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Comparison of the Risk of Drowsiness and Sedation between Levocetirizine and Desloratadine

A Prescription-Event Monitoring Study in England

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Abstract

Background and objectives: Desloratadine and levocetirizine are histamine H_1 receptor antagonists (antihistamines) that were launched in the UK in 2001. Our objective was to compare the frequency with which drowsiness and sedation were reported for desloratadine and levocetirizine within the first 30 days of observation, as monitored using the observational cohort technique of prescription-event monitoring (PEM).

Methods: Exposure data were derived from dispensed prescriptions written by primary care physicians and outcome data were derived from questionnaires that were posted to prescribers at least 6 months after the date of the first prescription for each patient. The odds ratio (OR) was calculated using unconditional logistic regression modelling. The effect of age, sex, reported prescribing indication (allergic rhinitis with asthma/wheezing, allergic rhinitis without asthma/wheezing, 'other'), pattern of use and reported previous antihistamine use on the OR was examined. A time-to-event analysis was performed.

Results: The cohorts comprised >24 000 patients in total. Cohort demographics were similar (both cohorts: median age 37 years; 60% women); the most frequently reported prescribing indication for both drugs was allergic rhinitis without asthma/wheezing (54%). The incidence of first reports of drowsiness/sedation for levocetirizine or desloratadine was low (46 [0.37%] and 9 [0.08%], respectively) and statistically different ($p < 0.0001$). These events tended to occur earlier for desloratadine than levocetirizine (50% at 7 or 14 days of observation, respectively; $p = 0.6487$), but the cumulative time to event differed, with more events observed for levocetirizine than expected ($p < 0.0001$; 46 vs 28.09). The final estimates of risk were the sex-adjusted ORs for each prescribing indication category: allergic rhinitis with asthma/wheezing (3.51; 95% CI 0.71, 17.43; n = 3357), allergic rhinitis without asthma/wheezing (6.75; 95% CI 2.37, 19.22; n = 12 627) and 'other' (3.11; 95% CI 0.86, 11.31; n = 6725).

Discussion: Although the reporting rates of drowsiness and sedation are low for both drugs, patients prescribed levocetirizine are more likely to experience

drowsiness and sedation in the first month of observation (after starting treatment) than patients prescribed desloratadine. For patients with allergic rhinitis without asthma/wheezing, the sex-adjusted odds of drowsiness/sedation were over six times greater in patients using levocetirizine than desloratadine in the first month of observation, with the OR being statistically significant. For the other two indication categories, allergic rhinitis with asthma/wheezing and 'other', the OR was not statistically significant.

Conclusions: Although the risk of drowsiness/sedation is low, conditions such as allergic rhinitis are common, which makes any impact on patient cognitive function important. Doctors should be aware of this when prescribing these products to patients where daytime sedation is undesirable. However, essential components of the comparative benefit-risk evaluation of these two products include assessment of efficacy and patient preference (neither of which forms part of this study).

Background

There has been much debate regarding the motivation behind the availability of levocetirizine (the biologically active [R] enantiomer of cetirizine, a piperazine derivative[1]) and desloratadine (the primary metabolite of loratadine, a piperadine derivative[2]) and whether such follow-on drugs provide extra benefit over their parent compounds.[3] Although the impact on the disease and quality of life of both of these products is apparent,[4,5] differences in their tolerability profile are less so. The persistence and severity of CNS-depressant effects is known to vary between histamine H_1 receptor antagonists (antihistamines)[6-8] and between patients.[9] Both cetirizine and levocetirizine have been reported to lack the CNS-depressant effects associated with first-generation antihistamines at routine clinical doses.[8,10] However, both may still cause sedation and impairment of performance at or slightly above the therapeutic dose.[1,9,11,12] Neither loratadine nor desloratadine is reported to be associated with an impairment of performance at routine clinical doses.[13,14]

The Drug Safety Research Unit (DSRU) provides a national postmarketing drug surveillance scheme that monitors the safety of newly marketed medicines during their immediate postmarketing period in England. Cohorts are frequently >10 000 patients. The non-interventional observational cohort technique of prescription-event monitoring (PEM) collects data on patients who have been prescribed new drugs in primary care clinical practice.[15] PEM is conducted in accordance with international ethical guidelines.[16-18]

Individual PEM studies have been conducted on six antihistamine drugs: acrivastine, cetirizine, loratadine, fexofenadine, desloratadine and levocetirizine, with desloratadine and levocetirizine being the most recent (both marketed in 2001). The DSRU has previously published the results of a comparison of the frequency of first reports of events: 'drowsiness' and 'sedation' reported during treatment with second-generation antihistamines using PEM data.[7] Although the incidence of reports was low (<0.8%), cetirizine and acrivastine were approximately three times more likely to result in reports of sedation than loratadine (age- and sex-adjusted odds ratio [OR] 3.53; 95% CI 2.07, 5.42 and 2.79; 95% CI 1.69, 4.58, respectively), with no significant difference observed between loratadine and fexofenadine (OR 0.63; 95% CI 0.36, 1.11).

