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Examining the Utilization and Tolerability of the Non-Sedating Antihistamine Levocetirizine in England Using Prescription-Event Monitoring Data

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Abstract

Background: Levocetirizine was launched onto the UK market in September 2001. It is indicated for symptomatic treatment of allergic rhinitis (AR), including persistent AR and chronic idiopathic urticaria.

Objective: The aim of the study was to monitor the safety of levocetirizine prescribed in the primary care setting in England, in the immediate post-marketing period.

Methods: Exposure data were derived from dispensed prescriptions written by primary care physicians (general practitioners [GPs]) for levocetirizine (November 2001–November 2002): patient demographic, indication, pattern of use and outcome (event) data from enhanced prescription-event monitoring (PEM) questionnaires (with additional questions to gather further relevant information) returned by GPs. Incidence density observation rates (IDobs) [number of first reports/1000 patient-months] between months 1 and 2 ($IDobs_{m1/m2}$) were compared for the whole cohort and by groups defined by indication and pattern of use.

Results: The cohort comprised 12 367 patients (median age 37 years [interquartile range 22–55]; 58% female). The most frequent indication was AR (67%; n = 8275). After 2 months, 35.7% (n = 2414) of patients were still taking levocetirizine. 'Condition improved' was the most common event and reason for stopping treatment. Headache/migraine was uncommon but associated with starting treatment ($IDobs_{m1/m2}$ 2.4 [95% CI 1.1, 6.0]), as was drowsiness/sedation ($IDobs_{m1/m2}$ 11.5 [95% CI 4.2, 43.9]). Cardiovascular events occurred rarely or very rarely, as did most 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 levocetirizine is well tolerated when used in general practice in England. No previously unrecognized ADRs were detected. This study highlights how modifications to PEM, such as additional questions, are contributing to the evaluation of drug utilization factors in relation to risks.

Background

Levocetirizine was launched onto the UK market in September 2001.[1] It was indicated at launch for the treatment of symptoms associated with seasonal allergic rhinitis (AR) [including ocular symptoms], perennial AR and chronic idiopathic urticaria (CIU) in adults, adolescents (12 years of age and over) and children (aged 6–12 years). The indications were subsequently revised to the symptomatic treatment of AR (including persistent AR) and CIU (September 2005), simplifying the indication to treatment of AR, regardless of whether it was seasonal or perennial, and CIU.[2]

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).[3] PEM is conducted in accordance with international ethical guidelines.[4-7] This study summarizes the results of a PEM study conducted for levocetirizine. Of particular interest were events reported within the first 2 months after starting treatment, particularly those within the Central and Peripheral Nervous System (CPNS) System Organ Class (SOC), Psychiatric SOC and Cardiovascular SOC. The aim was to monitor the safety of levocetirizine prescribed in the primary care setting in England by primary care physicians (general practitioners [GPs]), using the observational cohort technique of PEM.

Methods

PEM Study Data Collection

Exposure data were obtained from dispensed National Health Service prescriptions issued by GPs between November 2001 and November 2002, which were collected by the national prescription processing centre in England. Demographic and event[1] data 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 levocetirizine (continuous daily use [>15 days], a short course [<14 days inclusive] or multiple short courses [multiple responses possible to this additional question]) and previous histamine H_1 receptor antagonist (antihistamine) use. Importantly, additional information was collected on whether levocetirizine was prescribed to patients for AR with or without concurrent asthma because of the association between these conditions.[8]

An event was coded as an adverse drug reaction (ADR) if the GP specified that the event was attributable to levocetirizine. All events reported on Green Forms were coded onto the PEM database using the DSRU Event Dictionary. This hierarchical dictionary, which is arranged in system-organ classification, 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.

1 The term 'event' is defined as including '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 any other complaint that was considered of sufficient importance to enter in the patient's notes.'

