ORIGINAL RESEARCH ARTICLE

Drug Safety 2009; 32 (2): 169-179
0114-5916/09/0002-0169/$49.95/0

Examining the Tolerability of the Non-Sedating Antihistamine Desloratadine

A Prescription-Event Monitoring Study in England

Deborah Layton,[1,2] *Lynda Wilton*[1,2] and *Saad A.W. Shakir*[1,2]

1 Drug Safety Research Unit, Southampton, UK
2 University of Portsmouth, Portsmouth, UK

Abstract

Background: Desloratadine is a non-sedating, long-acting histamine H_1 receptor antagonist indicated for the symptomatic relief of allergic rhinitis (AR) and chronic idiopathic urticaria in patients aged >12 years.

Objective: To monitor the safety of desloratadine as prescribed in England, using the observational cohort technique of prescription event monitoring (PEM).

Methods: Exposure data were derived from dispensed prescriptions written by primary care physicians (general practitioners [GPs]) for desloratadine (March–May 2001); patient demographics, indication, pattern of use and outcome (event) data were obtained via simple questionnaires returned by GPs. Incidence density observation rates (IDobs) were calculated to compare the difference in event rates between months 1 and 2 $_{(m1/m2)}$ and were compared for the whole cohort and by groups defined by indication and pattern of use.

Results: The cohort comprised 11 828 patients (median age 37 years [interquartile range 22, 54]; 59.9% were female). The most frequent indication was AR (n = 8001; 67.6%). After 2 months, 36.8% (n = 2464) of patients were still taking desloratadine. 'Condition improved' was the most common event and reason for stopping. Headache/migraine was uncommon but associated with starting treatment ($IDobs_{(m1/m2)}$ ratio 3.99 [95% CI 1.70, 10.83]). Cardiovascular events occurred rarely or very rarely, as did central and peripheral nervous system events. No serious adverse drug reactions (ADRs) were reported. Events related to effectiveness were more frequent in month 1 than month 2 for all patient subgroups.

Conclusions: This postmarketing surveillance study shows that desloratadine is well tolerated when used in general practice in England. No previously unrecognized ADRs were detected. This study highlights how modifications to PEM are contributing to the evaluation of drug utilization factors in relation to risks.

Background

Desloratadine, launched in April 2001 in the UK, is the primary metabolite of loratadine.[1] It is a non-sedating, long-acting histamine H_1 receptor antagonist initially indicated for the relief of allergic rhinitis (AR) [seasonal] in adults and adolescents aged >12 years. The indication was extended to include chronic idiopathic urticaria in August 2001.[2] Some antihistamines have been associated with serious adverse drug reactions (ADRs), for example, cardiac arrhythmias.[3,4] Cases of ventricular arrhythmias have been reported in the literature for loratadine, this being relevant since desloratadine is the primary active metabolite.[5]

To complement the information regarding safety collected from clinical studies and spontaneous reporting schemes, the Drug Safety Research Unit (DSRU) carries out postmarketing surveillance studies of newly marketed drugs with widespread use in primary care in England, using the observational cohort technique of prescription event monitoring (PEM).[6] PEM is conducted in accordance with international ethical guidelines.[7-9] This report summarizes the results of a PEM study conducted for desloratadine. Of particular interest were events reported within the first 2 months after starting treatment, particularly within the central and peripheral nervous system (CPNS), psychiatric, and cardiovascular (CV) system organ classes (SOC). The objective was to monitor the safety of desloratadine prescribed in the primary care setting in England by primary care physicians (general practitioners [GPs]), using the observational cohort technique of PEM.

Methods

Exposure data were obtained from dispensed National Health Service prescriptions issued by GPs between March and May 2001, which were collected by the national prescription-processing centre in England. Demographic and event data (see table I for event definition) for each individual patient, plus information on prescribing indication and duration of treatment were obtained by sending questionnaires ('green forms') to the prescribing GP at least 6 months after the date of the patient's first prescription. The forms also included additional questions requesting information on pattern of use of desloratadine (continuous daily use [≥15 days], a short course [≤14 days] or multiple short courses; note: multiple responses possible) and previous antihistamine use. Importantly, additional information was collected on whether desloratadine was prescribed to patients for AR with or without concurrent asthma because of the association between these conditions.[10-13]

An event was coded as an ADR if the GP specified that the event was attributable to desloratadine. All events reported on green forms were coded onto the PEM database using the DSRU event dictionary. This hierarchical dictionary is arranged in a system organ classification. It groups associated doctor summary event terms (terminology used by the prescribing physician) under lower-level event terms, which are mapped to broader higher-level event terms.

Rare and serious events were followed up if an alternative explanation for their occurrence was not given. Pregnancies were also followed up to ascertain the outcome. If no clear cause of death could be established from the green form, the patient's GP was contacted to try to ascertain the certified cause of death.