Since data collection and analysis in the PEM studies for levocetirizine and desloratadine were different from the earlier PEM studies on antihistamines, this study examined data for levocetirizine and desloratadine only. Our objectives were to examine and compare the incidence of drowsiness and sedation reported during the first 30 days of observation after starting treatment in two large cohorts of

patients prescribed either desloratadine or levocetirizine by general practitioners (GPs) under primary care conditions. It is hoped that this study will provide useful information to clinicians and also patients on the relative likelihood of drowsiness and sedation in patients prescribed either drug under general practice conditions.

Methods

Data Collection

The methodology of PEM has been described in detail elsewhere.[15] Patients were identified from dispensed National Health Service (NHS) prescription data that were supplied in confidence by the Prescription Pricing Authority (PPA)[1] in England. Simple questionnaires (green forms) were posted to the prescribing GP at least 6 months after the date of the first prescription for each patient.

Data were collected on prescribing indication, patient demographics and outcomes (a definition for 'events' is provided in footnote a of table I) that were reported to have occurred during the study period. Information on the use of other antihistamines in the 12 months prior to starting either study drug was collected, to try to identify those patients for whom the condition being treated may have been chronic or more severe. The respective cohorts for desloratadine and levocetirizine comprised those patients for whom a completed questionnaire was returned (table II).

Statistical Power for the Detection of Adverse Events

The ability to detect adverse events (at a given frequency) in a PEM cohort (of a given size) has been described in detail elsewhere.[15] This is a retrospective analysis of selected PEM event data that had already been collected for large cohorts of patients who had been prescribed these antihistamines. Such comparisons are not the primary focus of PEM studies.

Table I. Drug Safety Research Unit (DSRU) outcome event[a] dictionary terms

Body SOC	Higher level term	Lower level term
Main analysis		
Central and peripheral nervous SOC	Drowsiness, sedation	Drowsiness
		Sedation
CNS-depressant events		
Central and peripheral nervous SOC	Drowsiness, sedation	Drowsiness
		Sedation
	Dizziness	Dizziness[b]
	Headache, migraine	Headache[b]
	Lost consciousness	Lost consciousness[b]
Psychiatric SOC	Confusion	Confusion[b]
	Malaise, lassitude	Lassitude[b]
		Malaise[b]

a 'Event' was defined as "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". Events were coded onto a computer using the DSRU hierarchical event dictionary, with doctor summary terms (the actual wording of the event reported from the general practitioner prescriber) grouped under specific 'lower' level terms, themselves grouped together under broader 'higher' level terms and arranged by SOC.

b Non-specific terms were evaluated by a clinician and the relevant lowest level (doctor terms) included in the analysis (data not shown).

SOC = system organ class.

Analysis

Summary statistics for the demographic characteristics of the patients in each cohort and the reported prescribing indications (higher level term [HT]: 'allergic rhinitis' with HT: 'asthma/wheezing'; 'allergic rhinitis' without HT: 'asthma/wheezing'; and 'other') for each of the study drugs were calculated; differences between categorical variables were tested using the Pearson Chi-squared (χ^2) test, and differences between continuous variables were tested using parametric two-sample Student's t-tests or non-parametric tests, where appropriate.

1 Now the Prescription Pricing Division of the National Health Service Business Services Authority (NHS BSA) for England (2006).

The selected incident events (first reports of the HT 'drowsiness/sedation') were those reported within the first 30 days of observation with either drug. Where a patient had an event of interest, but no event date was provided by the GP, these cases (n = 2 for levocetirizine only) were excluded from the final analyses since one could not be certain in which month the event had occurred.

