Austin Therapeutics

Austin Publishing Group

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Research Article

Adverse Events of Oral Loratadine Spontaneously Reported to Manufacturers in Poland in 6-Year Period

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Received: September 04, 2014; **Accepted:** October 07, 2014; **Published:** October 07, 2014

Abstract

Spontaneous (passive) reports of adverse drug reactions are very important in drug safety monitoring.

Aim of the Study: Analysis of the adverse events of oral loratadine marketed in Poland.

Methods and Material: We contacted all manufactures marketing loratadine in Poland (Hasco-LekS.A.Galena, US Pharmacia, Sandoz, MSD Polska) and analysed spontaneous reports on the adverse effects of oral loratadine reported in 2008-2013.

Results: There were five spontaneous reports concerning these medications registered in the period analyzed. Polish total loratadine market at that time was estimated at 3.2-5.3 million packs per year.

Conclusion: Oral loratadine is a safe medication rarely causing adverse effects. Single adverse events were reported in 6-year observation period when 26.7 million of medication units were distributed in Poland. The existing monitoring system of adverse effects in Poland may not be sensitive enough to detect all adverse effects.

Keywords: Pharmacoepidemiology; Drug safety; Phamacovigilance

Introduction

An azatadine-derivative, loratadine is a second-generation competitive histamine H1 receptor antagonist widely used in the treatment of allergic rhinitis and urticaria as a long-acting antihistamine drug. Unlike most classic first-generation antihistamines, it lacks central nervous system depressing effects such as drowsiness [1].

Patented in 1981, loratadine was introduced to the pharmaceutical market in 1988 in Belgium, and in 1993 in the USA by Schering-Plough as Claritin and is now available in 114 countries, as an over-the-counter medication in 33 of them [2].

The drug is effective in the management of allergic rhinitis and allergic skin reactions such as urticaria and itching sensations [3]. Loratadine is one of the most common antihistamines worldwide, which is demonstrated by the large number of loratadine-containing medications registered worldwide. There are five manufacturers of loratadine in Poland: HASCO-LEK S.A., the manufacturer of Loratan soft capsules containing 10mg of the active substance and syrup with loratadine concentration of 5mg/5 ml., Galena, the manufacturer of Loratadyna Galena 10 mg tablets and Loratadyna Pylox 10 mg tablets, US Pharmacia, the manufacturer of Aleric Lora 10 mg tablets, Sandoz, the manufacturer of Flonidan 10 mg tablets, Flonidan Control 10 mg tablets and Flonidan suspension (1mg/ml) and MSD Polska marketing Claritine 10 mg tablets, Claritine Alergy 10 mg tablets and Claritine Alergy syrup (1mg/ml).

According to current literature sources, loratadine is a very safe drug [3,4]. The most serious andfrequent adverse effects of loratadine include somnolence, tachycardia and headaches [5]. Furthermore, administration of the drug may cause sleep disorders, vertigo, cardiac arrhythmias, nausea, vomiting, diarrhoea or constipation, and vision disorders [4]. Allergic rash and a receding hairline were also reported [6]. Table 1 below lists the adverse effects contained in the Summary of Product Characteristics for the reference drug Claritine (Table 1).

In clinical trials in a paediatric population, in children aged 2 to 12, common adverse reactions reported in excess of placebo were: headache (2.7%), nervousness (2.3%), and fatigue (1%). In clinical trials involving adults and adolescents for a range of indications including allergic rhinitis and chronic idiopathic urticaria at the recommended dose of 10mg daily, adverse reactions with loratadine were reported in 2% of patients in excess of those treated with placebo. The most frequent adverse events reported in excess of placebo were: somnolence (1.2%), headache (0.6%), increased appetite (0.5%) and insomnia (0.1%). Other adverse reactions were reported very rarely during the post-marketing period (SmPC, Claritin, 2011).

Polish current pharmacovigilance system is based on EU legislation. As part of the pharmacovigilance system, the manufactures monitor spontaneous reporting i.e. adverse reaction reports submitted by healthcare professionals and patients or their guardians. The manufactures cooperate with the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products based in Warsaw, which is the central pharmacovigilance unit in Poland. The monitoring system is focused on the detection of new drug interactions and adverse reactions as well as groups of patients more prone to adverse reactions.

Citation: Karłowicz-Bodalska K, Han S, Miśkiewicz K, Kutycka E and Kuchar E. Adverse Events of Oral Loratadine Spontaneously Reported to Manufacturers in Poland in 6-Year Period. Austin Therapeutics. 2014;1(1): 3.

Table 1: The adverse effects of oral loratadine (Summary of Product Characteristics for the reference drug Clarityn Allergy®, own modification).

Organ/system involved	Adverse effects
Immune system	Anaphylaxis
Nervous system	Dizziness, Headache
Cardiac	Tachycardia, palpitation
Gastrointestinal	Nausea, dry mouth, gastritis
Hepatobiliary	Abnormal hepatic function
Skin and subcutaneous tissue	Rash, alopecia
General disorders and administration site conditions	Fatigue, somnolence, increased appetite

Aim of the Study

Analysis of the adverse events of oral loratadine marketed in Poland to detect new, as yet unknown adverse effects of loratadine and evaluates loratadine safety.

Material and Methods

We contacted all five manufactures marketing loratadine in Poland (Hasco-Lek S.A. Galena, US Pharmacia, Sandoz, MSD Polska) in last 6 years. Data concerning loratadine adverse reaction reports and sales volumes in Poland available in a passive spontaneous reporting system were analyzed, covering the period between January 2008 and December 2013.

