Safety and efficacy of oral fexofenadine in children with seasonal allergic rhinitis – a pooled analysis of three studies

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Allergic rhinitis is one of the most common clinical conditions in children; however, data regarding the safety of antihistamines in children with seasonal allergic rhinitis are limiting. To evaluate the safety and efficacy of fexofenadine in children with seasonal allergic rhinitis, data were pooled from three, double-blind, randomized, placebo-controlled, parallel-group, 2-week trials in children (6–11 year) with seasonal allergic rhinitis. All studies assessed fexofenadine HCl 30 mg b.i.d.; two studies included fexofenadine HCl at 15 and 60 mg b.i.d. Patients (and investigators) reported any adverse events during the trial. Physical examinations, including measurements of vital signs and laboratory tests, were performed. Efficacy assessments (total symptom score and individual symptom scores) were evaluated. Exposure to fexofenadine HCl 30 mg b.i.d. and to any fexofenadine dose exceeded 10,000 and 17,000 patient days, respectively. Incidences of adverse events, and discontinuations because of adverse events, were low and similar across treatment groups. In the placebo group, 24.4% of subjects reported adverse events compared with 24.1% for fexofenadine HCl 30 mg b.i.d., and 28.4% for all fexofenadine-treated groups. The most common adverse event overall was headache (4.3% placebo; 5.8% fexofenadine HCl 30 mg b.i.d.; and 7.2% any fexofenadine doses). Treatment-related adverse events were similar across treatment groups with no sedative effects. Fexofenadine HCl 30 mg b.i.d. was significantly superior to placebo in reducing the total symptom score and all individual seasonal allergic rhinitis symptoms, including nasal congestion ($p < 0.05$). Fexofenadine, at doses of up to 60 mg b.i.d., is safe and non-sedating, and fexofenadine HCl 30 mg b.i.d. effectively reduces all seasonal allergic rhinitis symptoms in children aged 6–11 years.

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Allergic rhinitis is one of the most common chronic conditions in childhood (1). In particular, many children who develop allergies to inhalant allergens in early life are at an increased risk of developing seasonal allergic rhinitis (SAR) and asthma in later childhood. This chronological progression of clinical manifestations of allergy is termed 'the allergic march'. Besides the potential serious implications of

leading to asthma and other symptoms, children with untreated allergy symptoms have been shown to exhibit poorer learning ability compared with non-allergic children (2). Moreover, data indicate that almost a million school days are missed per year as a direct result of allergic rhinitis in the USA (3). Estimates of its prevalence in children, which vary from country to country, have been reported to be as high as 40%

(4), and it appears that the incidence of allergic rhinitis in this patient population is rising (5).

Since 1942, antihistamines have been used as first-line treatment for SAR in patients of all ages (6–8). However, results from studies using first-generation antihistamines have demonstrated significant adverse effects as a result of their sedative effects, resulting in impairment of psychomotor and academic function in children (2). Fexofenadine (Allegra®/Telfast®, Aventis Pharmaceuticals, Kansas City, MO, USA), an optimal second generation antihistamine, demonstrates greater selectivity for the H₁-receptor and lacks the anti-cholinergic and sedating adverse effects associated with many of the older antihistamines (9). Fexofenadine has been approved for the treatment of SAR and chronic idiopathic urticaria in adults, and large, randomized trials have demonstrated the efficacy and safety of this agent in adult populations (10–14). Furthermore, results of dose–response trials in healthy adults show that doses of up to 690 mg b.i.d. administered for 1 month are safe and well-tolerated (15, 16). However, despite the greater emphasis on safety and tolerability in this population, data regarding the safety of antihistamines in children in controlled studies are limited. A previous report by Graft et al. (17) showed that doses of fexofenadine HCl, up to 60 mg b.i.d., are safe and well-tolerated in children aged 6–11 years, with no dose-related trends. In addition, a recent, worldwide study reported the efficacy and safety of fexofenadine HCl (30 mg b.i.d.) in children aged 6–11 years with SAR (18).

