Fexofenadine hydrochloride in the treatment of allergic disease: a review

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Abstract: Fexofenadine is a selective, non-sedating H1 receptor antagonist, marketed in the United States since 2000. The FDA approved an oral suspension in 2006, for the treatment of seasonal allergic rhinitis and chronic idiopathic urticaria in children. The tablet, capsule, and oral suspension are bioequivalent. Although fexofenadine does not use P450 CYP 3A4 it does interact with a number of drugs at P-glycoprotein and organic anion transporter polypeptides. The risk of toxicity from other drugs may increase with the administration of fexofenadine. Orange and grapefruit juices reduce the bioavailability of fexofenadine. Fexofenadine has been shown to have an impact on inflammatory mediators, other than histamine, such as decreasing the production of LTC_4, LTD_4, LTE_4, PGE_2, and $PGF_{2\alpha}$; inhibiting cyclo-oxygenase 2, thromboxane; limiting iNOS generation of NO; decreasing cytokine levels (ICAM-1, ELAM-1, VCAM-1, RANTES, I-TAC, MDC, TARC, MMP-2, MMP-9, tryptase); and diminishing eosinophil adherence, chemotaxis, and opsonization of particles. These effects may provide benefit to some of the inflammatory responses of an acute allergic reaction and provide a basis for future development of H1 antagonists with stronger anti-inflammatory effects. These studies also support the contention that fexofenadine is effective for the treatment of allergic rhinits and chronic idiopathic urticaria.

Keywords: fexofenadine, allergy, oral suspension, formulations, pharmacology

Introduction

The allergic response in people with atopic disorders involves exposure of the immune system to the antigen (Leung 1998), antigen presentation (Fokkens et al 1991), mediator release with amplification signals (Grewal and Flavell 1996; Vercelli et al 1989), and production of antigen specific IgE, which binds to mast cells. (Ishizaka and Ishizaka 1977). Upon re-exposure to the allergen, bridging of the mast cell bound allergen specific IgE results in the release of preformed and newly synthesized bioactive and pro-inflammatory mediators (Hirano 1989), which results in the symptoms of allergic rhinitis and chronic idiopathic urticaria, and contributes to the symptoms of atopic dermatitis and allergic asthma.

Antihistamines form the cornerstone of treatment for allergic disorders. Fexofenadine has been marketed in the US as a selective H_1 antagonist since 2000. However, the drug appears to exhibit some anti-inflammatory activity. The US Food and Drug Administration (FDA) approved an oral suspension of fexofenadine on October 16, 2006. The approval is for twice-daily dosing, for the treatment of symptoms associated with seasonal allergic rhinitis, in patients 2 to 11 years of age, and for the treatment of symptoms of chronic idiopathic urticaria, in patients 6 months to 11 years of age.

The studies cited in this text provide information based upon other oral formulations of fexofenadine. Information on fexofenadine oral suspension remains sparse. Information based upon efficacy studies financially supported only by the manufacturer is not included, unless stated in the text.

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Bioequivalence of oral suspension and solid formulations of fexofenadine

Morrison and Sahasranaman (2007) administered fexofenadine 30 mg by tablet or by oral suspension to 53 normal adult subjects. Their subjects reached maximum blood fexofenadine concentrations at 1 hour for the oral suspension and 1.5 hour for the tablet. They found equivalent areas under the curves for the oral suspension and the tablet formulation, suggesting bioequivalence of fexofenadine oral suspension and fexofenadine capsules. In a study focusing on the oral formulations, Grubbe et al (2007) evaluated the pharmacokinetics of fexofenadine oral suspension in 50 children, aged 2 to 5 years, which demonstrated the mean maximum plasma concentration of 224 ng/mL, and the mean area under the plasma concentration curve of 898 ng-h/mL. In capsule formulations in a double-blind, two-way crossover study in children with allergic rhinitis (with a mean age of 9.8 years, a mean height of 134 cm and a mean weight of 32.1 kg), Simons et al (1996) administered 30 or 60 mg of fexofenadine as a capsule and demonstrated the mean maximum plasma concentrations after the 30 mg dose of 78 ng/mL, and the mean maximum concentrations after the 60 mg dose of 286 ng/mL. They found no dose-dependent kinetics in the doses studied and no difference in the clearance rates or the mean terminal elimination half-life values after both doses. In another capsule and tablet formulation study designed as open-label, randomized crossover studies in healthy male non-smokers 18 to 43 years of age, within 10% of ideal body weight, Stoltz et al (1997) found that the relative bioavailability of fexofenadine capsules is 89% to 93% compared to the tablet formulation. Food decreased the area under the curves by 17% for the capsule and by 25% for the tablet compared to administration of the fexofenadine under a fasting state. Food did not change the proportionality of the fexofenadine pharmacokinetics.