Rare and serious adverse events (classified using the International Conference on Harmonization definitions)[9] 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 medically qualified) at the DSRU, using the criteria of temporality, pharmacological plausibility, clinical and pathological characteristics, concomitant treatment, re/dechallenge, past medical history and exclusion of other causes, and graded as probable, possible, unlikely or unassessable.[10]

Analysis

The statistical power for the detection of adverse events in PEM has been described elsewhere.[3] Summary statistics were calculated for the demographic characteristics of patients. The number of events reported during treatment and observation were calculated by month. Event incidence density observation rates (IDobs) [number of first reports/1000 patient-months] were calculated and ranked. For each patient, the denominator was calculated according to period of observation (i.e. the period between starting the drug and the end of the PEM survey period) rather than 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 signal detection of acute-onset events in this PEM study, month 2 of observation was chosen as the reference period to month 1 as pharmacologically related (acute-onset) events were less likely to occur during this period. 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 observation 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% CIs excluded the null value of one.

Results

Drug Utilization

Of the 29 503 Green Forms posted to GPs, 13 730 (46.5%) were returned. Of these, 1363 (9.9%) were classified as void because they did not contain any clinically relevant data.

The cohort comprised 12 367 patients (median age 37 years; interquartile range [22– 55]; 58.2% [n = 7201] female). Summary characteristics for the total cohort are provided in table I.

The leading primary indication for patients treated with levocetirizine was AR in 8275 patients (66.9%) and the most common secondary indication was asthma in 1602 patients (13%).

Table I. Summary characteristics of total cohort

Characteristics	No. (%) [n = 12 367]
Age at start of treatment (y)	
<10	245 (2.0)
10–19	1940 (15.7)
20–49	4930 (39.9)
50–79	2882 (23.3)
≥80	372 (3.0)
Not known	1998 (16.2)
Mean age (SD)	39.5 (20.7)
Sex	
Males	4928 (39.8)
Females	7201 (58.2)
Not known	238 (1.9)
Indication	
AR (with no record of asthma)	6688 (54.1)
AR with asthma/wheezing	1598 (12.9)
Urticaria	2348 (19.0)
Other indications	1200 (9.7)
Not known	533 (4.3)

AR = allergic rhinitis.

In total, where specified as a primary, secondary or tertiary indication (aggregate groups from primary, secondary and tertiary indications provided by GPs), 6688 (54.1%) patients had AR alone with no record of asthma as an indication, 1598 (12.9%) patients had AR with asthma, 2348 (19.0%) patients had urticaria and 1200 (9.7%) patients had other indications reported (e.g. allergy). Of all the 8287 patients who had AR, 88 patients also had urticaria. The GP did not state an indication for 533 patients (4.3%).

Use of levocetirizine in children aged 12 years and under was common (n = 760; 6.1% of the total cohort), with ten children (0.1% of the total cohort) aged between 2 and 5 years in the cohort. There were no children under the age of 2 years in the study. The majority of children aged 12 years and under were reported to be male (n = 429; 56.4% of children aged 12 years and under), whilst the most frequently reported primary indication in this subset was AR (n = 621; 81.7% of children aged 12 years and under).

Of 10 726 reports (86.7% of the total cohort) where information on starting dose was provided, 10 495 (97.8%) were for a prescription of 5 mg/day. A small number of patients were reported as having been prescribed doses outside of the recommended licensed daily dose (5 mg); 5 patients were prescribed 2.5 mg/day, 201 patients (1.9%) were prescribed 10 mg/day and 25 (<1.0%) were prescribed ≥15 mg/day. The current Summary of Product Characteristics (SmPC) for levocetirizine recommends a dose of 2.5 mg/day for patients aged between 2 and 6 years of age using the oral solution of Xyzal® rather than the tablet formulation,[11] although this was not included in the SmPC at the time of study. No dosage adjustment was available for children <6 years of age as the oral solution was not available; therefore, it was not recommended for use in this population.[1] Of the ten patients aged between 2 and 5 years, all were using the higher dose of 5 mg/day. Where an opinion by the prescriber was provided, 84.1% (5746/6833) felt that the drug was effective.