In order to further evaluate the safety of the recommended fexofenadine dose in this population, the safety results of these studies have been pooled. In addition, the efficacy of fexofenadine 30 mg b.i.d. in reducing the symptoms of SAR was determined.

Methods

Patients

Three trials (studies I–III) were included in the pooled safety analysis. Children aged 6–11 years, with spring or fall SAR, and a history of SAR of approximately 1 year or more during at least one previous relevant season, were enrolled. Subjects were required to have a positive skin-prick test (wheal diameter ≥ 3 mm than that with diluent within 15 min of the skin prick) to at least one allergen for the current season. To facilitate objective characterization of the subject's allergies, patients in study I also required the presence of an allergen-specific

immunoglobulin E (IgE) that was positive in the skin-prick test.

Excluded patients were (but were not limited to) those with a respiratory tract nasal infection, sinusitis, or otitis media within 30 days of study entry; clinically significant cardiovascular, hepatic, neurologic, psychiatric, endocrine or other major systemic disease; or immunotherapy treatment.

Written informed consent from a parent/guardian and each child was obtained before inclusion in the study.

Study design

Studies I–III were double-blind, randomized, placebo-controlled, parallel-group, 2-wk trials. All three studies had a similar design with regard to patient selection criteria and, primary and secondary outcome measures. Study I was conducted at 148 centers in 15 countries: Argentina (16), Australia (nine), Austria (one), Chile (three), Finland (three), France (12), Germany (five), Israel (three), Italy (seven), Poland (10), Portugal (two), South Africa (18), Spain (six), Uruguay (two) and the USA (51) (18). Studies II and III were identical trials conducted at 58 investigative sites in the USA and Canada (17).

All three trials had a similar study design. At visit 1 (baseline), the children (with the help of their caregiver) provided a 12-hour reflective assessment of the severity of their allergy symptoms. Seasonal allergic rhinitis symptom scores were recorded for sneezing; rhinorrhea; itchy nose, palate, throat and/or ears; itchy, watery and/or red eyes; and nasal congestion. Each symptom was evaluated on a five-point scale: 0 = absent; 1 = mild; 2 = moderate; 3 = severe; 4 = very severe. The total symptom score (TSS) was calculated by adding the individual symptom scores, excluding nasal congestion (maximum possible TSS = 16). For inclusion at visit 1, a reflective TSS = 6, with two or more symptoms with a minimum score of 2 (moderate), was necessary. Following visit 1, the studies included four additional visits: visit 2, randomization (day 1); visit 3, during double-blind treatment (day 6–10); visit 4, end of double-blind treatment (day 15–17); and visit 5, follow-up (day 22–24).

Following completion of a single-blind, placebo lead-in period, the children in study I were required to have a TSS = 5 for the average of the last two 19:00-hours reflective TSS, and patients in studies II and III required a TSS = 5 for >60% of the placebo lead-in period to qualify for randomization to the double-blind phase of

the study. All children were randomized to receive either fexofenadine HCl 30 mg b.i.d. or matching placebo; studies II and III also included doses of 15 and 60 mg b.i.d.. For the purpose of the present analysis, children treated with fexofenadine were analyzed in two groups: children treated with fexofenadine 30 mg b.i.d. and children treated with all fexofenadine doses (15, 30 and 60 mg b.i.d.). Safety data corresponding to the patient groups treated with either 15 or 60 mg b.i.d. fexofenadine HCl are reported elsewhere (17). Tablets were taken at 19:00 and 7:00 hours (± 1 hour) for 2 weeks, with no dosing instructions regarding food intake. Throughout the study, SAR symptoms were assessed daily at 19:00 (± 1) hours for the previous 12-hour period (hereafter referred to as PM reflective) by the subject and caregiver, immediately prior to dosing.

The individual study protocols were approved by the appropriate ethics committees.