Unconditional logistic regression modelling was used to calculate the OR (95% CI) estimate of drowsiness/sedation in patients prescribed levocetirizine compared with patients prescribed desloratadine. The effects of confounding factors (age and sex) and risk factors (prescribing indication and previous antihistamine use) were investigated. The prescribing indication of allergic rhinitis was stratified according to the presence or absence of concurrent asthma. This was based on the association between allergic rhinitis and asthma,[19] which was reflected in how the prescribing indication data were requested on the green forms for each drug. These categories of prescribing indications are mutually exclusive because of the way that data have been retrieved from the DSRU database (PEMbase2); therefore, stratum-specific ORs were calculated because patient characteristics within each sub-category are likely to be different. A sensitivity analysis was conducted to examine the effect of missing values in the model. Finally, differences in the incidence of drowsiness/sedation between the two drugs over time were examined by plotting Kaplan-Meier time-to-event curves and compared using the log rank test.

The analysis was repeated using a second event group that comprised drowsiness and sedation combined with other selected CNS-depressant effects (see table I). Although the terms within this second group are generally used to describe depressant effects on the CNS, it is recognised that an individual patient or GP's opinion of what is regarded as 'sedation' or 'drowsiness' may be subjective.[20] The event terms for this study were selected by DSRU clinical staff from the DSRU dictionary, according to their medical judgement *a priori*. Terms such as 'tiredness' were not included as these would not necessarily be related to drowsiness or sedation; it is noted that some of the selected terms could also have been associated with manifestations in patients other than those of drowsiness or sedation. The analysis was conducted in STATA 8.0 (Stata Corporation, College Station, TX, USA).

Results

Case and Cohort Description

Over 99% of patients within both PEM cohorts were observed for ≥30 days after starting treatment.

Table II. Survey dates and response rates for prescription-event monitoring (PEM) studies of desloratadine and levocetirizine

PEM study	Desloratadine	Levocetirizine
Prescription collection dates	March 2001–May 2001	November 2001–November 2002
Green form send dates	December 2001–February 2002	July 2002–April 2003
No. of patients identified	53 869	82 398
No. of green forms sent[a] (% of forms identified)	30 270 (56.2)	29 503 (35.8)
No. of green forms returned (% of forms sent)	13 536 (44.7)	14 502 (46.5)
No. of voids[b] (% of forms returned)	1 708 (12.6)	1 961 (13.5)
Size of cohort	11 828	12 367

a In PEM, green forms will not be sent for all patients identified during the immediate postmarketing period; generally, collection ceases when the size of the cohort reaches ≥10 000.

b Forms were classified as void if the forms were left blank (with no written information); the doctor had retired, resigned, died or moved; the patient was no longer registered with the practice, had moved or could not be traced; the details of the patient or drug were incorrect or incomplete; duplicate forms had been sent; the general practitioner did not wish to participate; or the drug had not been taken.

Table III. Summary characteristics for patients reported to have had drowsiness and sedation within 30 days of observation after starting treatment with levocetirizine or desloratadine

Characteristic	Levocetirizine (n = 46)	Desloratadine (n = 9)
Age (y)		
median	40	50.5
range	11–74	19–86
not known	7	3
Sex [n (%)]		
male	14 (30.4)	5 (55.6)
female	32 (69.6)	4 (44.4)
Indication [n (%)]		
allergic rhinitis with asthma/wheezing	6 (13.0)	2 (22.2)
allergic rhinitis without asthma/wheezing	29 (63.0)	4 (44.4)
other	10 (21.7)	3 (33.3)
not known	1 (2.2)	0
Use of antihistamine in previous 12 months [n (%)]		
yes	20 (43.5)	5 (55.6)
no	19 (41.3)	4 (44.4)
not known	7 (15.2)	0

Within this observation period, the incidence of a first occurrence of drowsiness/sedation for levocetirizine or desloratadine was low (46 [0.37%] and 9 [0.08%] cases, respectively) and statistically different (χ^2 $p < 0.0001$). Events tended to occur earlier for desloratadine than levocetirizine, but not statistically significantly so (50% at 7 or 14 days of observation, respectively, Kruskall-Wallis test $p = 0.6487$). These cases occurred predominantly in middle-aged patients, for whom the prescribing indication was allergic rhinitis without asthma/wheezing, and more often in previous antihistamine users (table III).