Of 6758 patients for whom it was recorded that treatment was continuing or that the date of stopping treatment was reported, 2414 (35.7%) patients were still being prescribed levocetirizine at the end of month 2. Where responses to additional questions were provided (yes or no) on pattern of use, the majority of patients (86.6%; 6283/7254) were reported to be continuous users (daily ≥15 days), 52.2% (2092/4010) had a short course (daily ≤14 days) and 28.0% (1041/3712) had multiple short courses. Of note, 47 patients for whom information from the additional questions were 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 II. '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 III) or pattern of use (data not shown). Headache/migraine occurred significantly more often in month 1 than month 2 for the whole cohort (n = 31; $IDobs_{m1/m2}$ 2.4; 95% CI 1.1, 6.0), along with drowsiness/sedation (n = 50; $IDobs_{m1/m2}$ 11.5; 95% CI 4.2, 43.9). There were no reports of somnolence in the PEM cohort. As expected, for patients being treated for AR with asthma/wheezing there was a tendency for a higher rate overall of respiratory-type adverse events related to the Respiratory SOC (upper respiratory tract infection [URTI], asthma/wheezing and asthma worse) than patients not reported to have asthma (although only significant for URTI at 5% level).

Clinical events of interest within the CPNS, Psychiatric and Cardiovascular SOCs, recorded as occurring during the first 2 months of treatment[2] for levocetirizine and assessed as possibly/probably related, are summarized in table IV. Headache, drowsiness and sedation were re-

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

Table II. ID of reported events in the first 2 months of treatment ranked for levocetirizine in order of $IDobs_{m1}$ per 1000 patient-months observation (where $IDobs_{m1} \geq 1$)[a]

Higher term	N_1	N_2	$IDobs_{m1}$	$IDobs_{m2}$	$IDobs_{m1/m2}$ (95% CI)	ADR	Reason for stopping[b]
Condition improved	1470	434	118.90	35.15	3.38 (3.04, 3.77)	NA	1896
No further request	640	59	51.77	4.78	10.83 (8.29, 14.40)	NA	699
Not effective	460	133	37.21	10.77	3.45 (2.84, 4.22)	NA	588
Course completed	160	29	12.94	2.35	5.51 (3.69, 8.49)	NA	189
Other drug substituted	62	26	5.02	2.11	2.38 (1.48, 3.92)	NA	88
Upper respiratory tract infection	**56**	**25**	**4.53**	**2.03**	**2.24 (1.37, 3.74)**	**0**	**4**
Drowsiness, sedation	**46**	**4**	**3.72**	**0.32**	**11.48 (4.19, 43.93)**	**5**	**43**
Headache, migraine	**22**	**9**	**1.78**	**0.73**	**2.44 (1.08, 6.02)**	**2**	**6**
Hospital referrals no admission	22	11	1.78	0.89	2.00 (0.93, 4.56)	**0**	**10**
Non-compliance	21	2	1.70	0.16	10.49 (2.56, 92.24)	NA	18
Rash	20	9	1.62	0.73	2.22 (0.97, 5.53)	1	8
Pregnancy	**11**	**2**	**1.53**	**0.28**	**5.49 (1.20, 51.00)**	NA	**5**
Urinary tract infection	18	12	1.46	0.97	1.50 (0.68, 3.41)	0	0
Anxiety	**17**	**4**	**1.38**	**0.32**	**4.24 (1.38, 17.34)**	**0**	**0**
Lower respiratory tract infection	17	21	1.38	1.70	0.81 (0.40, 1.61)	0	0
Pain joint	15	8	1.21	0.65	1.87 (0.75, 5.10)	0	0
Non-formulary product	13	8	1.05	0.65	1.62 (0.62, 4.52)	NA	21

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

b 3732 reasons for stopping during months 1 and 2 of observation, of 5509 (for whole study period).

ADR = events recorded as adverse drug reactions (25 reports [in months 1 and 2 of observation] of 31 [for whole study observation period]); **ID** = incidence densities; **$IDobs_{m1}$** = incidence density for each event during observation month 1; **$IDobs_{m2}$** = incidence density for each event during observation month 2; **$IDobs_{m1/m2}$** = relative difference between $IDobs_1$ and $IDobs_2$; **N_1** = total number of first reports of each event during observation in month 1; **N_2** = total number of first reports of each event during observation in month 2; **NA** = not applicable.

ported uncommonly (>0.1%, <1%), whilst migraine and syncope were rare (>0.01%, <0.1%). Chest pain, myocardial infarction (MI) and palpitations occurred rarely or very rarely, and there were no reports of bradycardia (detected by resting ECG), arrhythmia or atrial fibrillation (confirmed by ECG). Malaise was also reported rarely and lassitude was uncommon. Thirty-two events were reported by the GPs as suspected ADRs to levocetirizine in 27 patients, of which five (one each of cough, facial oedema, pharynx irritation, photophobia and rash) were documented on the Green Form as having been reported to the Committee on Safety of Medicines (now known as the Commission on Human Medicines).