Safety assessments

Children (and investigators) reported any adverse events (AEs) during the study. In order that AE coding was uniform across studies, data from studies II and III were re-coded using the Hoechst Adverse Reaction Terminology System (HARTS) dictionary. Comparison of the original safety data with the results following recoding using HARTS showed that this did not have an effect on the safety profile of fexofenadine, with the incidence of adverse events and their severity remaining the same (data not shown). The AE profiles were pooled and presented for the following treatment groups: fexofenadine HCl 30 mg b.i.d., all fexofenadine-treated subjects and placebo. Physical examinations, including vital signs measurements and laboratory tests, were performed in all three studies. Laboratory testing was performed on blood samples taken at visit 1 (screening) and visit 4 (end of treatment) and included assessments of liver function [alkaline phosphatase, total bilirubin, lactate dehydrogenase (LDH)], renal function (creatinine), electrolytes (potassium), other chemistry (glucose, triglycerides) and hematology/hemoglobin (hematocrit, platelet count, white blood cell count). Study I assessed predefined change abnormal (PCA) and clinically noteworthy abnormal laboratory values (CNALVs), whereas studies II and III assessed outlier values; however, the values for the ranges of the CNALV and outliers were similar. In addition, the use of concomitant medications was also evaluated during the study. Studies II and III also recorded

results from pre- and post-treatment electrocardiograms. These are reported elsewhere (17).

Efficacy measurements

Efficacy of fexofenadine was assessed only in those children treated with fexofenadine 30 mg b.i.d. In all three studies, the primary outcome measures were mean change from baseline in the average PM reflective TSS throughout the double-blind treatment period and the PM reflective assessment of individual symptom scores. The only difference in the studies is the definition of baseline TSS. For study I, baseline corresponded to the average assessment over the last 3 days prior to the first day of study medication; for studies II and III, baseline corresponded to the average over the whole placebo lead-in period. To assess the impact of this difference, the baseline for studies II and III was derived using the average TSS for the last 3 days prior to study medication. There is a slight decrease in the mean baseline for the placebo group and no change for the fexofenadine HCl 30 mg group, indicating that the alternative methods of calculating baseline values did not preclude pooling of the three studies.

Statistical analysis

Children included in the safety evaluations were required to have been exposed to at least one dose of the double-blind treatment. Adverse events recorded by these children were descriptively summarized and no formal statistical comparisons were made. The efficacy analysis was undertaken on the modified intention-to-treat (mITT) population, which was defined as all randomized subjects who received at least one dose of double-blind treatment and had a baseline and at least one double-blind period PM reflective assessment. Analysis of covariance (ANCOVA) was used to compare the efficacy of fexofenadine HCl 30 mg b.i.d. with placebo, and baseline score was included as a continuous covariate, with treatment and pool center as fixed effects. A two-sided 95% confidence interval of the treatment difference was derived using adjusted least squares mean from the ANCOVA.

Results

Patient population and demographics

A total of 1810 children were included in the overall pediatric safety population (placebo, $n = 700$; fexofenadine $n = 1110$). Of these, 673

children received fexofenadine HCl 30 mg b.i.d. and 437 children received fexofenadine at doses of either 15 mg or 60 mg b.i.d. Exposure to fexofenadine HCl 30 mg b.i.d. and to any fexofenadine dose exceeded 10,000 and 17,000 patient days, respectively.

The safety populations of the pooled studies were similar in terms of demographic characteristics (Table 1). For children receiving placebo or fexofenadine HCl 30 mg b.i.d., 62.2% of the children were male and the mean age was 8.9 years.

As part of this pooled analysis, efficacy measurements were also determined. A total of 1804 pediatric subjects were evaluable for efficacy and included in the mITT population (671 children received fexofenadine HCl 30 mg b.i.d.; 698 children received placebo). There were no marked differences in the demographic data of the mITT population either between studies or treatment groups. Similarly, within each study, there was no significant difference in baseline symptom scores between treatment groups.

