease
5- Xeroderma pigmentosum
6- Other indications of etretinate for skin diseases.
7- Attending the OPD of retinoid at least 4 times regularly and sequentially

Exclusion criteria:

1- Child bearing women not using safe methods of contraception
2- Hepatic insufficiency
3- Hyperlipidemia

Eight hundred patients participated to this study and 500 patients attended at least four times the retinoid OPD. Among them, 457 patients were admitted for the first time and responded to the questionnaire completely.

Chi-square and Student's tests were applied to determine relationships between adverse effects and other factors. These factors were sex, age and dosage of the drug.

RESULTS

The mean age of male and female patients was 35.294±17.320 and 34.765±17.640 years, respectively. The mucocutaneous adverse effects occurred in 93% of our patients. With regard to sex, 97 percent of females and 91 percent of males had acute adverse effects (Fig. 1).

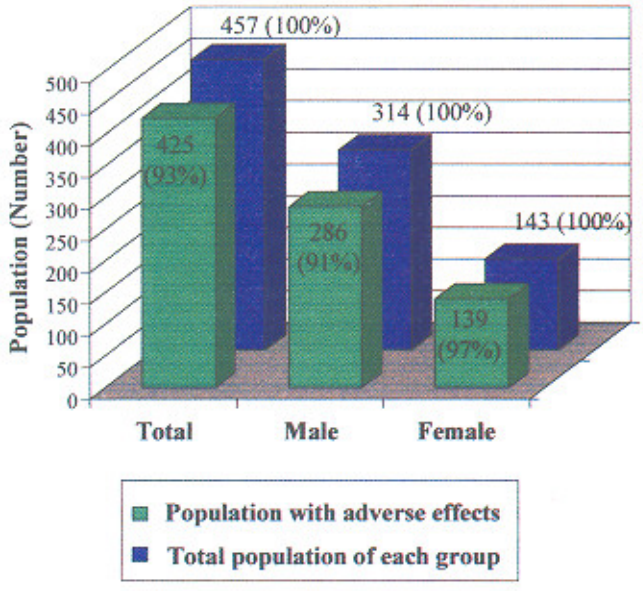

Fig. 1. Distribution of adverse effects by study population and gender

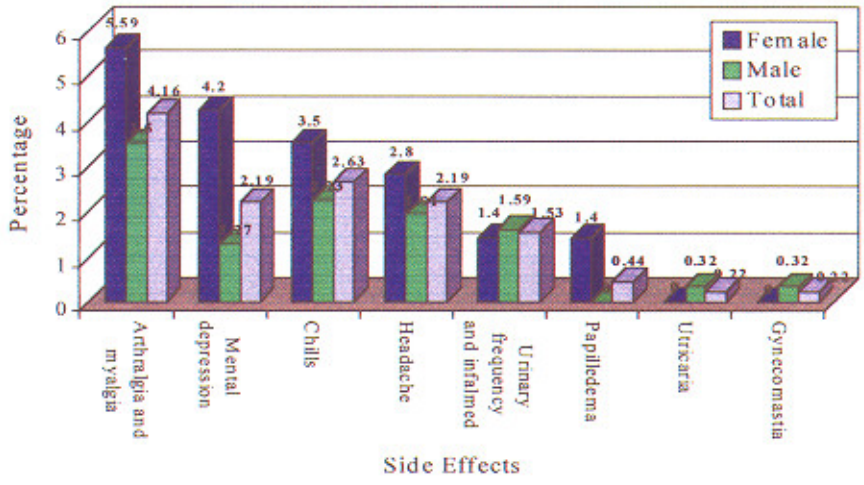

Fig. 2. Systemic adverse effects of etretinate in all study population by sex distribution

Distribution and percentage of acute adverse mucocutaneous effects of etretinate are shown in table 1. Distribution and percentage systemic adverse effects of etretinate are shown in figure 2.

Relationships between sex, age and dosage of the drug and mucocutaneous adverse effects were evaluated using chi-square test.

Association of mucocutaneous adverse effects with sex

The effect of gender on mucocutaneous adverse effects was significant with P value of 0. 0 17. In other words, the mucocutaneous adverse effects were seen significantly more frequent among females.

Association of mucocutaneous adverse effects with dosage of etretinate

The level of administrative dosage of etretinate was associated with acute mucocutaneouse adverse effects (P value=0.03). It meant that higher doses of etretinate were consistent with more mucocutaneous adverse effects (Fig. 3). We observed three rare acute mucocutaneous adverse effects, namely hair color lightening appearing as lightening or blondness, hair waving and dyspareunia which are shown in table 1. A woman suffering from pustular psoriasis using 60 mg etretinate per day complained of painful sexual intercourse, namely dypareunia. A case of gynecomastia was observed in male population. In this study we had no report of teratogenicity.