Two cases of visual disturbance (one possibly and one unlikely related to treatment) and three cases of eye irritation (one probably and two unlikely related to treatment) were reported during treatment. The only eye-related ADR was one case of photophobia.

Twenty-four suspected ADRs were reported to other drugs in 20 patients, of which nine were recorded during treatment with levocetirizine. Of these, six were listed as undesirable effects of that drug (for three, the event was not specified). No serious suspected ADRs to levocetirizine were reported during this study. Additionally, no suspected ADRs to levocetirizine were reported in the subset of patients aged 12 years and under.

Prior antihistamine use (within 12 months) was reported for 31.9% (3950/12 367) of patients. The most common antihistamines were cetirizine (1607 patients; 39.1%), followed by loratadine (827 patients; 20.1%) and desloratadine (641; 15.6%). New users of antihistamines were more likely to have a positive response to treatment than past users (condition improved, n = 851; $IDobs_A$ ratio 1.4; 95% CI 1.3, 1.5 [data not shown in table])

Table III. Selected higher term incidence density ratios comparing month 1 vs month 2 ($IDobs_{m1/m2}$), ranked in descending order of N_1, according to indication

Higher term	N_1	N_2	$IDobs_{m1/m2}$ (95% CI)
Allergic rhinitis (with asthma/wheezing) [n = 1598]			
Condition improved	139	70	1.98 (1.48, 2.68)
No further request	80	8	9.99 (4.84, 23.94)
Not effective	36	15	2.4 (1.28, 4.72)
Upper respiratory tract infection	9	1	8.99 (1.25, 394.23)
Asthma, wheezing	7	4	1.75 (0.44, 8.15)
Asthma worse	7	10	0.70 (0.23, 2.04)
Allergic rhinitis (without asthma/wheezing) [n = 6688]			
Condition improved	620	258	2.40 (2.07, 2.79)
No further request	350	41	8.53 (6.16, 12.09)
Not effective	213	58	3.67 (2.73, 4.99)
Drowsiness, sedation	29	3	9.66 (2.99, 49.53)
Anxiety	12	1	11.99 (1.77, 512.36)
Upper respiratory tract infection	28	16	1.75 (0.91, 3.46)
Asthma, wheezing	4	2	2.00 (0.29, 22.08)
Asthma worse	0	1	0.00 (0.00, 38.95)
Urticaria (n = 2348)			
Condition improved	470	69	6.80 (5.27, 8.89)
Not effective	119	36	3.30 (2.26, 4.93)
No further request	101	3	33.61 (11.18, 165.69)
Course completed	53	6	8.82 (3.79, 25.10)
Upper respiratory tract infection	13	3	4.33 (1.19, 23.67)
Other indications (n = 1200)			
Condition improved	33	5	6.59 (2.56, 21.63)
No further request	23	2	11.48 (2.84, 100.49)
Upper respiratory tract infection	4	3	1.332 (0.225, 9.09)

$IDobs_{m1/m2}$ = relative difference between $IDobs_1$ and $IDobs_2$; **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.

and less likely to have clinical events such as URTI (n = 115; $IDobs_A$ ratio 0.7; 95% CI 0.6, 0.9 [data not shown in table]) or headache/migraine (n = 45, $IDobs_A$ ratio 0.5; 95% CI 0.3, 0.8 [data not shown in table]).

Pregnancies

Thirty-five pregnancies were reported during the study period. Of these, 16 patients were exposed to levocetirizine during the first trimester, for which ten live births (no defects reported), two spontaneous abortions, two missed abortions and two therapeutic terminations were reported. Of the remaining 19 pregnancies, 17 women were recorded as taking levocetirizine 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 levocetirizine.

Deaths

The number of deaths reported during the study period was low (<1%; n = 73), of which the cause of death was not ascertained for 18 patients. For the remainder, the most common cause of death was cardiovascular related (18/55; 32.7%), followed by cancer (17/55; 30.9%). Two deaths were due to MI, one occurred off-treatment and the other was unknown treatment status. The reporting GPs attributed none of the deaths to the use of levocetirizine.