Safety assessments

Adverse events. Incidences of AEs, including discontinuations because of AEs, were low and comparable across treatment groups in the pooled analysis (Table 2). In the placebo group, 24.4% (171 of 700) of subjects reported AEs compared with 24.1% (162 of 673) for fexofenadine HCl 30 mg b.i.d., and 28.4% (315 of 1110) for all fexofenadine-treated (15 mg, 30 mg and 60 mg b.i.d.) children. The most common AE overall was headache, which occurred in 4.3% of placebo-treated children, 5.8% of fexofenadine HCl 30 mg b.i.d.-treated children and in 7.2% of children treated with either 15, 30 or 60 mg b.i.d. fexofenadine.

AEs resulted in the withdrawal of six children receiving fexofenadine HCl 30 mg b.i.d., one child receiving fexofenadine HCl 15 mg b.i.d., one child receiving fexofenadine HCl 60 mg b.i.d. and five children receiving placebo. The most common AE leading to discontinuation was asthma, which occurred in five children (three receiving placebo and two receiving fexofenadine HCl 30 mg b.i.d.). No AE that resulted in discontinuation was attributed to study medication.

The number of treatment-related AEs (possibly related, probably related or definitely related to study treatment) was also comparable between treatment groups (Table 3). In the placebo group, a total of 3.4% (24 of 700) of children reported at least one treatment-related AE com-

Table 1. Demographic characteristics for clinical safety population (for children receiving placebo or fexofenadine HCl 30 mg b.i.d.)

	Study I			Study II			Study III			Pooled		
	Total	Placebo	Fex	Total	Placebo	Fex	Total	Placebo	Fex	Total	Placebo	Fex
Total subjects	935	471	464	232	124	108	206	105	101	1373	700	673
Sex												
Male [n (%)]	592 (63.3)	314 (66.7)	278 (59.9)	141 (60.8)	74 (59.7)	67 (62.0)	122 (59.2)	65 (61.9)	57 (56.4)	855 (62.3)	453 (64.7)	402 (59.7)
Female [n (%)]	343 (36.7)	157 (33.3)	186 (40.1)	91 (39.2)	50 (40.3)	41 (38.0)	84 (40.8)	40 (38.1)	44 (43.6)	518 (37.7)	247 (35.3)	271 (40.3)
Age (yr)												
Mean ± s.d.	8.8 ± 1.64	8.8 ± 1.66	8.8 ± 1.61	9.1 ± 1.58	9.2 ± 1.53	9.0 ± 1.62	9.2 ± 1.49	9.3 ± 1.58	9.1 ± 1.39	8.9 ± 1.61	8.9 ± 1.64	8.9 ± 1.59
Weight (kg)												
Mean ± s.d.	34.04 ± 10.84	34.18 ± 11.22	33.89 ± 10.45	35.16 ± 10.55	35.87 ± 10.59	34.34 ± 10.51	36.50 ± 11.66	37.37 ± 11.74	35.59 ± 11.57	34.60 ± 10.95	34.96 ± 11.24	34.22 ± 10.63
Height (cm)												
Mean ± s.d.	136.13 ± 11.58	136.31 ± 12.13	135.95 ± 11.00	137.55 ± 11.38	138.64 ± 11.58	136.27 ± 11.06	138.81 ± 10.95	139.00 ± 11.01	138.61 ± 10.95	136.77 ± 11.49	137.12 ± 11.92	136.41 ± 11.03
Body mass index (kg/m ²)												
Mean ± s.d.	17.99 ± 3.67	17.98 ± 3.66	17.99 ± 3.68	18.29 ± 3.5	18.35 ± 3.34	18.23 ± 3.76	18.58 ± 4.0	19.03 ± 4.28	18.12 ± 3.66	18.13 ± 3.70	18.21 ± 3.72	18.05 ± 3.69
Ethnic group [n (%)]												
White/Caucasian	752 (80.4)	375 (79.6)	377 (81.3)	195 (84.1)	102 (82.3)	93 (86.1)	173 (84.0)	85 (81.0)	88 (87.1)	1120 (81.6)	562 (80.3)	558 (82.9)
Black	67 (7.2)	33 (7.0)	34 (7.3)	22 (9.5)	14 (11.3)	8 (7.4)	22 (10.7)	14 (13.3)	8 (7.9)	111 (8.1)	61 (8.7)	50 (7.4)
Asian/Oriental	13 (1.4)	7 (1.5)	6 (1.3)	7 (3.0)	5 (4.0)	2 (1.9)	2 (1.0)	2 (1.9)	0 (0.0)	22 (1.6)	14 (2.0)	8 (1.2)
Multiracial*	103 (11.0)	56 (11.9)	47 (10.1)	8 (3.4)	3 (2.4)	5 (4.6)	9 (4.4)	4 (3.8)	5 (5.0)	120 (8.7)	63 (9.0)	57 (8.5)