The characteristics of the two PEM drug cohorts from which the data for this retrospective analysis were derived are presented in table IV. Where specified, the demographics of the desloratadine and levocetirizine cohorts were similar (both cohorts: median age 37 years, interquartile range [IQR] 22–55 and 22–54 years, respectively; approximately 60% women). However there was a statistical difference for sex, with male patients being less likely to be prescribed desloratadine than levocetirizine. The proportion of patients for whom age was not known was large, with a higher proportion for the desloratadine cohort than the levocetirizine cohort (38.5% and 16.1%, respectively). This difference can be attributed to the way that information on this variable was collected (for levocetirizine, "year of birth" was requested, whereas for desloratadine "age at study start" was collected). The proportion of patients for whom information on past antihistamine use was missing was also large, but similar (approximately 18%) for both cohorts. Important differences between the cohorts were that the proportion of patients for whom the prescribing indication was specified as allergic rhinitis with asthma/wheezing was higher for desloratadine than for levocetirizine (16.0% vs 13.5% of values known, χ^2 $p < 0.0001$) and a greater proportion of patients who were reported to be previous antihistamine users were prescribed levocetirizine than desloratadine (38.7% vs 36.0% of values known, χ^2 $p < 0.0001$).

Univariate Analysis

Using Mantel-Haenszel methods, the crude OR suggests that the odds of drowsiness/sedation occurring are nearly five times greater in patients prescribed and dispensed levocetirizine than desloratadine in the first month of observation after starting treatment (OR 4.90; 95% CI 2.40, 10.02) [table V]. No significant association was observed between drowsiness/sedation and age (categorical variable of 10-year age bands; χ^2 $p = 0.606$), sex (χ^2

Table IV. Characteristics of the study cohorts

Characteristic	Levocetirizine (n = 12 367)	Desloratadine (n = 11 828)	χ^2 p-Value[a]
Age			
median age (y)	37	37	
IQR (y)	22–55	22–54	
not known [n (% of total cohort)]	1998 (16.1)	5303 (38.5)	0.9458[b]
Sex [n (%)]			
male	4928 (39.8)	4503 (38.1)	0.005
female	7201 (58.2)	7086 (59.9)	
not known	238 (1.9)	239 (2.0)	
Indication [n (%)]			
allergic rhinitis with asthma/wheezing	1598 (12.9)	1812 (15.3)	<0.0001
allergic rhinitis without asthma/wheezing	6688 (54.1)	6189 (52.3)	
other	3548 (28.7)	3312 (28.0)	
not known	533 (4.3)	515 (4.4)	
Use of antihistamine in previous 12 months [n (%)]			
yes	3950 (31.9)	3468 (29.3)	
no	6255 (50.6)	6161 (52.1)	<0.0001
not known	2162 (17.5)	2199 (18.6)	

a Excludes values not known.

b Kruskal-Wallis test.

IQR = interquartile range.

p = 0.429) or prescribing indication (χ^2 p = 0.651). There was weak evidence of an association for previous antihistamine use (χ^2 p = 0.035), with past users more likely to experience drowsiness/sedation (OR 1.82; 95% CI 1.03, 3.21). Sex (χ^2 p = 0.004), prescribing indication (χ^2 p < 0.0001) and previous antihistamine use (χ^2 p < 0.0001) were associated with exposure to either drug, whereas age was not (χ^2 p = 0.172). Therefore, at the univariate level, sex and previous antihistamine use were identified as confounders. Examination of stratum-specific ORs revealed no evidence of effect modification between any of these variables and drug exposure (data not shown).

Unconditional Logistic Regression Analysis

Since age and sex are strong confounding variables for adverse events, it would be preferable to adjust for both of these factors.[21,22] Adjusting for age would have the consequence of excluding 30% of the data and ten events from the analysis (both cohorts combined). However, given that the distribution of age was similar between the two drugs, where specified (Kruskal-Wallis test, p = 0.9458), and found not to be related to drowsiness/sedation at the univariate level, age was not adjusted for. Adjusting for use of an antihistamine in the previous 12 months would also have the consequence of excluding 18% of data and five events from the analysis, thus making interpretation of the final stratified models less meaningful. The OR adjusted for previous antihistamine use only is presented for completeness (see footnote c in table V).

The sex-adjusted OR of 4.92 (95% CI 2.41, 10.06) for the whole study cohort suggests that levocetirizine is associated with a higher incidence of drowsiness/sedation than desloratadine. The age- and sex-adjusted OR is also presented for completeness (see footnote b in table V), However, it is not possible to be certain whether the reduction in the number of observations within the statistical model (due to missing information on age) contributes to the change in the adjusted estimate of OR when adjusting for both age and sex. Table V also contains the results of the additional event analysis (see section on additional event analysis).