Individual case reports were assessed for causality by two research fellows (at least one of whom was medically qualified) at the DSRU, using the criteria of temporality, pharmacological plausibility, clinical and pathological characteristics, concomitant treatment, rechallenge/dechallenge, past medical history and exclusion of other causes, and graded as 'probable', 'possible', 'unlikely' or 'unassessable'.[14]

Analysis

The statistical power for the detection of adverse events in PEM has been described elsewhere.[6] Summary statistics were calculated for the demographic characteristics of patients. Event incidence densities by observation (IDobs)

Table I. Incidence densities (ID) of reported events[a] for desloratadine, ranked in order of $IDobs_{m1}$ per 1000 patient-months observation (where $IDobs_{m1} \geq 1$)

Higher term	N_1	N_2	$IDobs_{m1}$	$IDobs_{m2}$	$IDobs_{(m1/m2)}$ (95% CI)	Reason for stopping[b]
Condition improved[c]	**1384**	**606**	**117.04**	**51.34**	**2.28 (2.07, 2.51)**	**1984**
No further request	658	77	55.65	6.52	8.53 (6.73,10.95)	733
Not effective	537	238	45.41	20.16	2.25 (1.93, 2.63)	772
Course completed	177	24	14.97	2.03	7.36 (4.79, 11.80)	201
Upper respiratory tract infection	53	47	4.48	3.98	1.13 (0.75, 1.70)	5
Patient request	40	16	3.38	1.36	2.50 (1.37, 4.77)	56
Hospital referrals no admission	30	13	2.54	1.10	2.30 (1.17, 4.81)	14
Headache, migraine[c]	**28**	**7**	**2.37**	**0.59**	**3.99 (1.70, 10.83)**	**9**
Lower respiratory tract infection	24	17	2.03	1.44	1.41 (0.73, 2.79)	1
Other drug substituted	23	13	1.95	1.10	1.77 (0.86, 3.80)	36
Urinary tract infection[c]	**19**	**6**	**1.61**	**0.51**	**3.16 (1.21, 9.67)**	**0**
Effective	17	2	1.44	0.17	8.49 (2.01, 75.72)	19
Infection skin, unspecified/local bacterial	17	9	1.44	0.76	1.89 (0.79, 4.80)	0
Rhinitis allergic	17	18	1.44	1.52	0.94 (0.46, 1.94)	5
Asthma worse	16	12	1.35	1.02	1.33 (0.59, 3.08)	2
Depression	16	10	1.35	0.85	1.60 (0.68, 3.94)	1
Injury	15	12	1.27	1.02	1.25 (0.55, 2.92)	0
Pain abdomen	14	8	1.18	0.68	1.75 (0.68, 4.81)	4
Rash	14	7	1.18	0.59	2.00 (0.75, 5.84)	2
Menstrual disorder	8	9	1.01	0.85	0.89 (0.30, 2.59)	0
Pregnancy	8	8	1.13	1.13	1.00 (0.33, 3.05)	7
Eczema	12	10	1.01	0.85	1.20 (0.47, 3.10)	1

a Event: "any new diagnosis, any reason for referral to a consultant or admission to hospital, any unexpected deterioration (or improvement) in a concurrent illness, any suspected drug reaction, any alteration of clinical importance in laboratory values, or complaint of sufficient importance to enter into the patient's notes".

b Events recorded as reason for stopping (n = 3669) in first 2 months, of 5559 for total observation period.

c Clinical events associated with starting treatment are highlighted in bold.

$IDobs_{m1}$ = ID for each event during the first month of observation; **$IDobs_{m2}$** = ID for each event during observation month 2; **$IDobs_{(m1/m2)}$** = ratio between $IDobs_{m1}$ and $IDobs_{m2}$; **N_1** = total number of reports of each event during the first month of observation; **N_2** = total number of reports of each event during observation in month 2.

[no. of first reports/1000 patient-months of observation] were calculated and ranked. For each patient, the denominator was calculated according to the period of observation (i.e. the period between starting the drug and the end of the PEM survey period) rather than the period of treatment, to reflect the intermittent pattern of use of antihistamines. The numerator was the first report of events regardless of treatment status (on drug, off drug or status unknown). IDobs for events reported in month 1 ($IDobs_{m1}$), and month 2 ($IDobs_{m2}$) were compared for the whole cohort and subgroups defined by indication or pattern of use. For this PEM study for signal detection of pharmacologically related (type A) events, month 2 of observation was chosen as the reference period to month 1, when type A events were less likely to occur. This assumed that if an event occurred it was as likely to be reported to the prescriber during treatment as after stopping. For purposes of stratification by indication, patients were grouped into the following categories: AR with asthma/wheezing, AR without asthma/wheezing, urticaria, 'other' (all other specified indications) and 'not specified'. IDobs for the overall period ($IDobs_A$) were also compared between

subgroups of patients defined by selected characteristics. Significant IDobs ratios were regarded as signals of changes in event rates, where the 95% confidence intervals (CI) excluded the null value of one.

Results

Drug Utilization

The cohort comprised 11 828 patients (median age 37 years [interquartile range 22, 54]; 59.9% [n = 7086] were female). Where age was specified (n = 6525), 132 (2.1%) patients were aged <12 years. In total, 6189 (52.3%) patients were recorded as having AR (with no record of asthma) as an indication. An additional 1812 (15.3%) patients had AR with asthma/wheezing, 2015 (17%) patients had urticaria and 1297 (11%) patients had other indications reported (e.g. allergy). Of all the 8001 patients who had AR, 67 (0.8%) also had urticaria. Event data for these 67 patients were not examined separately since the number was very small; these patients were included within the relevant AR indication subsets. The GP did not state an indication for 515 (4.4%) patients.