*Multiracial includes those patients who did not consider themselves as White, Black or Asian/Oriental.

Table 2. Most frequently reported adverse events ($\geq 1\%$) – clinical safety population

	Pooled data [% (n)]		
	Placebo	Fexofenadine 30 mg b.i.d.	Fexofenadine all*
Subjects evaluable for safety in double-blind period	100 (700)	100 (673)	100 (1110)
Subjects with AEs	24.4 (171)	24.1 (162)	28.4 (315)
Coded Term			
Headache	4.3 (30)	5.8 (39)	7.2 (80)
Upper respiratory infection	1.3 (9)	2.1 (14)	2.2 (24)
Cough increased	0.9 (6)	1.6 (11)	1.7 (19)
Epistaxis	1.1 (8)	1.5 (10)	1.5 (17)
Accidental injury	1.6 (11)	1.3 (9)	1.6 (18)
Sore throat	1.6 (11)	1.2 (8)	1.7 (19)
Rash	0.6 (4)	1.2 (8)	1.2 (13)
Nausea	0.1 (1)	1.2 (8)	1.0 (11)
Fever	0.4 (3)	1.0 (7)	1.3 (14)
Sinusitis	0.9 (6)	1.0 (7)	0.8 (9)
Otitis media	0.1 (1)	1.0 (7)	0.8 (9)
Pain	0.3 (2)	0.9 (6)	1.1 (12)
Respiratory disorder	0.7 (5)	0.9 (6)	0.9 (10)
Pharyngitis	0.4 (3)	0.9 (6)	0.9 (10)
Gastrointestinal pain	1.9 (13)	0.7 (5)	1.4 (15)
Vomiting	0.4 (3)	0.7 (5)	0.8 (9)
Dyspepsia	0.1 (1)	0.7 (5)	0.7 (8)
Asthma	2.0 (14)	0.6 (4)	0.5 (5)
Infection	1.9 (13)	0.4 (3)	1.4 (16)
Flu syndrome	0.3 (2)	0.4 (3)	0.6 (7)
Ear pain	0.7 (5)	0.4 (3)	0.5 (5)
Chest pain	0	0.3 (2)	0.5 (5)
Diarrhea	0.1 (1)	0.3 (2)	0.4 (4)

*Fexofenadine HCl at doses of 15, 30 and 60 mg b.i.d.
AE, adverse event.

Table 3. Most frequently reported ($>0.5\%$) treatment-related adverse events – clinical safety population

	Pooled data		
	Placebo	Fexofenadine 30 mg b.i.d.	Fexofenadine All*
Subjects evaluable for safety in double-blind period, % (N)	100 (700)	100 (673)	100 (1110)
Subjects with possibly related AEs, % (N)	3.4 (24)	4.0 (27)	5.2 (58)
Coded Term			
Headache	1.0 (7)	1.0 (7)	1.4 (15)
Gastrointestinal pain	0.6 (4)	0.1 (1)	0.4 (4)
Rash	0.1 (1)	0.3 (2)	0.5 (5)
Insomnia	0	0.1 (1)	0.4 (4)
Somnolence	0.4 (3)	0.1 (1)	0.1 (1)

*Fexofenadine HCl at doses of 15, 30 and 60 mg b.i.d.
AE, adverse event.