These studies suggest that fexofenadine is bioequivalent in its three oral formulations.

Pharmacokinetics

In an industry-based[1] study, Robbins et al (1998) studied the pharmacokinetics of fexofenadine in 24 healthy male adult volunteers. The drug was undetectable at 48 hours after a single dose, and percent drug recovered in the urine ranged from 7.6% to 11.8%. In another industry-based study, Russell et al (1998) found similar pharmacokinetics, in healthy male adults, for both the single dose and twice-daily dose of fexofenadine, administered as an oral solution, with 80% of the administered drug passing through the intestinal tract (Russell et al 1998). These two studies suggest that the majority of the drug is excreted through the intestinal tract, with a small component via the kidneys, mostly unchanged.

Although high doses of fexofenadine do not appear to provide much toxicity, interaction with other drugs that use the P450 CYP3A4 degradation pathway, P-glycoprotein and the organic anion transporter peptides, prominent transporter proteins, may increase the risks of adverse events (Shukla et al 2008). Concomitant exposure to prescription and non-prescription drugs, as well as food, may significantly alter the blood and tissue levels of medications, as well as alter the risks to those medications. Factors that may affect the drug–drug and drug–food interactions include biodegradative pathways and transport mechanisms, particularly via the multi-drug transporters P-glycoprotein and organic anion transporter (Table 1) (Adenot et al 2004; Akiyama et al 1988; Baltes et al 2007; Charuk et al 1994; Chiou et al 2000; Choi et al 1998; Crowe et al 2006a, b; DiDiodato and Sharom 1997; Doran et al 2005; Ejsing et al 2007; Elsinga et al 2004; Faassen et al 2003; Feng et al 2008; Fromm 2000; Garrigues et al 2002; Gouaze et al 2005; Hanko et al 2003; Hayeshi et al 2006; Ibrahim et al 2000; Ito et al 1997; Jette et al 1995; Johnson 2002; Ketabi-Kiyanvash et al 2003; Kim and Kim 2002; King et al 2001; Lee and Lee 2002; Leung and Bendayan 1999; Ling 1992; Litman et al 2003; Loo et al 2003; Makowski and Pikula 1997; Mollgard et al 2001; Neuhoff et al 2000; Orlowski and Garrigos 1999; Pascaud et al 1998; Rebbeor and Senior 1998; Safa and Safa 2004; Savolainen et al 2002; Schinkel et al 1996; Sharom 1997; Shirasaka et al 2006; Shukla et al 2008; Smit et al 1998; Storch et al 2007; Terao et al 1996; Wang et al 2006; Weiss et al 2003).

Although sterioisomers are commonly found to have some preferential biological and pharmacological effects (Bielory et al), Miura et al (2007) did not find any difference in the pharmacokinetics of fexofenadine enantiomers in healthy subjects. They found that neither enantiomer underwent metabolism by CYP3A4. In addition, alfentanil, a selective inhibitor of the P450 CYP3A4 degradative pathway, did not significantly compete with fexofenadine (Kharasch et al 2005). Therefore, it appears that fexofenadine does not significantly interact with the P450 CYP3A degradative pathway. However, in a study

[1]Hoechst Marion Roussel first marketed fexofenadine. In 1999, Hoechst AG (parent company to Hoechst Marion Roussel) merged with Rhône-Poulenc to form Aventis, which was absorbed into Sanofi-Aventis in 2004.