Discussion

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

Strengths and Limitations

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 of patients (frequently over 10 000) prescribed newly marketed drugs under 'real life' conditions of general practice. Unlike premarketing 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 both a hypothesis-generating post-

marketing system for safety signals (and applies several methods for this purpose) and a method used to test safety signals detected within PEM or elsewhere.

As with all pharmacoepidemiological methods, PEM has weaknesses. This PEM study had a low response rate (46.5%) compared with the average response rate obtained for the 100 PEM studies (55.1%) completed by the DSRU in England to date. However, the response rate is still substantial compared with spontaneous reporting schemes.[12,13] 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.[12]

Compliance with treatment cannot be measured (as with most observational pharmacoepidemiological studies) and this may lead to an underestimate of the measure of effect, or to a false conclusion regarding any possible associations between the drug and any outcomes. Also, PEM only relates to general practice, and does not include hospital prescriptions. Lastly, detection of serious rare/very rare ADRs (such as drug-induced torsade de pointes, with an estimated incidence of the order of 1/12 000–1/120 000 patients[14]) is not always possible because PEM studies still have insufficient power to detect such events, despite larger cohort sizes than seen in many randomized controlled trials.[6]

Cohort Characteristics

The levocetirizine cohort demographics are similar to those reported in other observational studies conducted during a similar calendar period post-launch,[15,16] and appear to be representative of patients from the general population with AR and other allergic conditions.[17,18] In this PEM study, the most common prescribing indication reported overall was AR (either with or without asthma/wheezing) [67.0%], reflecting licensed indications. However, levocetirizine was also prescribed for a range of acute conditions, predominantly allergic in

Table IV. Number and incidence of reports of clinical events of interest within the CPNS and Cardiovascular SOCs in the first 2 months of treatment, and summary of events followed up and assessed as possibly or probably related to levocetirizine use

SOC lower-term event	Total no. reported in months 1 and 2 of treatment (no. followed up)	Information on follow-up cases reported in months 1 and 2 of treatment			
		DSRU causality assessment as probable or possible	age at start of treatment (range)	sex (M/F)	days to event (range)
CPNS					
Drowsiness	37 (29)	21	15–74	7/14	1–60
Headache	23 (11)	4	11–45	3/1	0–28
Migraine	6 (4)	2	29–45	0/2	0–19
Sedation	13 (9)	7	11–67	4/3	1–29
Syncope	1 (1)	1	28	0/1	5
Cardiovascular					
Pain chest	5 (4)	2	30–NS	0/2	11–17
Palpitation	1 (1)	1	26	0/1	19
Myocardial infarction	1 (1)	1	37	1/0	32
Psychiatric					
Lassitude	14 (10)	7	14–79	2/5	2–57
Malaise	2 (0)	NA	NA	NA	NA

CPNS = Central and Peripheral Nervous System; **DSRU** = Drug Safety Research Unit; **F** = female; **M** = male; **NA** = not applicable; **NS** = not specified; **SOCs** = System Organ Classes.

nature. Such use is supported by a recent review summarizing several *in vivo* studies that demonstrate the potent anti-inflammatory effects of levocetirizine in a range of conditions, including the allergen-induced wheal and flare reaction, patients with atopic asthma and patients with allergic asthma concomitant to AR.[19]

Recently, the US FDA has approved the use of levocetirizine in children as young as 6 months of age for perennial AR and CIU,[20] although this is not licensed in the UK. In our study, we found no children under the age of 2 years who were using levocetirizine, which is possibly due to the tablet formulation being difficult for young children to use. Use in children aged 2–12 years was reported, which are licensed ages for use in the UK.[11] At the time of this study, the SmPC stated that no dose adjustment was available for children aged <6 years, and levocetirizine was not recommended in this population,[1] although a dose of 2.5 mg is now available using the oral solution; therefore, ages 2–6 years are now licensed ages for the use of levocetirizine.[11]

Incidence Densities and Events of Interest

For this PEM study, the justification for the calculation of incidence densities using the observation period was based on the limited information on exposure for such drugs, which are 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 first 2 months was specific for this study to examine data for signals of acute-onset events only.