pared with 4.0% (27 of 673) for fexofenadine HCl 30 mg b.i.d., and 5.2% (58 of 1110) for all fexofenadine treatment groups. No sedative effect or other class effects evident with first-generation antihistamines were observed. The

most commonly reported treatment-related AE was headache, which had an incidence of 1.0% (7 of 700) for placebo, 1.0% (7 of 673) for fexofenadine HCl 30 mg b.i.d., and 1.4% (15 of 1110) for all fexofenadine-treated groups. The majority of the treatment-related AEs were considered to be of mild or moderate intensity.

The number of children requiring concomitant medication (i.e. medication that was not provided in the study protocol) was comparable between treatment groups. For study I, the percentage of children taking concomitant medication was 10.8% (51 of 471) for placebo and 10.3% (48 of 464) for those children treated with fexofenadine HCl 30 mg. For studies II and III, the percentage of children taking concomitant medication was 28.8% (66 of 229) and 24.9% (161 of 646) for placebo- and fexofenadine-treated children, respectively.

Two subjects in the three studies reported serious AEs. One child in study I experienced neutropenia in the fexofenadine-treated group (30 mg b.i.d.) on routine evaluation that was thought to be related to treatment by the investigator. Laboratory tests revealed decreased neutrophil levels on day 15 following 14 days of double-blind treatment ($0.4 \times 10^9/l$ compared with $2.3 \times 10^9/l$ at screening). This event was reported as mild in intensity and the child was asymptomatic, and recovered without sequelae. Total leukocyte counts for this child remained stable during follow-up, but still below the normal range. Because serologic work was consistent with recent seroconversions for *Mycoplasma pneumoniae* and *Varicella* IgG, subclinical infections may offer an alternative explanation for the event. In addition, in study III, one child in the 30 mg b.i.d. fexofenadine-treated group experienced increased asthma and was diagnosed with status asthmaticus. The investigator felt that the event was severe, and unlikely to be related to study medication, and instead related to underlying disease with exposure to outdoor allergens as a trigger.

Vital signs and clinical laboratory evaluations. No clinically relevant changes were observed in vital signs data between fexofenadine and placebo-treated groups.

With the exception of one child with neutropenia described above, in all studies and in all treatment groups there were no clinically relevant differences in laboratory values. In study I, the most frequently observed PCA and CNALV for both treatment groups was an increase in eosinophils. In studies II and III, the most frequent outlier was high hematocrit levels.

Fig. 1. Mean ($\pm$ s.e.) change in PM reflective TSS with mITT population; $p \leq 0.0001$ vs. placebo (for children receiving placebo or fexofenadine HCl 30 mg b.i.d.).

Fig. 2. Reflective individual symptom scores with mITT population. * $p < 0.05$, ** $p < 0.01$, *** $p \leq 0.0001$ vs. placebo (for children receiving placebo or fexofenadine HCl 30 mg b.i.d.).

Efficacy assessments

Efficacy analysis showed that fexofenadine HCl 30 mg b.i.d. was significantly superior to placebo in the PM reflective TSS pooled analysis ($p \leq 0.0001$; Fig. 1). The mean change from baseline was -1.75 for the fexofenadine-treated group and -1.14 for the placebo group.

In the pooled analysis, all PM reflective individual symptom scores, including nasal congestion, were significantly reduced compared with placebo (sneezing $p \leq 0.0001$; rhinorrhea $p < 0.0058$; itchy nose, mouth, throat and/or ears $p \leq 0.0001$; itchy, watery, red eyes $p \leq 0.0001$; nasal congestion $p < 0.0334$) (Fig. 2).

Discussion

The safety data from these three pooled studies showed that over a 2-wk period fexofenadine HCl (30 mg b.i.d.) is well tolerated, with a placebo-like safety profile in children with SAR. The most commonly reported AE was headache, which occurred with a similar incidence in both fexofenadine- and placebo-treated groups. The results of this study also demonstrate that fexofenadine HCl (30 mg b.i.d.) is effective in

reducing both the TSS and individual symptom scores of SAR compared with placebo.