Table V. Odds ratios (ORs)[a] [crude and sex-adjusted] plus sex-adjusted ORs stratified by prescribing indication for drowsiness/sedation, alone and combined with selected CNS-depressant events, in the first month of observation in users of levocetirizine compared with desloratadine[b,c]

Event/drug	No. of events reported in first month of observation of total cohort (%)	Total cohort OR (95% CI) [no. of cases]		Sex-adjusted OR by indication (95% CI) [no. of cases]		
		crude (n = 24 195)	sex-adjusted (n = 23 718)	AR with asthma/wheezing (n = 3357)	AR without asthma/wheezing (n = 12 627)	other (n = 6725)
Drowsiness/sedation						
Desloratadine	9/11 828 (0.08)	(referent)	(referent)	(referent)	(referent)	(referent)
		[9]	[9]	[2]	[4]	[3]
Levocetirizine	46/12 367 (0.37)	4.90 (2.40, 10.02)	4.92 (2.41, 10.06)	3.51 (0.71, 17.43)	6.75 (2.37, 19.22)	3.11 (0.86, 11.31)
		[46]	[46]	[6]	[29]	[10]
Drowsiness/sedation plus selected CNS-depressant events						
Desloratadine	9/11 828 (0.08)	(referent)	(referent)	(referent)	(referent)	(referent)
		[9]	[9]	[2]	[4]	[3]
Levocetirizine	48/12 367 (0.39)	5.12 (2.51, 10.43)	5.13 (2.51, 10.45)	4.03 (0.84, 19.47)	6.98 (2.46, 19.81)	3.11 (0.86, 11.31)
		[48]	[48]	[7]	[30]	[10]

a Calculated using logistic regression modelling.

b Age- and sex-adjusted OR (n = 16 697): drowsiness and sedation, 4.12 (95% CI 1.74, 9.74); drowsiness and sedation plus selected CNS-depressant events, 4.33 (95% CI 1.84, 10.22).

c OR adjusted for use of an antihistamine in previous 12 months (n = 19 834): drowsiness/sedation, 4.03 (95% CI 1.95, 8.34); drowsiness and sedation plus selected CNS-depressant events, 4.24 (95% CI 2.06, 8.74).

AR = allergic rhinitis; **n** = no. of observations included in the model.

The sex-adjusted ORs were the final estimates of risk calculated for each prescribing indication category (table V). The odds of drowsiness/sedation in patients for whom the prescribing indication was allergic rhinitis without asthma/wheezing were over six times greater in patients prescribed and dispensed levocetirizine than desloratadine in the first month of observation, this estimate being statistically significant (OR 6.75; 95% CI 2.37, 19.22). There was an approximate 3-fold non-significant increase in the sex-adjusted odds for the other two indication categories – allergic rhinitis with asthma/wheezing (OR 3.51; 95% CI 0.71, 17.43) and 'other' (OR 3.11; 95% CI 0.86, 11.31) – for patients prescribed levocetirizine compared with desloratadine, respectively.

Sensitivity Analysis

We conducted a complete case analysis of the data and looked at a sensitivity analysis to see if this was different to the full set analysis and thus ascertain whether the reduction in sample size may have contributed in some way to the adjusted OR moving towards the null value. We found that the significant crude models for the whole study cohort and the subgroup of patients for whom the prescribing indication was reported as allergic rhinitis without asthma/wheezing remained significant once we reduced the number of subjects to that for which we have sex information, without adjusting: OR 4.90; 95% CI 2.40, 10.02, n = 23 718 and OR 6.73; 95% CI 2.36, 10.17, n = 12 627, respectively.

For completeness, the crude OR estimates for the whole study cohort also remained significant after excluding patients for whom values for age and, separately, previous antihistamine use were missing: OR 4.10; 95% CI 1.74, 9.70, n = 16 894 and OR 4.10; 95% CI 1.98, 8.47, n = 19 834. There was a change of <0.8 in the OR point estimate for both models. Therefore, confounding was likely to be introduced by missing values, albeit low (<10%).

Survival Analyses

The cumulative time-to-event curves for each drug cohort over the first month of observation were plotted using the Kaplan-Meier method (figure 1). The curve for levocetirizine separates from desloratadine early after the start of treatment and this divergence persists. For the levocetirizine cohort, more cases of drowsiness and sedation were observed than expected (log rank test $p < 0.0001$, χ^2 *df* [1]; 46 vs 28.09, respectively).