Of the 9943 (84% of the total cohort) reports where information on starting dose was provided, 9618 (97%) patients were initially prescribed 5 mg/day. A small number of patients were reported as having been prescribed doses outside of the recommended licensed daily dose (5 mg); 305 patients (3%) were prescribed 10 mg/day, 14 (<1%) were prescribed ≥15 mg/day and 6 patients were prescribed 2.5 mg/day. Starting dose (categorized as <5 mg, 5 mg or >5 mg) was not associated with indication {chi-squared (χ^2) test degrees of freedom (df) [6]; $p = 0.110$}. Where an opinion by the prescriber was provided, 82.3% (5460/6633) felt that the drug was effective; dose was not associated with effectiveness (χ^2, df [2]; $p = 0.232$).

Of the 6705 patients for whom it was recorded that treatment was continuing or that the date of stopping was reported, 2464 (36.8%) patients were still being prescribed desloratadine at the end of month 2. Where responses to additional questions were provided (yes or no) on pattern of use, the majority of patients (86.7%; 5885/6788) were reported to be continuous users (daily ≥15 days), 51.8% (1991/3841) had a short course (daily ≤14 days) and 29.8% (1086/3639) had multiple short courses. Of note, 37 patients for whom information from the additional questions was in conflict were excluded from subsequent relevant analyses.

Incidence Densities and Events of Interest

The most frequently reported events during the first 2 months of observation of the whole cohort are presented in table I. Condition improved had the highest $IDobs_{m1}$ and was frequently reported as a reason for stopping for the whole cohort and for subgroups of patients defined by prescribing indication (table II) or pattern of use (data not shown). Headache/migraine occurred significantly more often in month 1 than month 2 for the whole cohort (n = 35, $IDobs_{m1/m2}$ ratio 3.99 [95% CI 1.70, 10.83]) and also for patients with AR without asthma/wheezing (n = 19, $IDobs_{m1/m2}$ ratio 5.33 [95% CI 1.52, 28.52]). As expected, patients being treated for AR with asthma/wheezing had a significantly higher IDobs overall for events related to the respiratory SOC than patients with AR without asthma; the most frequent being 'asthma worse' (n = 60, $IDobs_A$ ratio 22.20 [95%CI 10.47, 54.11]).

Clinical events of interest within the CPNS, psychiatric SOC and CV SOC recorded as occurring during the first 2 months of treatment[1] for desloratadine and assessed as 'possibly' related are summarized in table III. Headache was reported uncommonly (>0.1%, <1%), whilst drowsiness, migraine, syncope and sedation were rare (>0.01%, <0.1%). Chest pain, palpitations, bradycardia (detected by resting ECG), arrhythmia and atrial fibrillation (confirmed by ECG) occurred rarely or very rarely, with no reports of myocardial infarction (MI). Malaise and lassitude were also reported rarely. Twenty events were reported by the GPs as ADRs to desloratadine in

1 Event treatment status coded as 'on drug'; the first 2 months after starting treatment was chosen to reflect length of exposure in clinical studies of desloratadine.

Table II. Significant higher term incidence densities (IDobs) ratios comparing month 1 with month $2_{(m1/m2)}$, ranked in descending order of $IDobs_{(m1/m2)}$, by indication

Higher term	N_1	N_2	$IDobs_{(m1/m2)}$ (95% CI)
Allergic rhinitis (with asthma/wheezing)			
No further request	76	9	8.43 (4.22, 19.15)
Course completed	13	4	3.25 (1.00, 13.67)
Not effective	69	32	2.15 (1.40, 3.39)
Condition improved	127	86	1.48 (1.11, 1.96)
Allergic rhinitis (without asthma/wheezing)			
Urinary tract infection	10	1	9.98 (1.42, 433.31)
No further request	341	49	6.95 (5.14, 9.58)
Hospital referrals no admission	12	2	5.99 (1.33, 55.11)
Course completed	46	8	5.74 (2.68, 14.08)
Headache, migraine	16	3	5.33 (1.52, 28.52)
Patient request	24	9	2.66 (1.19, 6.51)
Not effective	237	125	1.89 (1.52, 2.37)
Condition improved	565	375	1.50 (1.32, 1.72)
Urticaria			
No further request	117	9	12.99 (6.61, 29.12)
Course completed	57	7	8.14 (3.70, 21.15)
Condition improved	462	88	5.25 (4.17, 6.67)
Not effective	122	34	3.59 (2.43, 5.41)
Other indications			
Course completed	52	3	17.27 (5.59, 86.48)
No further request	96	6	15.95 (7.06, 44.53)
Condition improved	200	40	4.98 (3.53, 7.18)
Not effective	93	41	2.26 (1.55, 3.35)

N_1 = total number of reports of each event during the first month of observation; N_2 = total number of reports of each event during observation in month 2.