For the whole cohort, the most frequently reported clinical events in month 1 were URTI (4.5/1000 patient-months observation [pmo]), drowsiness/sedation (3.7/1000 pmo) and headache/migraine (1.8/1000 pmo). All of these events occurred significantly more often in the first month of observation with levocetirizine compared with the second month ($IDobs_{m1/m2}$ ratio 2.2 [95% CI 1.4, 3.7], 11.5 [95% CI 4.2, 43.9] and 2.4 [95% CI 1.1, 6.0], respectively), as was anxiety ($IDobs_{m1/m2}$ ratio 4.2 [95% CI 1.4, 17.3]). The high incidence of URTI during the observation period is as expected, given that this is a common presenting complaint in general practice. A higher frequency of URTI in the first month of treatment compared with the second month of treatment may be explained by patients who started treatment in the winter season. The winter season is associated with an increased incidence of influenza and respiratory tract infections,[21-23] which could provide one explanation for the significant association between URTIs and starting treatment. Another explanation is protopathic bias, which occurs when the pharmacological agent is prescribed for early manifestation of a condition that has not yet been diagnosed, but which then appears to be the cause of the condition when it is eventually diagnosed.[24] Thus, our hypothesis is that patients sought medical advice because of symptoms similar to those found in hayfever and AR, which later turned out to be associated with URTI and this diagnosis was recorded at the same time as starting levocetirizine.

The UK SmPC at launch[1] and updated in September 2005[2] referred to the combined incidence of sedating ADRs (such as somnolence, fatigue and asthenia) as more common for levocetirizine 5 mg than placebo (incidence 10.2%[1] and 8.1%[2] vs 4.4%[1] and 3.1%,[2] respectively, although the duration of exposure is not provided).[1,2] Synonymous terms within the DSRU dictionary – lassitude and malaise, and drowsiness and sedation – were collectively uncommon (0.5%; n = 66) in the first 2 months of treatment[3] in this PEM study. Headache was listed as common in the UK SmPC at launch,[1] whilst in this PEM study, headache was uncommon (<1%) in the first 2 months of treatment.

3 In this PEM study, for calculation of ID difference statistic, the denominator of months of observation (irrespective of treatment status 'on', 'off' or 'unknown') is used. However, because clinical trial data referenced in the SmPC is assumed to reflect continuous use 'on drug', only counts of events known to be 'on drug' were used to make any informal comparisons with such data.

These results are similar to those reported elsewhere.[25] The difference between results reported from the SmPC and this PEM study could be explained by the closer observation of events and the reporting responsibilities in a clinical trial. Patients are studied closely in a clinical trial with all adverse events reported,[26] whereas in this observational study, events were only included if they were reported to the GP, as per the methodology of PEM.[27] For some less serious events such as headache and drowsiness, patients may not have reported these to their GP as they felt they were not serious, but in a clinical trial these would have been reported regardless of the severity and seriousness.

Visual disturbances are reported as very rare in the SmPC, and only two cases of visual disturbance (one possibly and one unlikely related to treatment) and three of eye irritation (one probably and two unlikely related to treatment) were reported during treatment. The only eye-related ADR was one case of photophobia. This was an accompanying symptom in a recent case report of levocetirizine-induced iridocyclitis,[28] although no specific reports of iridocyclitis were received during this study.

Importantly, no serious ADRs were reported in this PEM study, as defined by the DSRU rare iatrogenic ADR list. Levocetirizine has been reported in some studies to have no effect on cognitive or psychomotor function[29-33] or driving ability.[34] However, reports of somnolence, fatigue and asthenia are noted in the label of the product and in some studies a small percentage of patients reported somnolence after taking levocetirizine, compared with those on placebo.[1] In this PEM study, there were no reports of somnolence, and reports of drowsiness and sedation were uncommon.