Additional Event Analysis

Within the first month of observation, the number of cases for both levocetirizine and desloratadine that were identified as a result of this additional event search remained low (48 [0.39%] and 9 [0.08%], respectively). The sex-adjusted ORs of 5.13 (95% CI 2.51, 10.45) suggest that levocetirizine is associated with a higher incidence of CNS-depressant events including drowsiness and sedation than desloratadine in this period (table V).

Discussion

Our study was a retrospective comparison of selected events from previously conducted PEM studies on levocetirizine and desloratadine. Although the number of reports of drowsiness and sedation in the first month of observation for both the levocetirizine and desloratadine cohorts was low (n = 46 [0.4%] and n = 9 [0.1%], respectively), our study suggests that patients prescribed levocetirizine are more likely to experience drowsiness and sedation in the first month of observation (after starting

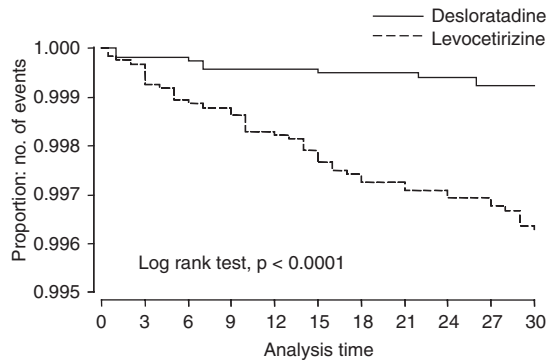

Fig. 1. Kaplan-Meier cumulative time to first event estimates for drowsiness/sedation between the desloratadine and levocetirizine cohorts in the first month of observation after starting treatment.

treatment) than patients prescribed desloratadine. Fifty percent of the incident reports for each drug occurred within 2 weeks after starting treatment, and though they tended to occur sooner for desloratadine, over the 30-day observation period the cumulative time to first event was worse for levocetirizine.

The sex-adjusted OR was considered for the unconditional regression modelling of the final estimates of risk for each prescribing indication category. Each was calculated separately for patients with allergic rhinitis with asthma/wheezing (3.51; 95% CI 0.71, 17.43; n = 3357), allergic rhinitis without asthma/wheezing (6.75; 95% CI 2.37, 19.22; n = 12 627); and 'other' (3.11; 95% CI 0.86, 11.31; n = 6725). Importantly, the number of cases within two of the strata was small, which may have contributed to the findings being non-significant. In the sensitivity analysis, there was a suggestion of slight confounding introduced by missing values for the adjusting variable – a change of <0.2 in the OR point estimate where patients with missing values for sex were excluded from the stratified models – but the reduced model was still highly significant. All results were similar for drowsiness/sedation combined with other selected CNS-depressant events.

Strengths and Limitations

The strengths and limitations of PEM methodology have been described in detail elsewhere.[15] When undertaking comparison studies, it is important that the information used is standardised to minimise bias; in this retrospective study, exposure and outcome data were collected in an identical manner, from day-to-day clinical practice from a large cohort of the general population within a 2-year period. The sizes of the levocetirizine and desloratadine cohorts were substantial (12 367 and 11 828 patients, respectively), enabling the collection of a considerable amount of clinical information from cohorts with similar characteristics (median age 37 years, with approximately two-thirds being female) and that appear to be representative of patients from the general population with allergic rhinitis and other allergic conditions.[23,24]

Prescribers of either drug were asked to report all clinical events from medical records without making an assumption of causality, and cases were subsequently identified according to predefined criteria. Since both PEM studies were conducted in England, this minimises bias attributable to international differences in background prevalence of allergic rhinitis (diagnosed or not), diagnosis, prescribing, recording or reporting practices.[23] Importantly, since the population consists of those patients who were prescribed treatment by nature of their disease, this makes the drug cohorts similar in this regard. Although we acknowledge that observational studies are subject to bias introduced by missing values for important variables, we have no reason to believe that those patients included within either drug cohort and for whom data are missing are inherently different to those patients for whom we have data.