18 patients, of which five (neck pain, drowsiness, sore eye, stammer and syncope) were documented on the green form as having been reported to the Committee on Safety of Medicines (now called the Commission on Human Medicines) with all assessed as possibly related to use of desloratadine. Fourteen ADRs to other drugs were reported in 12 patients, of which five were recorded during treatment with desloratadine. Of these, four (cough, photosensitivity, convulsion and allergy) were listed in the summary of product characteristics as undesirable effects of that drug (for the fifth ADR, the event was not specified). There were no serious ADRs to desloratadine reported during this study.

Prior antihistamine use (within 12 months) was reported for 33.7% (3468/10 294) of patients, of which use of more than one drug was reported for 67 (1.93%) patients. The most common were loratadine/Clarityn® (1760 reports [49%]), cetirizine/Zirtek® (875 reports [24%]) and fexofenadine/Telfast® (437 reports [12%]). New users were more likely to have a positive response to treatment than past users (condition improved, n = 190, $IDobs_A$ ratio 2.77 [95% CI 1.89, 4.19]) and less likely to have clinical events such as upper respiratory tract infection (n = 324, $IDobs_A$ ratio 0.69 [95% CI 0.55, 0.87]) or asthma (n = 64, $IDobs_A$ ratio 0.56 [95% CI 0.33, 0.95]).

Pregnancies

There were 40 pregnancies reported during the study period, of which 29 occurred during treatment or within 3 months of stopping desloratadine. Of these, 18 patients were exposed to desloratadine during the first trimester, for which nine live births (no defects reported), two spontaneous abortions, one missed abortion and one therapeutic termination were reported, whilst for five the outcome was not ascertained. One woman was exposed to desloratadine in the third trimester, resulting in a live birth (no further information provided). Of the remaining ten, eight women were recorded as taking desloratadine in the 3 months prior to conception but stopped treatment before the last menstrual period, whilst for two pregnancies the GP could not be sure when the patient had last taken desloratadine.

Deaths

The number of deaths reported during the study period was low (<1%, n = 64), of which the cause of death was not ascertained for 18 patients. For the remainder, the most common cause was cancer (19/46 [41%]), followed by CV causes (9/46 [20%]) with one death (from congestive heart failure) in a female patient of unknown age, occurring in the first month of treatment. There were three deaths due to a MI; two occurred during treatment (both more than 6 months after starting) and one occurred more

Table III. Number and incidence of reports of clinical events of interest within the central and peripheral nervous system (CPNS) and cardiovascular (CV) system organ classes (SOC) in the first 2 months of observation, and summary of events followed up and assessed as possibly related to desloratadine use

SOC lower term event	Total no. (%) reported in months 1 and 2 of treatment [no. followed up][a]	Information on follow-up cases				
		DSRU causality assessment as 'possible'	age (y) at start of treatment	sex (M; F)	days to event (range)	ADR to desloratadine
CPNS						
Drowsiness	8 (0.07) [7][b]	4	28; NS	2; 2	1–32	1 (CSM)
Headache	25 (0.21) [16][c]	5	10–83	2; 3	1–28	0
Migraine	5 (0.04) [4][d]	2	39; 61	0; 2	1–24	0
Sedation	3 (0.03) [3]	2	31; 49	1; 1	1–15	1
Syncope	2 (0.02) [2]	1	20	1; 0	4	1 (CSM)
CV						
Pain chest	6 (0.05) [4][e]	1	NS	0; 1	53	0
Bradycardia	1 (<0.01) [1]	1	90	0; 1	21	0
Atrial fibrillation	1 (<0.01) [1]	1	87	1; 0	43	0
Palpitation	4 (0.03) [4]	2	NS	0; 2	17–57	0
Psychiatric						
Lassitude	7 (0.06) [4][f]	2	30; 57	1; 1	22–57	1
Malaise	5 (0.04) [5]	2	91; NS	0; 2	1–13	0

a Footnotes in this column describe the reasons events were not selected for follow-up.

b Not reason for stopping (n = 1).

c Pre-existing (n = 1), not reason for stopping (n = 6), other cause (n = 1), details included with related event (n = 1).

d Re-occurred off drug (n = 1).

e Other cause (n = 1), pre-existing (n = 1).

f Not reason for stopping (n = 2), details included with related event (n = 1).

ADR = adverse drug reaction; **CSM** = Committee on Safety of Medicines (now known as Commission on Human Medicines); **DSRU** = Drug Safety Research Unit; **F** = female; **M** = male; **NS** = not specified.

than 5 months after stopping. No deaths were attributed to the use of desloratadine by the reporting GPs.

Discussion

This PEM study provides a descriptive and quantitative analysis of a population prescribed desloratadine under primary care conditions in England and a summary of the events reported during use.

Strengths and Limitations

The strengths and limitations of this study design have been described in detail elsewhere.[15] PEM uses a non-interventional observational cohort design that does not interfere with the prescribing decisions of the GPs, as patients are identified from dispensed prescriptions. It is a form of active surveillance in that the prescriber is prompted to respond, unlike passive spontaneous reporting schemes.

PEM collects information on large cohorts (frequently over 10 000) of newly marketed drugs prescribed under 'real life' conditions of general practice. Unlike pre-marketing clinical trials, no specific inclusion criteria are applied. Data include health-related events recorded in the patients' notes after treatment with the drug being monitored, thus minimizing recall bias, and provides reliable exposure denominators. PEM is regarded as a hypothesis-generating postmarketing system for safety signals and applies several methods for this purpose.