Table 1 Site and effect of drug interactions with fexofenadine

Drug	Interaction	Effect of interaction on fexofenadine peak concentration
Ketoconazole	Inhibit P-glycoprotein	Decrease intestinal absorption and increased fexofenadine peak concentration
Itraconazole	Inhibit P-glycoprotein	Decrease intestinal absorption and increased fexofenadine peak concentration
Verapamil	Inhibit P-glycoprotein	Decrease intestinal absorption and increased fexofenadine peak concentration
Erythromycin	Inhibit P-glycoprotein	Decrease intestinal absorption and increased fexofenadine peak concentration
Ritonavir	Inhibit P-glycoprotein	Decrease intestinal absorption and increased fexofenadine peak concentration
Lopinavir/ritonavir	Inhibit P-glycoprotein	Decrease intestinal absorption and increased fexofenadine peak concentration
St John's Wort	Inhibit P-glycoprotein	Decrease intestinal absorption and increased fexofenadine peak concentration
Omeprazole	Interacts at P-glycoprotein	None
Indomethacin	Inhibit multidrug resistant-associated protein	None
Probenecid	Inhibit multidrug resistant-associated protein	Decreased renal clearance and no change in peak concentration
Rifamycin	Inhibit organic anion-transporting polypeptide	None
Rifampin	Induction of P-glycoprotein	Increased fexofenadine clearance

using MDR1a/1b knockout mice, Tahara et al (2005) showed that P-glycoprotein does have a role in moving fexofenadine from the brain to the plasma, and from the plasma to the liver, but had no effect on fexofenadine biliary excretion.

Cvetkovic et al (1999) found that the human organic anion transporting polypeptide mediates ^{14}C-labeled fexofenadine cellular uptake. The bile acid transporter, human sodium taurocholate co-transporting polypeptide, did not exhibit such activity. The authors identified P-glycoprotein as a fexofenadine efflux transporter, using the LLC-PK1 cell, a polarized epithelial cell line that lacks P-glycoprotein, and a derivative cell line (L-MDR1), which overexpresses P-glycoprotein. Oral and intravenous administration of ^{14}C-labeled fexofenadine to mice lacking MDR1-encoded P-glycoprotein resulted in 5- and 9-fold increases in the drug's plasma and brain levels, respectively, compared with wild-type mice. A number of drug inhibitors of P-glycoprotein effectively inhibited organic anion transporting polypeptide. Because organic anion transporting polypeptide transporters and P-glycoprotein co-localize in organs of importance to drug disposition, such as the liver, their activity may provide an explanation for the mechanism(s) responsible for fexofenadine disposition, and suggests potentially similar roles in the disposition of other xenobiotics (Cvetkovic et al 1999).

Inhibitors of P-glycoprotein (ketoconazole, itraconazole, verapamil, and erythromycin) inhibited the intestinal absorption of fexofenadine. However, inhibitors of multidrug resistant associated protein (indomethacin, probenecid) and organic anion transporting polypeptide (rifamycin) had no effect upon fexofenadine transport. Rifampin increases fexofenadine clearance, presumably by the induction of P-glycoprotein (Hamman et al 2001). Fexofenadine does not appear to affect the pharmacokinetics of omeprazole, a substrate of P-glycoprotein, suggesting that these two drugs have different transport mechanisms, or fexofenadine does not saturate P-glycoprotein.

Drescher et al (2002) described a number of distinct P-glycoprotein mutations that may affect the transport of fexofenadine. The MDR1 G2577T/C3435T haplotype of P-glycoprotein, in the presence of itraconazole, altered the disposition of fexofenadine, with no change in the elimination half-life and the renal clearance of fexofenadine. Itraconazole resulted in a 3-fold increase in the peak concentration of fexofenadine and the area under the curve. It increased the mean area under the plasma concentration-time curve of fexofenadine. This suggests that the interaction between itraconazole and fexofenadine may occur at the gut wall before reaching the portal vein circulation. The C3435T mutation does not affect the disposition of fexofenadine.

However, subjects with the 2677AA/3435CC haplotype had lower plasma fexofenadine concentrations than those with the G2677T/A and C3435T haplotypes (Yi et al 2004). These findings suggest that P-glycoprotein is responsible for the intestinal absorption of fexofenadine.

Van Heeswijk et al (2006) studied the time-dependent interaction between lopinavir/ritonavir and fexofenadine. Ritonavir and lopinavir/ritonavir increased the area under the plasma concentration-time curve for fexofenadine. They did not observe a change in the fexofenadine elimination half-life. They postulated that the increased area under the curve related to increased bioavailability due to P-glycoprotein inhibition. This effect of lopinavir/ritonavir would inhibit the intestinal elimination of fexofenadine. St John's Wort, in a single dose of 900 mg, inhibits the intestinal transport of fexofenadine, increasing the maximum plasma concentration of fexofenadine by 45%. St John's wort decreases the oral clearance of fexofenadine by 20%, without changing the half-life and renal clearance (Milne et al 2000; Petri et al 2004; Shon et al 2005; Takahata et al 2004; Tannergren et al 2003; Uno et al 2006; Wang et al 2002). These data suggest that fexofenadine may affect the blood levels of other drugs through its interaction with P-glycoprotein.