Our study had a few limitations. First, our study was a retrospective comparison of data from two PEM cohorts of patients for whom a green form questionnaire was returned (response rate 46.5% and 44.7%, for levocetirizine and desloratadine respectively). There may be differences in the characteristics and experiences of those patients for whom the prescriber did not return a green form (non-response bias), but these response rates are still substantial compared with spontaneous adverse drug reaction reporting schemes.[25-27]

Second, the PEM studies on these two drugs were not specifically designed to investigate this topic. Thus, specific information on potential confounding factors for drowsiness/sedation (e.g. past history or family history of such events and/or concurrent psychoactive drugs and/or alcohol use[19]) was not requested on the green form. Therefore, the importance of these factors could not be examined in this study. Elsewhere, research is limited to coadministration of alcohol (an additive effect) or the decongestant pseudoephedrine (a counteractive effect) according to psychomotor tests and driving ability.[28] This study is unable to contribute further information on this issue.

Third, since these drugs could be taken intermittently, the accuracy of exposure data cannot be

confirmed. Questions on patterns of use were asked on the green form questionnaire but not answered by all participating GPs, and this prevented us from examining the effect of different lengths of treatment in our analysis.

Fourth, we did not examine possible dose-related effects because each drug is licensed for use as a single dose.

Fifth, under-reporting of adverse events including serious or fatal events is possible in PEM, as for other observational pharmacoepidemiological studies and spontaneous reporting schemes.[26,29] However, we have no reason to believe that prescriber-related or patient-related under-reporting of events occurred differentially with either drug.

Sixth, there is seasonal variation in the severity of disease, with differences in patient symptoms;[30,31] however, short-term clinical studies suggest that there is little seasonal difference in the incidence of common treatment-emergent adverse events.[32] The total PEM observation period for both drugs spanned all four seasons, thus allowing for the monitoring of adverse events in patients who take the drug during times of varying allergen exposure. We acknowledge that the prescribing of desloratadine was such that sufficient patients were identified within the first two months after marketing; thus, the first months of observation were in the spring season. However, we have no reason to believe that seasonality had any significant impact on the tolerability profile of these drugs as recorded during PEM.

Seventh, misclassification bias may have occurred, related to exposure where antihistamines were purchased over the counter (such information was not routinely reported during each PEM study) or to outcome where events have not been recognised or underestimated (this is analogous to use of other chemicals such as alcohol[19]). However, we do not expect this to be different for either cohort.

Finally, another important issue is the categorisation of prescribing indication. Allergic rhinitis has traditionally been subject to a long-standing classification system based on the time of allergen exposure.[33] This system was cited in each summary of product characteristics at launch and subsequently used on the green form questionnaires. In this study, patients for whom the prescribing indication was reported by the GP as perennial or seasonal allergic rhinitis were grouped together. There may be unobservable characteristics that differ between these subgroups, but we are unable to evaluate these because of the small numbers of patients for whom perennial allergic rhinitis was recorded for desloratadine (n = 7 [<0.1%]) compared with levocetirizine (n = 1558 [12.6%]). We acknowledge that there are differences in the licensed prescribing indication for both drugs, in that levocetirizine has a specific indication for perennial allergic rhinitis. This information was requested on the levocetirizine green form only (to reflect licensed indications), which may account for the disproportionate numbers of perennial allergic rhinitis recorded for this drug. However, because the reported indications for desloratadine included some doctor summary event terms of perennial allergic rhinitis and other related prescribing indications, it was considered justifiable to examine allergic rhinitis as a whole (which includes event terms related to seasonal and perennial allergic rhinitis).

The inclusion of a differentiation according to the reporting of prescribing indications related to presence (or absence) of asthma/wheezing was also considered justifiable, despite asthma not being a specific licensed indication for either drug.[34] Allergic rhinitis and asthma are linked by common genetic, environmental and pathophysiological factors; both are mediated at the tissue level by similar effector cells and mediators,[35] and early- and late-phase allergic response patterns are similar.[36] We acknowledge that the classification of patients according to symptoms and severity has recently changed,[33,37] with each category having clear distinct clinical patterns.[38] Because this analysis was retrospective and based on information provided to us on the green forms, it is not possible to re-classify prescribing indications according to the new recommended guidelines.

Confounding by indication is another important consideration, in that there is a possibility that drow-

siness and sedation may be associated with the disease being treated. Sedation may be a direct result of histamine overload during allergic reactions in patients with allergic rhinitis.[39] Furthermore, daytime sedation may also be due to nocturnal symptoms of allergic rhinitis or urticaria causing sleep deprivation.[19] Our study findings, that past users are significantly nearly twice as likely to experience drowsiness/sedation as new users, without accounting for study drug use, supports this further.