As for all pharmacoepidemiological methods, PEM has weaknesses. This PEM study had a low response rate (44.7%) compared with the average response rate obtained for 93 PEM studies performed by the DSRU (55.6%). However, the response rate is still substantial compared with spontaneous reporting schemes.[16,17] Bias introduced from the low response rate is possible; the degree to which non-response bias may have affected the results was not assessed. Outcome misclassification is a potential bias in any study dependent on reporting by a third party, and bias introduced by under-reporting of events cannot be ruled out. Evidence suggests that reporting of suspected ADRs in PEM is higher than spontaneous reporting for both serious and non-serious events.[16]

Compliance with treatment cannot be measured (as with most observational pharmacoepidemiological studies) and this may lead to an underestimation of the measure of effect, or to a false conclusion regarding any possible associations between the drug and any outcomes. PEM only relates to general practice, and does not include hospital prescriptions. Lastly, detection of serious rare or very rare ADRs (such as drug-induced torsade de pointes, with an estimated incidence of the order of 1 per 12 000 to 1 per 120 000 patients[18]) is not always possible because PEM studies still have insufficient power to detect such events, despite larger cohort sizes than seen in randomized controlled trials.[6]

Cohort Characteristics

This desloratadine cohort has similar demographic characteristics to those in other post-marketing studies and randomized clinical trials reported elsewhere,[11,19] and appears to be representative of patients with AR and other allergic conditions from the general population.[20,21] Desloratadine use was reported outside the terms of license with regard to age (in children aged <12 years), although the proportion was low (2%). In this PEM study, the most common prescribing indication reported overall was AR (either with or without asthma/wheezing) [67.6%], reflecting licensed indications. However, desloratadine was also prescribed for a range of acute conditions, predominantly allergic in nature.

Incidence Densities and Events of Interest

For this PEM study, the justification for the calculation of incident densities using the observation period was based on the limited information on exposure for such drugs, which were often taken on a short-term basis and for which concordance is unknown. We acknowledge that the choice of month 2 as the reference period does not allow for examination of adverse events with delayed onset. Testing of the null hypothesis of no difference in rates between the 2 months was specific for this study to examine data for signals of type A events only.

For the whole cohort, the most frequently reported clinical events in month 1 were upper respiratory tract infection (4.48/1000 patient-months) and headache/migraine (2.37/1000 patient-months). The incidence of upper respiratory tract infection in month 1 was similar to month 2. This is expected, given that this is a common presenting complaint in general practice. Conversely, headache/migraine occurred significantly more often in the first month than the second month ($IDobs_{(m1/m2)}$ ratio 3.99 [95% CI 1.70, 10.83]). Headache was listed as common in the UK summary of product characteristics at launch,[1] whilst in this PEM study headache was uncommon (0.21%) in the first 2 months of treatment. Fatigue was also listed as uncommon in the SPC.[1] Terms synonymous with terms in the DSRU dictionary, of lassitude and malaise and other sedating adverse events of drowsiness and sedation, were uncommon (0.2%) in the first 2 months of treatment. These results are similar to that reported elsewhere.[11] Importantly, there were no serious ADRs reported in this PEM study as defined by the DSRU rare iatrogenic ADR list.

Treatment with desloratadine is associated with minimal CNS effects in symptomatic patients,[22,23] but performance has been found to be worse than in asymptomatic patients.[24] CNS effects may be related to the indication (histamine overload during allergic reaction,[25] or due to

nocturnal symptoms and sleep deprivation[26]). Thus, in this study, the reporting and recording of events related to cognitive or psychomotor impairment was not unexpected. Misclassification or under-reporting of CNS adverse effects is possible since people may fail to recognize or underestimate the impact of drug use; this is analogous to use of other chemicals such as alcohol.[26] Desloratadine has been reported to increase drowsiness at higher than recommended doses (particularly 20 mg/day) when compared with placebo.[27] It has also been reported that there are subgroups of individuals who are slow metabolizers of desloratadine in whom the risk of drug accumulation and associated dose-related events cannot be ruled out.[28] Furthermore, concomitant chemicals or co-morbidities that might lead to drug accumulation in the CNS might increase the risk of CNS adverse events[26] but this risk appears low for desloratadine.[29] In this PEM study, there is limited information regarding dose at time of the event, concomitant drug use, genotype or other co-existing medical conditions, therefore the impact of such risk factors on the reporting of CNS (or any other events) cannot be established. Specific information on potential confounding factors such as past or family history of events of interest[26] is not routinely requested on the green form and therefore cannot be examined.

How the frequency of CNS events reported for desloratadine compares with other antihistamines of the same generation used in clinical practice is of interest. The DSRU has conducted a comparison of the frequency of drowsiness/sedation reported during treatment with desloratadine and levocetirizine, using PEM data. Although the number of reports was low (46 [0.37%] and 9 [0.08%], respectively), levocetirizine was more likely to result in reports of drowsiness/sedation than desloratadine in patients with AR without asthma/wheezing (odds ratio [OR] 6.75 [95% CI 2.37, 19.22; n = 12 627]) but no significant difference was observed in patients with AR and asthma/wheezing or other indications (OR 3.51; [95% CI 0.71, 17.43; n = 3357] and OR 3.11; [95% CI 0.86, 11.31; n = 6725], respectively), after adjusting for sex.[30] This study concluded that although the risk of drowsiness/sedation was low, conditions such as AR are common, which makes any impact on patient cognitive function important.