Probenecid has been shown to inhibit the interaction of fexofenadine with the organic anion transporter 3 (OAT3) in the kidney (Tahara et al 2006). However, as the renal excretion of fexofenadine is small (<10%), the effect upon systemic fexofenadine levels is limited (Robbins et al 1998). There may also be preferential binding of fexofenadine by OAT subtypes. Organic anion transporter Protein 1B3 preferentially accepts fexofenadine over organic anion transporter proteins 1B1 and 2B1 in human embryonic kidney cells, suggesting that organic anion transporter Protein 1B3 is a transporter involved in hepatic uptake of fexofenadine (Shimizu et al 2005).

Although fexofenadine does not undergo significant metabolism by the P450 CYP 3A4, it does interact with a numbers of drugs at P-glycoprotein and the organic anion transporter polypeptides. These interactions may increase the blood levels of a number of drugs, and increase the risk of adverse effects with concomitant administration of those drugs.

Fruit juices and their effect upon fexofenadine absorption

Administration of fexofenadine with grapefruit juice reduces the bioavailability of fexofenadine (Banfield et al 2002). This reduction in bioavailability, which also occurs with apple juice, appears to result from preferential inhibition of organic anion transporter polypeptide mediated transport (Dresser et al 2002, 2005; Kamath et al 2005). These data have led to the recommendation that patients should not ingest apple or grapefruit juice while taking fexofenadine.

Mechanism of action (Table 2)

At 1 to 2 hours following the ingestion of fexofenadine, both the 30 mg and 60 mg doses suppressed the epicutaneous wheal response to histamine through 24 hours post dosing and suppressed the epicutaneous flare response to histamine through 8 hours post dosing (Simons et al 2003). In another study, fexofenadine inhibited the histamine-induced wheal and flare with a maximum effect reached between 1 and 2 hours and lasting through the 12-hour dosing schedule

Table 2 Mechanisms of action of fexofenadine on components of the immune system

Component of immune system	Effect of fexofenadine
H1 receptor	Competitive inhibition
LTC_4, LTD_4, and LTE_4	Inhibit production
PGE_2 and $PGF_{2\alpha}$	Inhibit production
Cyclo-oxygenase 2	Competitive inhibition
Thromboxane	Inhibit production
iNOS mRNA	Inhibit production
ELAM-1	Inhibit production
VCAM-1	Inhibit production
Tryptase	Inhibit production
Nasal epithelial cells	Attenuate electrical resistance to eosinophils and opsonized latex beads
	Decreased release of IL-6 and TNFα
Mucosal fibroblasts	Decreased release of MMP-2 and MMP-9
Eosinophils	Decreased release of RANTES
	Decreased release of IL-8
	Decreased release of GM-CSF
	Decreased release of sICAM-1
	Decreased IFNγ- and TNFα-induced release of ICAM-1
	Decreased trichinella-induced eosinophilia
Keratinocyte	Decreased expression RANTES
	Decreased expression of I-TAC
	Decreased expression of MDC and TARC
Peripheral blood leukocyte	Decreased production of IL-4

for 60 mg, while the fexofenadine 120 mg dose inhibited the histamine-induced wheal and flare for 23 hours. The authors did not note tolerance to the anti-histamine effect over a period of 28 days (Russell et al 1998). Allocco et al (2002), with grants from the NIH and industry, studied the effect of fexofenadine upon the early response to nasal allergen challenge and demonstrated that fexofenadine reduced symptoms and vascular permeability. However, it did not reduce the release of histamine or tryptase. Their data suggest that while fexofenadine antagonizes mediators of the acute allergic response, it does not prevent mast cell degranulation.

Older anti-histamines have anti-cholinergic properties that may induce increased intraocular pressure, leading to glaucoma and prostatism associated with urinary retention. However, in a cholinergic linked capsaicin-induced cough model, pretreatment with fexofenadine had no adverse effect (Dicpinigaitis et al 2003).