Results

During the analysed period the manufacturers marketing loratadine in Poland received only five adverse event reports.

The first report involved an 82-year-old female patient who suffered a sudden rise in blood pressure up to 195/105 mmHg accompanied by tachycardia (pulse132/minute) following administration of one Loratan capsule. The patient was treated for chronic depression, ischaemic heart disease and arterial hypertension with: Coaxil, Doxepin, Amlozek, Effox long and Hydroxyzine syrup. Once the drug was withdrawn, the adverse effects did not reoccur.

The second patient was over 60-year old woman taking aspirin and dietary supplements (Bodymax, magnesium containing products). A rash on the trunk was observed after she had taken a single LoratanPro capsule (over the counter medication).

The third patient was a 39-year old woman chronically treated with several antipsychotic medications (Absenor 500, Chlorprotixen Zentiva 50mg, Sulpiryd 50 mg) for psychosis associated with schizophrenia. An exacerbation of allergic symptoms including swelling around the eyes, tearing, burning and redness of the skin was observed when she had taken a loratadine tablets.

The fourth patient was 28-year old man treated for allergic rhinitis with Buderhin (budesonide intranasal aerosol)and Loratadine Galena 10 mg tablets. The patient complained about drowsiness and vertigo, which disappeared after discontinuation of loratadine tablets.

The fifth patient was 61-year old diabetic woman chronically treated with insulin, Prestarium and Bisocard. Adisseminated erythematic rash on the trunk and extremities with itching was observed after she had taken a single loratadine tablet (Loratadyna Galena). Similar adverse reaction had been observed 2 months before, when she had taken a tablet of Claritine.

The Polish total loratadine market in period 2008-2013 was estimated at 3.2 to 5.3 million packs per year. About 26.7 million packs of loratadine containing products were sold in Poland in ^{3} year period analyzed.

Discussion

The adverse effects of loratadine are similar to other non-sedating antihistamines in general. In contrast to sedating antihistamines which the most common adverse effect is Central Nervous System (CNS) depression, non-sedating antihistamines generally cause little or no drowsiness. The most commonly reported adverse effects of standard loratadine dosage (10 mg/daily) were: headache (12%), somnolence (8%), fatigue (4%) and dry mouth (3%) [7]. Loratadine like most non-sedating antihistamines has little anti-muscarinic effect. That is why typical anti-muscarinic effects, such as dry mouth, thickened respiratory-tract secretions, blurred vision, urinary difficulty or retention, constipation, and increased gastric reflux are reported rarely. The other adverse effects include headache, psychomotor impairment and occasional gastrointestinal symptoms: nausea, vomiting, diarrhea and epigastric pain. Palpitations and arrhythmias although reported occasionally were a particular disadvantage of the astemizole and terfenadine, the non-sedating antihistamines. The hazardous ventricular arrhythmias led to important restrictions on their use but were not reported with loratadine, which has a broad therapeutic margin and does not prolong the QT interval [8]. Antihistamines sometimes cause rashes and other hypersensitivity reactions (including bronchospasm, angioedema, and anaphylaxis). Blood dyscrasia (agranulocytosis, leucopenia, haemolytic anaemia, and thrombocytopenia) although rare, have been reported. Jaundice has also been seen. Convulsions, sweating, myalgia, paraesthesias, extrapyramidal effects, tremor, sleep disturbances, depression, confusion, tinnitus, hypotension, and hair loss have been reported with the antihistamines [9].

According to FDA records, loratadine is characterized by very good clinical safety and adverse reaction reports are recorded approximately twice every 100,000 therapies [2]. Analyses of loratadine-containing medicinal products during their 6-year market presence on the Polish market prove their safety. Only five adverse reaction reports against a 26.7 million packs distributed(less than 1 adverse event per million) may, however, suggest low sensitivity of the existing polish pharmacovigilance system. According to FDA records, approximately 60 reports should be expected [2]. Similarly, the electronic drug safety RxISK database (https://www.rxisk.org/Default.aspx) also including consumer reports, contains 2,685 reports where loratadine was the suspect drug covering 8,942 reactions, of which 1,868 do not specify the patient's country. RxISK data base is based on 3.9 million reports submitted to the FDA's MedWatch from 1st January 2004 to 31st March 2012, of which approximately a third of these reports come from outside the United State. This may result from a lack of awareness among medical professionals on the usefulness of any adverse drug related data, including known and common adverse reactions. The weakness of this paper is that it is based on passive adverse event reports and the cases were confounded and there was no dechallenge-rechallenge data available. Presented cases leave unanswered question regarding causality. The strength

is of our study is a 6-year observation period of the entire Polish population.

Conclusion

No new adverse effect of loratadine was identified. Oral loratadine is a very safe medication rarely causing already known adverse effects. However, the existing spontaneous monitoring system of adverse effects in Poland is not sensitive enough and needs improvement.

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Austin Therapeutics - Volume 1 Issue 1 - 2014
ISSN: 2472-3673 | www.austinpublishinggroup.com

Citation: Karłowicz-Bodalska K, Han S, Miśkiewicz K, Kutycka E and Kuchar E. Adverse Events of Oral Loratadine Spontaneously Reported to Manufacturers in Poland in 6-Year Period. Austin Therapeutics. 2014;1(1): 3.