The pro-arrythmogenic potential of non-sedating antihistamines is also of interest.[31-41] Palpitations and tachycardia are listed as very rare undesirable effects of desloratadine.[2] No clinically relevant cardiotoxic effects have been observed for desloratadine at standard or supratherapeutic doses.[2,42] In this PEM study, CV events of interest were rarely or very rarely reported; during the first 2 months of treatment there were no reports of MI. No deaths were attributed to the use of desloratadine by the reporting GPs.

Fetal safety data on antihistamines are extremely important, given that AR is common and that many users of antihistamines tend to be younger women. Loratadine does not appear to increase the risk of major congenital abnormalities.[43] However, a signal has been published regarding increased risk of hypospadias;[44] but remains to be confirmed.[45,46] In this PEM study, no congenital abnormalities were reported.

Drug Utilization

An essential component of pharmacoepidemiological studies is drug utilization research. A strength of PEM is its ability to evolve and adopt modifications to help examine determinants of drug exposure. For example, PEM can collect information on events related to the use of the drug for its intended indication. In this study, events related to effectiveness were the most frequently reported events for the whole cohort and subgroups. This is to be expected for two reasons: first, seasonal AR being the most common indication reported inevitably improves after the causative pollen has ceased to be in season; and second, allergic conditions often vary in severity for individuals over time. Of GPs expressing an opinion, 82% rated desloratadine as effective. This is a subjective indication of a GP's overall assessment of a patient's response, and is not a specific enquiry based on clinical assessments.

This PEM study was among the first PEM studies to request data from the prescriber regarding the pattern of use and history of previous

use, by the inclusion of additional questions on the green forms. In comparing event rates within the first 2 months of observation within and between different subgroups of patients, this study aimed to ascertain whether event profiles would vary. We acknowledge that the classification of patients according to symptoms and disease severity has recently changed.[47-49] In this study, there was some commonality across subgroups defined by prescribing indication, pattern of use and the whole cohort in that event terms related to effectiveness were more frequently reported in the first than the second month of observation (although some ID ratios were not statistically significant) [pattern of use data not shown]. This suggests that effectiveness is unrelated to why the drug was prescribed or subsequently used. However, one explanation for this observation may be related to the fact that the most frequently reported pattern of use was continuous and the most frequently reported indication was AR (with or without asthma/wheezing combined) for which the counts are the highest; these being strongly associated.

However, differences in clinical event profiles were noted when event rates were compared between months within each subgroup and also between subgroups for the whole observation period (although this may be related to subgroup sample size and subsequent effect on significant differences to be observed). As expected, patients with AR with asthma/wheezing had a significantly higher rate over the whole observation period of respiratory SOC-related events. In contrast, it has been reported elsewhere that adequate management of AR in patients with AR and asthma results in a lower incidence of asthma-related complications.[50] Our study did not routinely request information on efficacy in the treatment of asthma, concomitant treatment such as inhaled corticosteroids or long-acting β_2-adrenergic receptor agonists or confounding factors such as smoking[51] or other respiratory diseases;[20] therefore, the severity of disease in these subsets of patients could not be examined. Previous antihistamine exposure was associated with lower rates of (positive) events related to effectiveness and compliance than in new users. This supports the assertion that some people who change treatment may have worse or difficult-to-control symptoms; thus, disease severity should be regarded as an important determinant of drug exposure.

Finally, consideration should be given to seasonality because of variation in allergen exposure. The market penetration of this product was rapid and thus the period during which patients were identified for this PEM study was short (2 months) and was during the spring season. Green forms were sent approximately 9 months later (December 2001–February 2002). Approximately one-quarter of the cohort were still being prescribed desloratadine more than 6 months after starting treatment; thus, their observation period encompassed at least three seasons during which allergen exposure is likely to vary. With regard to tolerability, published short-term clinical studies suggest that there is little difference in the incidence of common treatment-emergent adverse events (headache, pharyngitis, dry mouth and somnolence) during the spring or autumn seasons.[52,53] We have no reason to believe that seasonality had any significant impact on the tolerability profile of desloratadine as recorded in our PEM study.

Conclusions

This postmarketing surveillance study shows that desloratadine is well tolerated when used in general practice in England. No previously unrecognized ADRs were detected. This study highlights how modifications to PEM are contributing to the evaluation of drug utilization factors in relation to risks.

Acknowledgements

The DSRU is an independent charity (no. 327206) that works in association with the University of Portsmouth. It receives unconditional donations from pharmaceutical companies. The companies have no control on the conduct or publication of the studies conducted by the DSRU. The DSRU has received such funds from the manufacturer of desloratadine. Saad Shakir receives honoraria consulting for companies unrelated to desloratadine and acts as an expert

witness on matters unrelated to desloratadine or its manufacturer.