In an industry-sponsored study, Juergens et al (2006a) evaluated the effect of fexofenadine on arachidonic acid metabolism in cultured human monocytes. Lipopolysaccharide stimulated human monocytes from healthy volunteers co-cultured with and without fexofenadine, followed by stimulation with zymosan, led to inhibition of LTC_4, LTD_4, and LTE_4 production. Fexofenadine also inhibited lipopolysaccharide-stimulated production of PGE_2 and $PGF_{2\alpha}$, which the authors suggest may explain the beneficial effects of fexofenadine upon nasal congestion. In addition, fexofenadine selectively inhibited cyclo-oxygenase 2, which may also contribute to its apparent anti-inflammatory properties (Juergens et al 2006b). Sakairi et al (2005), in an industry-based study, demonstrated that fexofenadine inhibited the increase in nasal airway resistance in a guinea pig antigen-induced model of rhinitis. They found a similar result with ramatroban, a thromboxane inhibitor. They did not reduce nasal airway resistance with a selective leukotriene antagonist. The authors suggest that fexofenadine may inhibit the release of chemical mediators, including thromboxane, to reduce antigen-induced nasal airway resistance, in part by its inhibitory effect on cyclo-oxygenase 2.

Asano et al (2007), in an industry-sponsored study, evaluated the effect of nitric oxide production by fexofenadine from nasal fibroblasts, which demonstrated inhibition of iNOS mRNA, with the suppression of TNFα-induced NO production from nasal fibroblasts. Mice treated for 2 and 3 weeks with fexofenadine had diminished LPS-induced NO production with inhibition of iNOS mRNA expression in lung tissues, suggesting a role for fexofenadine in asthma. However, Brannan et al (2001) and Fardon et al (2005) did not show a direct benefit of fexofenadine in patients with asthma.

Fexofenadine treatment appeared to decrease endothelial leukocyte adhesion molecule-1 (ELAM-1), vascular cell adhesion molecule-1 (VCAM-1), and tryptase in subjects with chronic idiopathic urticaria, suggesting that fexofenadine may express other anti-inflammatory properties by the modulation of these cytokines (Cassano et al 2002).

Abdelaziz et al (1998) studied the effects of fexofenadine on eosinophil-induced changes in electrical resistance and adherence to human nasal endothelial cells, as well as the effects of fexofenadine on eosinophil adherence and chemotaxis, in the presence and absence of opsonized latex beads. Fexofenadine significantly attenuated the decrease in electrical resistance of the human nasal epithelial cells with exposure to both eosinophils and opsonized latex beads. Human nasal epithelial cells, on exposure to eosinophils with opsonized latex beads, released RANTES, IL-8, GM-CSF, and sICAM-1. Fexofenadine diminished the release of these chemokines with human nasal epithelial cell exposure to eosinophils and opsonized latex beads. In the presence of IFNγ and TNFα, fexofenadine decreased the expression of ICAM-1, increased the percentage of apoptotic cells, but did not change the expression of LFA-1. Fexofenadine did not change the expression of keratinocyte expression of IL-8 and Mig, but fexofenadine did down-modulate keratinocyte RANTES, I-TAC, MDC, and TARC, suggesting that fexofenadine had a selective effect on TH2 cytokines, a mechanism by which fexofenadine provided an anti-inflammatory effect. Fexofenadine did not affect peripheral blood leukocyte proliferation induced by Cry j 1 stimulation. However, fexofenadine significantly inhibited the ability of peripheral blood leukocytes to produce IL-4, but not IFN-γ with Cry j 1 stimulation (Asano et al 2004b). Fexofenadine pretreatment reduced the intranasal levels of IL-6 and TNFα in subjects given an intranasal challenge of *Parietaria officinalis* (Ciprandi et al 2004).

Watanabe et al (2004) studied the effect of fexofenadine upon eosinophilia and systemic anaphylaxis in mice infected with *Trichinella spiralis*. Fexofenadine provided a dose-dependent suppression of eosinophilia in C57BL/6 mice but not in mast cell-deficient W/W^v mice. Fexofenadine suppressed rectal temperature, a marker for systemic anaphylaxis, in C57BL/6 mice. In an IgE-anti-IgE model of anaphylaxis in CBF1 mice, fexofenadine suppressed this same marker of anaphylaxis, without an effect on peripheral IL-5 or eotaxin levels. Fexofenadine diminished mRNA

expression of RANTES, as well as limited the elaboration of eotaxin from nasal polyp fibroblasts, in response to LPS (Asano et al 2004a).