Earlier, we described our reasons for stratifying groups of patients according to presence or absence of asthma, in that patients with allergic rhinitis and asthma may be different in some way to patients only diagnosed with allergic rhinitis. We acknowledge that overlap is possible and that asthma (or allergic rhinitis) may not be diagnosed by the GP in patients with an existing medical history of allergic rhinitis (or asthma), respectively. It is possible that patients with both allergic rhinitis and asthma may have worse clinical responses (and subsequently may experience worse outcomes) than those with either allergic rhinitis or asthma alone.[30] In this study, the sex-adjusted OR estimates differed across the three indication categories. Specific comparisons of risk between indication groups were not part of our prespecified objectives.

What Has Been Published Elsewhere?

Our study findings are not unexpected. The UK summary of product characteristics at launch for desloratadine and levocetirizine referred to the event 'fatigue' as an uncommon or common undesirable event, respectively. An observational study conducted in Germany in clinical practice conditions to assess the safety and efficacy of up to 1 month of desloratadine treatment of seasonal allergic rhinitis in 47 953 patients[40] reported that the most common probable/possible treatment-related adverse event was fatigue (n = 47 [0.1%]). Desloratadine does not appear to impair wakefulness or psychomotor performance or to impair driving performance as found in standard objective tests compared with placebo[14,40] or in simulated real-world performance tests on individuals with seasonal allergic rhinitis.[41,42] However, desloratadine does not eliminate CNS effects in patients with allergic rhinitis with active symptoms to the same degree as in allergic rhinitis patients without active symptoms,[42] which suggests that the severity of the condition might be important. This supports our findings.

For levocetirizine, there are no published observational studies. The XPERT (Xyzal in Persistent Rhinitis Trial) study conducted in 551 patients with pre-existing persistent rhinitis provides some data on this topic.[31] Although this study reported no specific details on incidence, the duration (per 100 days treatment) of sedating effects (fatigue, asthenia, somnolence) was low (3.72 days) for levocetirizine and similar to placebo (3.26 days), although it is unclear in the study report as to the temporal relationship between these events and starting treatment. Short-term studies in healthy human volunteers reported that levocetirizine did not produce any deleterious effects on cognitive and psychomotor functions[8] or affect driving performance[39] compared with placebo. There is evidence of a linear relationship of an increasing dose of levocetirizine on the incidence of fatigue, headache and somnolence.[12] Drowsiness is also included in the symptoms associated with overdose.[1]

Biological Mechanisms

Pharmacokinetic and pharmacodynamic differences in rate and extent of body distribution between these two antihistamines may be important in the incidence of clinical effects.[43] The reduced volume of distribution for levocetirizine compared with desloratadine (49 L/kg vs 0.4 L/kg) implies that there will be fewer adverse effects with levocetirizine,[44] which is in contrast to our findings. It is possible that levocetirizine may behave like cetirizine (an ionic molecule with separate positive and negative charges, resulting in a net charge of zero, often called a 'zwitterion'), which under specific environmental conditions may become sufficiently lipophilic to penetrate cell membranes and have a biological effect without accumulating in tissues.[45] Differences between the two drugs in their interaction with the P-glycoprotein (P-gp)

transporter efflux pump that is expressed on the blood-brain barrier,[43,46,47] together with the existence of P-gp genetic polymorphisms,[48] may provide alternative explanations of plausible biological mechanisms.

Conclusion

Our study suggests that, while the reporting rates of drowsiness and sedation are low for both products, patients prescribed levocetirizine are more likely to experience drowsiness and sedation in the first month of observation (after starting treatment) than patients prescribed desloratadine. For patients with allergic rhinitis but without asthma/wheezing, the sex-adjusted odds of drowsiness/sedation alone or in combination with other sedating events were over six times greater in patients using levocetirizine than desloratadine in the first month of observation, the OR being statistically significant. There was an approximate 3-fold non-significant increase in odds for the other two reported indication categories of allergic rhinitis with asthma/wheezing and 'other'. Although the risk of drowsiness/sedation is low, allergic conditions such as allergic rhinitis are common, which makes any impact on patient cognitive function important. Doctors should be aware of this when prescribing these products to patients where daytime sedation is undesirable. However, essential components of the comparative benefit-risk evaluation of these two products include an assessment of efficacy and patient preference (neither of which form part of this study).

Although our PEM study comparison provides useful information on the relative likelihood of drowsiness/sedation in patients prescribed either drug under general practice conditions, our study did not compare the frequency of such events with other second-generation antihistamines used in clinical practice or the parent compounds, loratadine and cetirizine.

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