We thank Dr Victoria Cornelius for her contribution to the statistical analyses conducted for this study.

References

1. Schering-Plough Europe. Summary of product characteristics: Neoclarityn (desloratadine) 5 mg tablets. Belgium: SP Europe, 2001 Jan
2. Schering-Plough Europe. Summary of product characteristics: Neoclarityn (desloratadine) 5 mg tablets. Belgium: SP Europe, 2005 Jan
3. Meltzer EO. Comparative safety of H1 antihistamines. Ann Allergy 1991 Dec; 67 (6): 625-33
4. Yap YG, Camm J. Risk of torsades de pointes with non-cardiac drugs: doctors need to be aware that many drugs can cause QT prolongation. BMJ 2000 Apr 29; 320 (7243): 1158-9
5. Clark S. Dangers of non-sedating antihistamines. [letter]. Lancet 1997 May 3; 349 (9061): 1268
6. Shakir S. Prescription-event monitoring. In: Strom BL, editor. Pharmacoepidemiology. 4th ed. Chichester: John Wiley & Sons Ltd, 2005: 203-16
7. CIOMS/WHO. International guidelines for biomedical research involving human subjects. Geneva: CIOMS, 2002
8. Royal College of Physicians of London. Guidelines on the practice of ethical committees in medical research involving human subjects. London: RCP, 1996
9. General Medical Council. Frequently asked questions supplement to: confidentiality: protecting and providing information. London: General Medical Council, 2004: 9
10. Spector SL. Overview of comorbid associations of allergic rhinitis. J Allergy Clin Immunol 1997 Feb; 99 (2): S773-80
11. Bachert C, Virchow Jr CJ, Plenker A. Desloratadine in the treatment of seasonal allergic rhinitis: results of a large observational study. Clin Drug Invest 2002; 22 Suppl. 2: 43-52
12. Broide DH. Molecular and cellular mechanisms of allergic disease. J Allergy Clin Immunol 2001 Aug; 108 (2 Suppl.): S65-71
13. Baena-Cagnani CE. Desloratadine activity in concurrent seasonal allergic rhinitis and asthma. Allergy 2001; 56 Suppl. 65: 21-7
14. Shakir S. Causality and correlation in pharmacovigilance. In: Talbot J, Waller P, editors. Stephens' detection of new adverse drug reactions. 5th ed. Chichester: John Wiley & Sons Ltd, 2004: 329-43
15. Shakir SA. PEM in the UK. In: Mann RD, Andrews E, editors. Pharmacovigilance. 1st ed. Chichester: John Wiley & Sons Ltd, 2002: 333-44
16. Heeley E, Riley J, Layton D, et al. Prescription-event monitoring and reporting of adverse drug reactions. Lancet 2001 Dec 1; 358 (9296): 1872-3
17. Martin RM, Kapoor KV, Wilton LV, et al. Underreporting of suspected adverse drug reactions to newly marketed (''black triangle'') drugs in general practice: observational study. BMJ 1998 Jul 11; 317 (7151): 119-20
18. De Ponti F, Poluzzi E, Montanaro N. QT-interval prolongation by non-cardiac drugs: lessons to be learned from recent experience. Eur J Clin Pharmacol 2000 Apr; 56 (1): 1-18
19. Ring J, Hein R, Gauger A, et al. Once-daily desloratadine improves the signs and symptoms of chronic idiopathic urticaria: a randomized, double-blind, placebo-controlled study. Int J Dermatol 2001 Jan; 40 (1): 72-6
20. Bauchau V, Durham SR. Prevalence and rate of diagnosis of allergic rhinitis in Europe. Eur Respir J 2004 Nov; 24 (5): 758-64
21. Kozel MM, Sabroe RA. Chronic urticaria: aetiology, management and current and future treatment options. Drugs 2004; 64 (22): 2515-36
22. DuBuske L. Pharmacology of desloratadine: special characteristics. Clin Drug Invest 2002; 22 Suppl. 2: 1-11
23. Henz BM. The pharmacologic profile of desloratadine: a review. Allergy 2001; 56 Suppl. 65: 7-13
24. Satish U, Streufert S, Dewan M, et al. Improvements in simulated real-world relevant performance for patients with seasonal allergic rhinitis: impact of desloratadine. Allergy 2004 Apr; 59 (4): 415-20
25. Verster J, De Weert A, Bijtjes S, et al. Driving ability after acute and sub-chronic administration of levocetirizine and diphenhydramine: a randomized, double-blind, placebo-controlled trial. Psychopharmacology 2003; 169: 84-90
26. Simons FE. Advances in H1-antihistamines. N Engl J Med 2004 Nov 18; 351 (21): 2203-17
27. Spangler DL, Brunton S. Efficacy and central nervous system impairment of newer-generation prescription antihistamines in seasonal allergic rhinitis. South Med J 2006 Jun; 99 (6): 593-9
28. Schering Corporation. Clarinex (desloratadine product information package insert) [online]. Available from URL: http://www.spfiles.com/piclarinex.pdf [Accessed 2007 Nov 15]
29. Geha RS, Meltzer EO. Desloratadine: a new, nonsedating, oral antihistamine. J Allergy Clin Immunol 2001 Apr; 107 (4): 751-62
30. Layton D, Wilton L, Boshier A, et al. Comparison of the risk of drowsiness and sedation between levocetirizine and desloratadine: a prescription-event monitoring study in England. Drug Saf 2006; 29 (10): 897-909
31. Rankin AC. Non-sedating antihistamines and cardiac arrhythmia. Lancet 1997 Oct 18; 350 (9085): 1115-6
32. Yap YG, Camm AJ. Arrhythmogenic mechanisms of non-sedating antihistamines. Clin Exp Allergy 1999 Jul; 29 Suppl. 3: 174-81
33. Davies AJ, Harindra V, McEwan A, et al. Cardiotoxic effect with convulsions in terfenadine overdose. BMJ 1989 Feb 4; 298 (6669): 325
34. Honig PK, Woosley RL, Zamani K, et al. Changes in the pharmacokinetics and electrocardiographic pharmacodynamics of terfenadine with concomitant administration of erythromycin. Clin Pharmacol Ther 1992 Sep; 52 (3): 231-8
35. Mathews DR, McNutt B, Okerholm R, et al. Torsades de pointes occurring in association with terfenadine use. JAMA 1991 Nov 6; 266 (17): 2375-6