Fexofenadine inhibited the production of matrix metalloproteinases (MMP) MMP-2 and MMP-9 from nasal polyp and mucosal fibroblasts in response to TNF-α, and inhibited MMP mRNA expression and NF-κB, but not tissue inhibitor of metalloproteinase (TIMP-1 and TIMP-2) (Asano et al 2004c). Fexofenadine improved performance on the Digit Symbol Substitution Test, but it did not have a blocking effect upon the dopamine transporter (Theunissen et al 2006a, b)

Fexofenadine is primarily prescribed for its H_1 antagonist activity. However, it appears to have effects upon other mast cell mediators, as well as mediators produced by other cell types. Fexofenadine, in addition to antagonizing H_1 receptors, decreases the production of LTC_4, LTD_4, and LTE_4, PGE_2, and $PGF_{2\alpha}$, inhibits cyclo-oxygenase 2, inhibits the generation of thromboxane (perhaps through cyclo-oxygenase 2), and limits the iNOS generation of NO, as well as the generation of ICAM-1, ELAM-1, VCAM-1, RANTES, I-TAC, MDC, TARC, MMP-2, MMP-9, and tryptase. Fexofenadine appears to decrease eosinophil adherence, chemotaxis, and opsonization of particles. These effects may decrease the inflammatory responses initiated by an acute allergic reaction and provide a basis for future development of H1 antagonists with stronger anti-inflammatory effects.

Efficacy and safety

Fexofenadine reduced airway sensitivity to mannitol compared to placebo. However, fexofenadine did not alter the final percent reduction in FEV_1 (Brannan et al 2001). In transfer experiments, fexofenadine prevented the development of airway hyper-responsiveness as well as primary sensitization and challenge, with a decrease in bronchoalveolar lavage and tissue eosinophilia, lymphocyte numbers, and TH2 cytokine production (Gelfand et al 2002). However, fexofenadine did not have an additive effect to inhaled corticosteroid therapy or on inflammatory markers in subjects with atopic asthma (Fardon et al 2005).

In children aged 2 to 5 years with allergic rhinitis, fexofenadine had a frequency of adverse effects no different from placebo. The most frequently involved adverse events were upper respiratory tract infection, fever, infection, and vomiting. Of the adverse events, 8.2% were attributable to the placebo, and 9.5% to fexofenadine. There were no clinically relevant differences for laboratory measures, vital signs, and physical examinations (Milgrom et al 2007). Grubbe et al (2007) evaluated effects of fexofenadine oral suspension in 50 children, aged 2 to 5 years. Seven of their subjects experienced 10 adverse events, which resolved without sequelae. One subject suffered pyrexia. Ngamphaiboon et al (2005) studied the efficacy and safety of fexofenadine 30 mg in pediatric patients with allergic rhinitis. No adverse event resulted in dropout. Headache was the most common reported adverse event. In their 88 subjects, they did not appreciate "meaningful change in any electrocardiogram".

In a double blind, two-way crossover study, Simons et al (1996) administered 30 or 60 mg of fexofenadine as a capsule to 14 children with allergic rhinitis (mean age of 9.8 years, with a mean height of 134 cm and a mean weight of 32.1 kg). Somnolence occurred in one child 10 hours after the ingestion of a 30 mg dose. They found no electrocardiogram abnormalities at peak plasma concentrations.

Miyabe et al (2003) studied the effect of fexofenadine upon cedar pollinosis. They found that fexofenadine administered before or after the onset of cedar pollinosis prevented or controlled nasal obstruction, sneeze, and rhinorrhea.

In a multi-center placebo controlled safety and efficacy study of 861 subjects with moderate to severe autumn allergic rhinitis, fexofenadine at doses of 120 mg and 180 mg fexofenadine, given once daily, significantly reduced total symptom score (for nasal congestion), through the 24-hour trough. There were no differences between the two doses of fexofenadine and placebo groups in adverse events, as both subjects and controls reported headache as the most common adverse event (Casale et al 1999).

Fexofenadine had no effect on the quality of life and work productivity in adult subjects with seasonal allergic rhinitis during the peak season for cedar pollinosis (Okubo et al 2005).