The combined results reported here are consistent with the previously published safety data for fexofenadine studies II and III (17, 18), in which there were no dose-related trends for AEs in children. Similar to the present study, the report by Graft et al. (17) showed that headache was the most frequently reported AE, with a similar incidence for all doses of fexofenadine (15, 30 and 60 mg b.i.d.) compared with placebo. In addition, early investigation of the clinical pharmacology of fexofenadine in healthy children has shown single doses of 30 and 60 mg are safe and well-tolerated (19). These findings are supported by the established safety profile of fexofenadine in adults for treatment of allergic rhinitis (15, 16). The two most commonly reported AEs in these long-term studies were headache and viral infection (15, 16). Moreover, since first approved for use in children in 1999, a systematic review of spontaneous adverse event reports has not revealed any new risk that could modify the current safety profile of fexofenadine tablets.

The potential for sedation is important in terms of safety, and the ability of both adults and school children to undertake everyday activities. Superior cognitive functions such as attention, memory, co-ordination, cognition and psychomotor performance may all be affected by sedation and central nervous system impairment, with associated safety implications. The findings from this study show that no clinically meaningful sedative or other class effects associated with first-generation antihistamines were observed. These findings are consistent with studies in adults, in which fexofenadine, even at doses in excess of those recommended by the manufacturer, did not impair cognitive or psychomotor function (15, 20, 21). In particular, Hindmarch and Shamsi (21) conducted a comprehensive review of published data from well-controlled trials evaluating the effects of antihistamines on sedation, psychomotor performance and cognition in healthy volunteers, using standardized, quantitative methods determining drug-related effects. Unlike cetirizine, fexofenadine was not associated with objective or subjective performance or cognitive impairment in any test, even at higher than recommended doses (21). Furthermore, qualitative and quantitative cerebral H_1 -binding data from PET studies have shown that fexofenadine does not bind to the H_1 -receptor in the brain, suggesting that it does not cross the blood-brain barrier, thereby supporting the lack of somnolence or impairment observed with fexofenadine in clinical studies (22).

A number of reports have linked some antihistamines to prolongation of the QT interval corrected for heart rate (QTc) interval when administered in the presence of hepatic impairment or with drugs that inhibit the cytochrome P450 hepatic enzyme system. Electrocardiograms were performed in studies II and III, and showed that fexofenadine has no effect on the QTc (17). Other studies, conducted in children and adults with SAR, in healthy children and adults, and in drug interaction studies with ketoconazole and erythromycin, also showed no effect of fexofenadine on the QTc compared with placebo (15, 17, 20, 23). Furthermore, the cardiovascular safety of fexofenadine in adults has been established at daily doses up to 690 mg b.i.d. (24).

Traditionally, antihistamines have not been considered to be effective in relieving nasal congestion (25–27) and, accordingly, second-generation antihistamines are not indicated for this purpose. The results of this pooled analysis shows that fexofenadine HCl (30 mg b.i.d.) is effective in reducing both the TSS and all individual symptoms, including nasal congestion, in children with SAR. These results are consistent with the recently published efficacy data from one of the studies reported here, in which fexofenadine was shown to be efficacious across all symptoms of SAR (18). Similarly, other studies in adults with SAR have shown significant efficacy with fexofenadine in relieving all symptoms of SAR, including nasal congestion (10, 12, 14). It is hypothesized that the ability of certain antihistamines, such as fexofenadine, to inhibit the late-phase response may be attributable in part to anti-inflammatory effects that are not necessarily directly related to H₁-receptor antagonism (28–30).

Conclusion

The results from this pooled analysis of three clinical studies show that fexofenadine HCl at doses of 15, 30 and 60 mg b.i.d. is safe and well tolerated in children aged 6–11 years over a period of 2 weeks. In this large pediatric population, fexofenadine is also effective at relieving all symptoms of SAR, including nasal congestion.

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