36. Monahan BP, Ferguson CL, Killeavy ES, et al. Torsades de pointes occurring in association with terfenadine use. JAMA 1990 Dec 5; 264 (21): 2788-90
37. Woosley RL. Cardiac actions of antihistamines. Annu Rev Pharmacol Toxicol 1996; 36: 233-52
38. Zimmermann M, Duruz H, Guinand O, et al. Torsades de pointes after treatment with terfenadine and ketoconazole. Eur Heart J 1992 Jul; 13 (7): 1002-3
39. Simons FE, Kesselman MS, Giddins NG, et al. Astemizole-induced torsades de pointes [letter]. Lancet 1988 Sep 10; 2 (8611): 624
40. Snook J, Boothman-Burrell D, Watkins J, et al. Torsades de pointes ventricular tachycardia associated with astemizole overdose. Br J Clin Pract 1988 Jun; 42 (6): 257-9
41. De Bruin ML, van Puijenbroek EP, Egberts AC, et al. Non-sedating antihistamine drugs and cardiac arrhythmias: biased risk estimates from spontaneous reporting systems? Br J Clin Pharmacol 2002 Apr; 53 (4): 370-4
42. Kreutner W, Hey JA, Chiu P, et al. Preclinical pharmacology of desloratadine, a selective and nonsedating histamine H1 receptor antagonist. 2nd communication: lack of central nervous system and cardiovascular effects. Arzneimittelforschung 2000 May; 50 (5): 441-8
43. Gilbert C, Mazzotta P, Loebstein R, et al. Fetal safety of drugs used in the treatment of allergic rhinitis: a critical review. Drug Saf 2005; 28 (8): 707-19
44. Kallen B. Use of antihistamine drugs in early pregnancy and delivery outcome. J Matern Fetal Neonatal Med 2002 Mar; 11 (3): 146-52
45. Centers for Disease Control and Prevention (CDC). Evaluation of an association between loratadine and hypospadias: United States, 1997-2001. MMWR Morb Mortal Wkly Rep 2004 Mar 19; 53 (10): 219-21
46. Loratadine, desloratadine and pregnancy: don't use, risk of hypospadias [letter]. Prescrire Int 2003 Oct; 12 (67): 183
47. Bachert C, van Cauwenberge P. The WHO ARIA (allergic rhinitis and its impact on asthma) initiative. Chem Immunol Allergy 2003; 82: 119-26
48. Bauchau V, Durham SR. Epidemiological characterization of the intermittent and persistent types of allergic rhinitis. Allergy 2005 Mar; 60 (3): 350-3
49. Khanna P, Shah A. Categorization of patients with allergic rhinitis: a comparative profile of ''sneezers and runners'' and ''blockers''. Ann Allergy Asthma Immunol 2005 Jan; 94 (1): 60-4
50. Crystal-Peters J, Neslusan C, Crown WH, et al. Treating allergic rhinitis in patients with comorbid asthma: the risk of asthma-related hospitalizations and emergency department visits. J Allergy Clin Immunol 2002 Jan; 109 (1): 57-62
51. Bousquet J, Boushey HA, Busse WW, et al. Characteristics of patients with seasonal allergic rhinitis and concomitant asthma. Clin Exp Allergy 2004 Jun; 34 (6): 897-903
52. Meltzer EO, Prenner BM, Nayak A, et al. Efficacy and tolerability of once-daily 5 mg desloratadine, an H1 receptor antagonist, in patients with seasonal allergic rhinitis: assessment during the Spring and Fall allergy seasons. Clin Drug Invest 2001; 21 (1): 25-32
53. Laforest L, Bousquet J, Pietri G, et al. Quality of life during pollen season in patients with seasonal allergic rhinitis with or without asthma. Int Arch Allergy Immunol 2005 Mar; 136 (3): 281-6

Correspondence: Dr *Deborah Layton*, Drug Safety Research Unit, Bursledon Hall, Blundell Lane, Southampton, UK SO31 1AA.
E-mail: deborah.layton@dsru.org