Bronsky et al (1998) studied 550 subjects who had previously responded to other anti-histamines for seasonal allergic rhinitis, for 17 days. Subjects sustained significant improvements in total symptom score 1 to 3 hours after the first dose at doses of 40 mg, 60 mg, and 120 mg, all twice daily. Adverse events occurred in about 13% of both the fexofenadine and placebo groups. These authors did not find increases in the QT_C intervals in their subjects treated with fexofenadine.

In an industry-sponsored study, Meltzer et al (2004) studied the safety and efficacy of fexofenadine in children with seasonal allergic rhinitis. They polled data from 3 double-blind, randomized, placebo-controlled, parallel group, 2-week trials in children ages 6 to 11 years with seasonal allergic rhinitis. The studies used 30 mg twice daily while 2 other studies also used 15 or 60 mg twice daily.

Adverse events did not differ between the fexofenadine and placebo groups. Headache was the most common adverse event. They did not identify any sedative effect of fexofenadine. Fexofenadine at 30 mg twice daily significantly reduced the total symptom score, sneeze, rhinorrhea, itchy nose/mouth/throat/ears, itchy watery red eyes, and nasal congestion. Kawashima et al (2002) found that doses as low as 20 mg twice daily were effective in the treatment of chronic idiopathic urticaria, and in another study, Kawashima et al (2003) found that fexofenadine improved the pruritus associated with atopic dermatitis more than placebo.

With assistance from industry, Nelson et al (2000) tested the efficacy of fexofenadine in the treatment of chronic idiopathic urticaria. Fexofenadine administered over a period of 4 weeks was better than placebo. They noted no significant differences in the responses to doses between 60 mg twice daily and 240 mg twice daily. All subjects noted improvement in pruritus severity, number of wheals, and interference with sleep. Handa et al (2004) did not find great benefit of fexofenadine n the treatment of chronic idiopathic urticaria. In an open-label, non-comparative study, Kulthanan et al (2001) studied the efficacy and toxicity of fexofenadine in the treatment of chronic idiopathic urticaria. Of 108 patients enrolled, 10 withdrew for lack of efficacy. Fexofenadine reduced the number of wheals, the severity of itch, interference with sleep, and interference with daily activities. Twenty subjects experienced at least one adverse event. The adverse events included headache, drowsiness, dizziness, increased appetite with weight gain, and cough.

With industry support, Russell et al (1998) studied the fexofenadine dose and subject tolerance to fexofenadine, as well as the drug single dose and steady-state pharmacokinetics in 87 adult subjects. Their subjects tolerated doses of fexofenadine ranging from 10 to 800 mg, with no clinically significant trends for cardiac conduction parameters, vital signs, adverse event reporting, or clinical laboratory parameters despite exposure to fexofenadine plasma concentrations as high as 12,250 ng/mL. At doses of 15 and 30 mg twice daily in children aged 6 months to 2 years with allergic rhinitis, treatment-emergent adverse events were similar between the placebo and treatment groups. Vomiting was the most common adverse event. There were no differences between fexofenadine and placebo for vital signs, electrocardiographic results, or physical examination results (Hampel et al 2007). An industry study of the effect of fexofenadine in a single dose up to 800 mg and multiple doses of 690 mg did not appear to change the QTc interval (Pratt et al 1999).

Pinto et al (et al 1999) described a patient on fexofenadine with a prolonged QTc interval. While on fexofenadine, the patient experienced an episode of syncope, with injury to a tooth. Taken off the fexofenadine, the patient's QTc interval normalized. When replaced on fexofenadine 180 mg daily, QTc interval increased and the patient experienced an episode of polymorphic ventricular tachycardia, which progressed to ventricular fibrillation. The authors did not find an alternative reason for the prolonged QTc interval or the ventricular arrhythmia. Industry contested this finding. However, in a response, Pinto et al addressed industry's concerns. (Giraud and Giraud 1999). Craig-McFeely et al (2000, 2001) surveyed general practitioners in Britain for adverse events to fexofenadine. Less than 1% of respondents stopped the fexofenadine for intolerance. They found no reports of drug interactions. Cardiac events, including palpitations, chest pain, arrhythmia, and chest tightness, but without reports of QTc interval lengthening, resolved upon cessation of the drug. Dhar et al (2000) were unable to find QTc prolongation with fexofenadine.

