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Research Article

SCREENING OF SUMMARY OF PRODUCT CHARACTERISTICS OF DESLORATADINE (5 MG) FOR CARDIOVASCULAR SAFETY

Ozaydin Ayse Nilufer[1] and Ozaydin Fuat Nihat[2,3]

[1]Medical Faculty, Puplic Health Department, Marmara University
[2]Medical Faculty, Pharmacology Department, Okan Univesity
[3]Vocational School of Health Services, Yakındoğu University

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ABSTRACT

Objective: Antihistaminic drugs are frequently used in the treatment of allergic diseases. Second-generation antihistamines such as desloratadine are preferred because they are more reliable in terms of side effects. In this study, Turkey Summary of Product Characteristics of desloratadine was examined in terms of cardiovascular safety.

Methods: Desloratadine Summary of Product Characteristics has been obtained from Turkey, Food and Drug Association and European Medicines Agency web page, if not possible, from web sites of producers with non-profit organizations, and evaluated with current literature.

Results: Tachycardia, palpitations and QT prolongation are mentioned in the "undesirable effects" section of desloratadine Summary of Product Characteristics. No other side effect has been specified. However, some in vitro studies have shown that high-dose desloratadine interacts with cardiac muscar ini creceptors and may affect normal cardiac function. Moreover investigators have indicated that patients with cardiovascular disease should be monitored closely. Turkey Pharmaceutical and Medical Devices Agency Technical Pharmacology Commission has sent an announcement to producers of desloratadine in 2012 and stated that "the use of desloratadine in patients with cardiovascular problems requires careful observation" should be added to the "special warnings and precautions for use" of Summary Product Characteristics.

Conclusion: "Patients with cardiovascular disease using desloratadine should be closely monitored" should be written in the desloratad in Summary Product Characteristics. This warning will protect healthcare workers from medico legal responsibilities.

INTRODUCTION

Non-communicable diseases are increasing in Turkey. The Turkish Ministry of Health published the "Chronic Diseases and Risk Factor Identification Study" to produce policies aimed at preventing noncommunicable diseases (1). The prevalence of cardiovascular diseases over the age of 15 years was found to be 12.7% in this study (1, 2). It was also found that the mean age of the coronary events was 58.8 years and the median age was significantly lower than 6 years ago (3).

For this reason, the Public Health Institution affiliated to the Ministry of Health explained the "2015-2020 Action Plan for Prevention and Control of Cardiovascular Diseases in Turkey". Some of the targets of the described plan are "to implement treatment successfully with rational drug applications, to apply drug treatment according to national and international guidelines by making cardiovascular risk assessment for individuals aged 40 years and over" (1, 2). One of the sources to be used for rational drug use is the Summary of Product Characteristics (SPC). The SPC is an official statement containing indications, posology, warnings, side effects and other essential information about drug. It is prepared by the drug manufacturer and approved by the official authority. It is forbidden to change the content without the approval of the official authority (4).

Antihistamines are one of the most frequently prescribed drug groups in the treatment of adult allergic diseases. Second-generation antihistamines such as desloratadine are preferred because they are more reliable with respect to psychomotor and cardiovascular side effects (5, 6).

Corresponding author:* **Ozaydin Ayse Nilufer
Medical Faculty, Puplic Health Department, Marmara University

In this study; Turkey SPC of desloratadine 5 mg was examined in terms of cardiovascular safety and compared with the content of desloratadine 5 mg SPC originating from the Food and Drug Administration (FDA) and European Medicines Agency (EMA) and interpreted in the light of the current literatures.

MATERIALS AND METHODS

Desloratadine SPCs were obtained from Turkey, Food and Drug Administration and the European Medicines Agency web sites. If it was not possible to obtain from these sources, obtained from the websites of producers and non-profit organizations.

The following sections of the SPC have been examined and, if any, the differences were noted: Posology and method of administration, Contraindications, Special warnings and precautions for use, Interaction with other medicinal products and other forms of interaction, Undesirable effects, overdose, pharmacodynamic properties, pharmacokinetic properties. Literatures were searched with desloratadine, cardiovascular, disease, mortality, pharmacovigilance keywords in the PubMed database,.

RESULTS

Posology and method of administration, Contraindications, Special warnings and precautions for use, Interaction with other medicinal products and other forms of interaction and Overdose sections do not have cardiovascular safety information in the Turkey SPC. Tachycardia, palpitations were noted in the side effects section (7).

In the pharmacokinetic section, 4-6% of adults have been reported to metabolize desloratadine slowly. In this group the maximum blood concentration of desloratadine was 3 times higher and the half lifewas up to 89 hours. However, the safety profile of slow metabolizers was not different from the general population (7). Under the title of elimination, grapefruit juice and desloratadine interaction were mentioned, and no information was given about elimination of the molecule. Careful use in severe renal failure was recommended. There was no specific information for the liver failure and geriatric population (7).

Tachycardia, palpitations and QT prolongation have been reported in undesirable effects section of the Turkish SPC. There is no further information (7). The content of Turkey SPC was compatible with EMA-derived SPC. However, there were differences between Turkey and FDA-based SPC content (7,8,9,10).