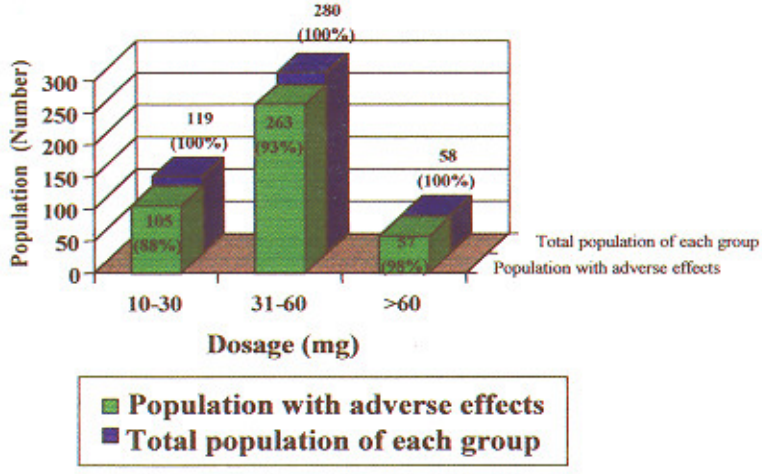

Fig. 3. Distribution of adverse effects by drug dosage (P= 0.03)

Table 1. Distribution of mucocutaneous adverse effects in Iranian patients in all study population by sex

Adverse effects	Females %	Males %	Total %
Cheilitis	93.01	85.99	88.18
Hair loss	32.17	18.79	22.97
Dry mouth with thirst	13.29	15.92	15/09
Mucosal dryness	16.08	11.78	13.12
Palmoplantar peeling	9.79	12.74	11.81
Exrosis with pruritus	11.18	11.15	11.15
Epistaxis	7.69	8.6	8.31
Paronychia	7.69	4.46	5.47
Facial dermatitis	6.99	1.27	3.06
Conjunctivitis	2.79	2.87	2.84
Hair discoloration	1.4	0.32	0.66
Waving of hair	0.7	0	0.22
Dyspareunia	0.7	0	0.22

DISCUSSION

As we know chronic toxicities of etretinate are seen after at least 2 years of therapy and most important of these are bony changes (9). These chronic adverse effects were not studied in this research. In this research, acute clinical adverse effects of etretinate namely mucocutaneous and systemic, which were seen during the first to fourth visits of the patients, were studied. The interval between visits were two months. In case of urgent needs, patients were visited sooner than this interval. In case of using two or more drugs simultaneously, the adverse effects were evaluated after cessation of other drugs than etretinate. Therefore, the adverse effects were related to etretinate.

The most common adverse effects of retinoid therapy are mucocutaneous side effects (4). Mucocutaneous adverse effects such as cheilitis, particularly involving lower lips and hair loss due to anagen arrest, are the most common dose-dependent side effects, requiring dose reduction in some patients (2,13,14).

According to LA.J. Kovacs and N.H. Shear mucocutaneous adverse effects of retinoids occur in greater than 90% of treated patients (10). In the present study, mucocutaneous adverse effects occured in 93% (Table 1) of the patients.

Like other studies (15-17), our study demonstrated that severity of acute mucocutaneous adverse effects is related to drug dosage.

In this research papilledema, due to etretinate, occured in 0.44% of study population. Papilledema has been reported with administration of isotretinoin alone or in combination with tetracycline (18). According to our knowledge, there is only one report of papillederna due to acitretin, not etretinate, in the literature (5).

Etretinate may lead to dryness of mucosae as well as dryness of skin; therefore dyspareunia might be due to dryness of vaginal mucosae. We reported hair lightening and blondness but others described hair darkening (19). There is only one report of gynecomastia in the literature and we do not have a clear-cut explanation for this adverse effect (20).

In this study, the adverse effects of etretinate were evaluated in males (21) and females separately. Therefore, the results showed that females were more prone to mucocutaneous adverse effects of etretinate. This result maybe due to:

1.The females' skin is more liable to mucocutaneous adverse effects of etretinate than the males skin.

2.The females are more concerned about mucocutaneous adverse effects and record these adverse effects more precisely.

Since all adverse effects of acitretin are the same as etretinate (22,23) and through metabolism back phenomenon, it is converted to etretinate, generalization of the results of this study to acitretin is possible.

We concluded that there is a straight relationship between mucocutaneous adverse effects with sex and drug dosage. In other words, the mucocutaneous adverse effects were more prevalent in females and with higher dosages. Color changing of hair, hair waving, dyspareunia, and gynecomastia were observed as rare adverse effects.

Etretinate: Tigasone Roche Co.
Acitretin: Soriatane 9
Isotretinoin: Accutane
Bexarotene: Targretin

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