Hindmarch et al with industry support, studied the effect of fexofenadine upon cognitive and psychomotor function (Hindmarch et al 1999, 2002; Kamei et al 2003; Ridout et al 2003a, b). The authors tested critical flicker fusion (CFF), choice reaction time (CRT), and assessment of subjective sedation (LARS) after up to 180 mg fexofenadine, from 1 to 24 hours. They were unable to find a difference between fexofenadine and placebo. Stone et al (1999) studied the central effects of fexofenadine (120, 180 and 240 mg) on digit symbol substitution, tracking and vigilance tasks and on objective sleepiness (multiple sleep latency test) and subjective sleepiness. They found no effect of the fexofenadine on any of these variables. Potter et al (2003) were unable to find differences in reaction time, decision-making, and driver behavior with and without fexofenadine 180 mg compared to placebo. They found no differences between the fexofenadine and the placebo groups. Nicholson et al (2000) found that fexofenadine in doses of 120 g, 180 mg, and 240 mg did not affect digit symbol substitution, tracking, vigilance tasks, multiple sleep latencies, and subjective sleepiness. Mansfield et al (2003) found that fexofenadine at a dose of 180 mg did not change self-reported drowsiness, omission errors, and response time. Bower et al (2003) studied the effects of single-dose fexofenadine, diphenhydramine, and placebo on cognitive performance in flight personnel. Although diphenhydramine resulted in significant psychomotor decrements, the effect of fexofenadine was not different from placebo. In an industry-supported study, Tashiro et al (2005) studied

the effect of fexofenadine upon brake reaction time, while using a cellular phone. Compared to hydroxyzine, fexofenadine did not impair brake reaction time in otherwise healthy subjects. Weiler et al (2000) compared the effects of fexofenadine, diphenhydramine, and alcohol on driving performance. Subjects received one of these drugs or placebo, weekly, 1 hour prior to driving. Subjects had significantly better coherence after taking alcohol or fexofenadine than after taking diphenhydramine. Lane keeping (steering instability and crossing the centerline) was impaired after alcohol and diphenhydramine use compared with fexofenadine use. Alcohol increased the mean response time to stop the vehicle compared to fexofenadine. Self-reported drowsiness did not predict lack of coherence and weakly related to the minimum following distance, steering instability, and left lane excursion. In a review by Banerji et al (2007), the authors found that fexofenadine was less sedating than diphenhydramine.

Graft et al (2001), in an industry-sponsored study, demonstrated the safety of fexofenadine in 875 children, 6 to 11 years of age, treated for seasonal allergic rhinitis. They administered 15 mg, 30 mg, or 60 mg, twice daily. Ten of their subjects (5 in the fexofenadine group and 5 in the placebo group) stopped the medication because of an adverse event, which included upper respiratory congestion, otitis media, and asthma, although the authors could not link any of the adverse events to the drug. They reported no changes in electrocardiograms.

Saraswat et al (2006) presented a case of stable psoriasis, who developed a severe pustular flare within 24 hours of taking fexofenadine. Following resolution of the pustular psoriasis, they rechallenged the patient with fexofenadine, with recurrence of the rash. These studies support the contention that fexofenadine is effective for the treatment of allergic rhinits and chronic idiopathic urticaria, perhaps without benefit to patients with asthma. With the possible exception of rare adverse cardiac and cutaneous events, fexofenadine appears no more toxic than placebo when administered in the absence of other drugs.

Conclusion

The FDA approved fexofenadine for treatment of the symptoms of allergic rhinitis and chronic idiopathic urticaria. The drug appeared effective in the treatment of its indicated conditions. Subjects tolerated fexofenadine well. However, concern remains regarding fexofenadine's interactions with other medications that use the P-glycoprotein and the organic anion transporter peptides, which may result in an increased risk of adverse events to those other medications. This concern comes from the pharmacokinetic data, which suggest that although only a small proportion of fexofenadine is metabolized, fexofenadine moves into and out of the blood and tissues by at least P-glycoprotein and organic anion transporter peptides, which transport a number of other medications. In addition to blocking H_1 receptors, fexofenadine appears to diminish the production of LTC_4, LTD_4, and LTE_4, PGE_2, and $PGF_{2\alpha}$; inhibits cyclo-oxygenase 2; inhibits the generation of thromboxane (perhaps through cyclo-oxygenase 2); and limits iNOS generation of NO, as well as ICAM-1, ELAM-1, VCAM-1, RANTES, I-TAC, MDC, TARC, MMP-2, MMP-9, and tryptase, which may contribute to its benefit.

Disclosures

Neither author has conflicts of interest to disclose.

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