According to FDA SPC, a starting dose of 5 mg tablet every other day was recommended in adult patients with liver or renal impairment, based on pharmacokinetic data. (table 1)

Table 1 Differences between Desloratadine (5mg) SPCs of Turkey, EMA and FDA

	SPCs of Turkey	**SPCs of EMA**	**SPCs of FDA**
Undesirable effects/Adverse reactions/Side-effects	Tachycardia, palpitations	Tachycardia, palpitations (Very rare) QT prolongation (Not known)	tachycardia, palpitations
Clinical Pharmacology (Pharmacodynamics and Pharmacokinetics)	In a pharmacokinetic study where the patient profile was similar to he general seasonal allergic rhinitis population, 4% of the volunteers had a higher desloratadine concentration. This percentage varies by ethnic background. The Cmax concentration was 3-fold higher at about 7 hours and the terminal phase half-life was about 89 hours. The safety profile of these patients did not differ according to the general population. Elimination: In a single dosetrialusing a 7.5 mg dose of desloratadine, there was no effect of food (high-fat, high caloric breakfast) on the disposition of desloratadine. In another study, grape fruit juice had no effect on the disposition of desloratadine. Linearity / non-linearity:	In a pharmacokinetictrial in which patient demographics were comparable to those of the general season alallergic rhinitis population, 4 % of the subjects achieved a higher concentration of desloratadine. This percentage may vary according to ethnic background..The safety profile of these subjects was not different from that of the general population. Elimination: In a single dosetrialusing a 7.5 mg dose of desloratadine, there was no effect of food (high-fat, high caloric breakfast) on the disposition of desloratadine. In another study, grape fruit juice had no effect on the disposition of desloratadine.	Subjects who are poor metabolizers of desloratadine cannot be prospectively identified and will be exposed to higher levels of desloratadine following dosing with there commended dose of desloratadine. Although not seen in these studies, an increased risk of exposure-related adverse events in patients who are poor metabolizers cannot be ruled out. Elimination: The mean plasma elimination half-life of desloratadine was approximately 27 hours. Cmax and AUC values increased in a dose proportion almanner following single oral doses between 5 and 20 mg. The degree of accumulation after 14 days of dosing was consistent with the half-life and dosing frequency. A human mass balance study documented a recovery of approximately 87% of the 14C-desloratadine dose, which was equally distributed in urine and feces as metabolic products. Analysis of plasma 3- hydroxydesloratadine showed similar Tmax and half-life values compared to desloratadine.
Use in special populations	Hepatic Impairment: No data are available in patients with hepatic impairment Renal Insufficiency: In the case of severe renal insufficiency, 5 mg desloratad in should be used with caution Geriatric Population: There are no specific studies targeting the geriatric population.	Renal Insufficiency: In the case of severe renalin sufficiency, desloratad in should be used with caution	Adults with Hepaticor Renal Impairment: In adult patients with liver or renal impairment, a starting dose of one 5-mg tablet *every other day* is recommended based on pharmacokinetic data. Geriatric Use: Clinical studies of desloratadine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Dose selection for elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. In the case of severe renal insufficiency, desloratadine 5mg a day should be used with caution. Finally there were dose differences between SPCs (7,8,9,10).

In the pharmacokinetic part of the FDA-derived SPC, it was stated that the risk of increased side effects due to exposure can not be ignored in those who metabolize desloratadine slowly (7,8,10).

DISCUSSION

Treatment protocols recommend high doses in unresponsive patients. According to the treatment protocol for urticaria, if no response to a standard dose is elicited, increasing the dose up to fourfold is recommended (11). In slow metabolizers, the blood concentration of desloratadine and possibility of side effects will be much higher than in non-slow-metabolizers.

Some *in vitro* studies have shown that high dose of desloratadine affects normal cardiac function through muscarinic receptors. Hence, authors have suggested that patients with disorders of the cardiovascular system should be monitored closely while using desloratadine (12,13).

In another study where European countries and the FDA Side-effect reporting system were analyzed together, the pro-arrhythmic potential of antihistamines was investigated. Torsades de Pointes, QT anomaly, ventricular arrhythmia, and sudden cardiac death / cardiac arrest were considered as criteria. At the end of the study, it was decided that one of the antihistamines with a strong pharmacovigilance signal was desloratadine. Cardiac side effects with desloratadine usage were not common. But the results were very serious. For this reason, it was proposed to conduct further analytical researches and to take risk-reducing activities with health authorities and clinicians (14).

Finally; the Turkish Drug and Medical Devices Agency sent an announcement to the producers of desloratadine and stated that "The use of desloratadine requires careful observation in persons with cardiovascular problems" should be added to precaution section of SPC upon the decision made by the Technology Pharmacology Commission (15,16).

Cardiovascular safety information is important for patients who metabolize the desloratadine slowly and also use high-dose desloratadine.

In order to protect the healthcare provider from potential medicolegal responsibility, producers should add this precaution to SPC of desloratadine immediately (17).

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