CNS effects may be related to the indication (histamine overload during allergic reaction,[34] or due to nocturnal symptoms and sleep deprivation[35]). Thus, in this study, the reporting and recording of events related to cognitive or psychomotor impairment was not unexpected. Misclassification or underreporting 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.[35] Levocetirizine has been reported to increase somnolence at higher-than-recommended doses (particularly 10 mg/day) when compared with lower doses.[16] Furthermore, concomitant chemicals or co-morbidities that might lead to drug accumulation in the CNS might increase the risk of CNS adverse events[35] but this risk appears low for levocetirizine.[2] In this PEM study there is limited information regarding dose at 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[35] is not routinely requested on the Green Form and therefore cannot be examined.

How the frequency of CNS events reported for levocetirizine 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 in both cohorts, levocetirizine was more likely to result in reports of drowsiness/sedation than desloratadine in patients with AR without asthma/wheezing but no significant difference was observed in patients with AR and asthma/wheezing or other indications after adjusting for sex.[36] 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. However, this result regarding safety should be viewed in conjunction with efficacy data as comparison studies have previously shown levocetirizine to be more effective than desloratadine.[37,38] As such, safety data should always be examined in conjunction with efficacy data to gain a thorough knowledge of the benefit-risk profile of a product.

The proarrythmogenic potential of non-sedating antihistamines is also of interest.[39-49] No clinically relevant cardiotoxic effects have been observed for levocetirizine at standard or

supratherapeutic doses.[2] In this PEM study, cardiovascular events of interest were rarely or very rarely reported; during the first 2 months of treatment there were three reports of MI during treatment (one possibly associated with treatment). No deaths were attributed to the use of levocetirizine 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. Cetirizine does not appear to increase the risk of major congenital abnormalities.[50,51] Since levocetirizine is the (R) enantiomer of cetirizine, it is assumed that it has a similar safety profile to cetirizine during use in pregnancy, although no human studies have been conducted.[52] 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 by including additional questions to help examine determinants of drug exposure. For example, PEM can collect information on events related to the use of the drug in 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. Firstly, seasonal AR, being the most common indication reported, inevitably improves after the causative pollen has ceased to be in season and, secondly, that allergic conditions often vary in severity for individuals over time. Of GPs expressing an opinion, 84.1% rated levocetirizine 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 requested 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 changed.[53-55] 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 month of observation than the second month of observation (although some ID ratios were not statistically significant [pattern of use data not shown]). These data suggest that pattern and duration of treatment may not be important in whether a patient will experience such events. This may reflect the short seasonal AR season and the rapid beneficial effect of antihistamines on AR and urticaria, allowing both the patient and the doctor to assess whether this drug is successful within a very short period of time. These findings are similar to that found according to prescribing indication (but may also be related to the fact that the most frequently reported pattern of use was continuous, for which the counts are the highest).

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, AR patients 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.[56] 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 agonists, or confounding factors such as smoking[57] or other respiratory diseases;[17] 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 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. This is also supported by the result that new users of antihistamines were more likely to have a positive response to treatment than past users, and less likely to have clinical events such as URTI or headache and migraine.

Finally, another important consideration is seasonality. The period during which eligible patients were identified spanned 1 year (November 2001–November 2002). Green Form questionnaires collecting demographic and outcome data were sent approximately 6 months later between July 2002 and April 2003, inclusive. A strength of our study is that the observation period of the whole cohort comprised of groups of patients who started treatment during the four calendar seasons, and who continued to take the drug despite varying allergen exposure.[58] Whilst long-term studies for levocetirizine have measured quality of life indicators over spring and autumn seasons, there are no studies providing specific information regarding the incidence of common treatment-emergent adverse events.[15] We acknowledge that indication-related events may vary, but we cannot be certain whether seasonality has had any significant impact on the adverse event profile of levocetirizine, as recorded in our PEM study.

Conclusions

This postmarketing surveillance study shows that levocetirizine is fairly well tolerated when used in general practice in England. Frequently reported adverse events were those commonly associated with treatment with antihistamines and included in the prescribers' information. Events not specifically listed in the SmPC, and more frequently reported for the whole cohort in the first month after starting treatment with levocetirizine than the second month, were drowsiness/sedation (although somnolence is listed) and anxiety. Stratification of event rates according to prescribing indications, channelling of past users and pattern of use suggested that the risk of certain events could be related to differences in patient characteristics and use of the drug. Such analyses should be considered when monitoring safety of other drugs that may be used for chronic and/or self-limiting conditions.

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