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Fexofenadine

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Contents

Summary

▲ The nonsedating histamine H_1 receptor antagonist fexofenadine is the active metabolite of terfenadine.

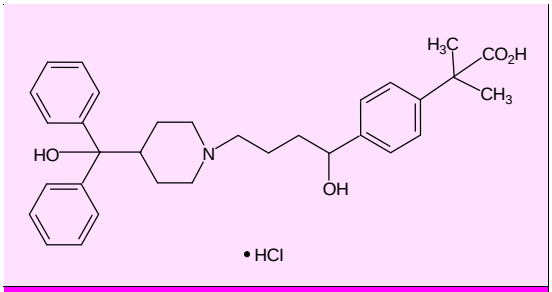
▲ It reduced the allergic response in animal models of allergy and did not prolong the QT interval (QT_c) in dogs or rabbits at plasma concentrations many times higher than those seen after administration of therapeutic dosages.

▲ Similarly, relative to placebo, fexofenadine did not affect mean QT_c in patients given dosages of up to 480 mg/day for 2 weeks or in volunteers who received up to 800 mg/day for 6 days or 240 mg/day for 12 months.

▲ In a double-blind clinical trial, oral fexofenadine 120 or 180mg once daily controlled symptoms in patients with seasonal allergic rhinitis as effectively as cetirizine. Other double-blind clinical trials showed that fexofenadine 40 to 240mg twice daily was significantly more effective than placebo. Fexofenadine 180 or 240mg once daily was significantly more effective than placebo in patients with chronic idiopathic urticaria.

▲ The drug was well tolerated in these clinical trials, with an adverse event profile similar to that seen with placebo. The most common adverse events were headache, throat irritation, viral infection, nausea, dysmenorrhoea, drowsiness, dyspepsia and fatigue.

Features and properties of fexofenadine (MDL 16455, MDL 16455A)	
Indications	
Seasonal allergic rhinitis, chronic idiopathic urticaria	Launched
Mechanism of action	
Antihistamine	Histamine H_1 receptor antagonist
Dosage and administration	
Usual oral dosage	
in seasonal allergic rhinitis	60mg twice daily *or* 120mg once daily
in chronic idiopathic urticaria	180mg once daily
Pharmacokinetic profile after 60mg twice daily	
Peak plasma concentration	286 μg/L
Time to peak plasma concentration	1.3h
Area under the plasma concentration-time curve	1521 μg/L • h
Clearance (renal)	3.42-3.49 L/h
Half-life	14.4h
Adverse events	
Similar to placebo	



Fexofenadine (MDL 16455, MDL 16455A)

Fexofenadine is the active metabolite of the nonsedating antihistamine terfenadine. It shares the histamine H_1 receptor antagonist and nonsedative properties of the parent compound but does not affect the cardiac QT interval (QT_c).

1. Pharmacodynamic Profile

- Fexofenadine did not cross the blood-brain barrier in radio-distribution studies in rats.[1]

- Antigen-induced bronchospasm in sensitised guinea-pigs was inhibited by fexofenadine, as was histamine release from peritoneal mast cells in rats.[1]

- One characteristic of allergic inflammation is enhanced endothelial/epithelial expression of adhesion molecules, leading to leucocyte migration into the inflamed tissue. *In vitro*, fexofenadine significantly decreased basal expression of the adhesion molecule ICAM-1 in human conjunctival epithelial cells and concentration-dependently decreased spontaneous interleukin-6 release from a fibroblast cell line.[2]

- Fexofenadine 10^{-9} to 10^{-3} mol/L significantly attenuated *in vitro* eosinophil-induced release of interleukin-8, granulocyte-macrophage colony-stimulating factor and soluble ICAM-1 from nasal epithelial cell samples taken from patients with seasonal allergic rhinitis.[3]

- In a murine model of allergic sensitisation, oral administration of fexofenadine 5mg prior to and during aerosolised methacholine challenge prevented the development of airway hyper-responsiveness without affecting eosinophilic inflammation.[4]

- Fexofenadine did not prolong QT_c in dogs when administered at a dosage of 10 mg/kg/day orally for 5 days, or in rabbits when administered at a dosage of 10 mg/kg intravenously, despite these dosages producing respective plasma concentrations at least 28 and 63 times greater than those seen after administration of therapeutic dosages (60mg twice daily) to humans.[1]

- Similarly, mean QT_c in 714 patients treated with fexofenadine capsules 60 to 240mg twice daily for 2 weeks, and in 40 volunteers given the drug as an oral solution at dosages of up to 400mg twice daily for 6 days, was not significantly different from that seen in placebo recipients.[1]

- This lack of propensity to cause QT_c irregularities has been confirmed in 2 long term studies in volunteers. Fexofenadine 60mg twice daily for 6 months, or 240mg once daily for 12 months, had

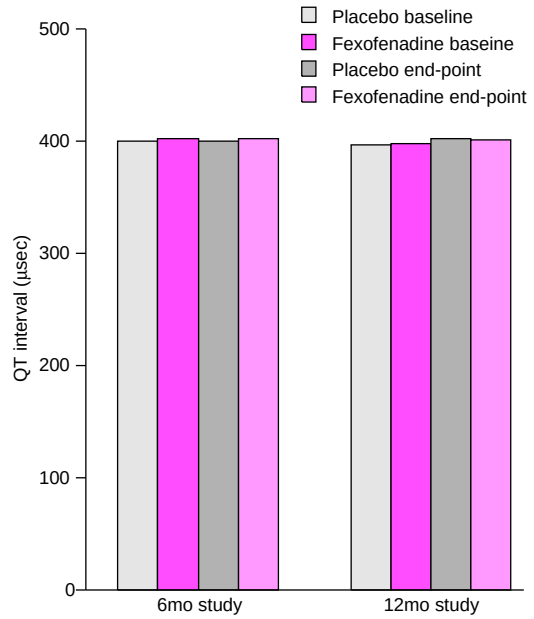


Fig. 1. Mean QT interval (QT_c) after 6 and 12 months' treatment with fexofenadine 60mg twice daily (n = 216) or placebo (n = 209), or 240mg once daily (n = 231) or placebo (n = 233), respectively, in volunteers.[5]

no significant effect on QT_c relative to placebo (fig. 1).[5]

• The median time to clinically important relief after administration of single dose fexofenadine [60 (n = 33) or 120mg (n = 33)] was 60 minutes, compared with 100 minutes with placebo (n = 33), in sensitive volunteers subjected to controlled exposure to allergen (ragweed pollen) in an environmental exposure unit. Fexofenadine reduced the total symptom score to a considerably greater extent than placebo (30 or 28% *vs* 14% reduction). Onset of effect and efficacy were similar with each fexofenadine dose.[6]

• In a randomised double-blind crossover study in volunteers (n = 20), fexofenadine 60mg twice daily (2 doses) or 120mg (single dose) suppressed histamine-induced wheal and flare significantly faster than a single 10mg dose of loratadine. Fexofenadine 120mg once daily was significantly more effective than loratadine in wheal inhibition from 2 to 6 hours and at 8 and 10 hours. This dosage was also significantly more effective than loratadine in flare suppression from 2 to 5 hours. All 3 active treatments were significantly more effective than placebo 2 (fexofenadine 120mg) or 3 (loratadine and fexofenadine 60mg twice daily) hours after administration and at all measured time points thereafter during the 24-hour study period.[7]

• In 20 evaluable volunteers, single-dose fexofenadine (60mg) suppressed histamine skin prick–induced flares significantly more effectively than single-dose loratadine (10mg) at 5, 6 and 7 hours postdose. Terfenadine 60mg was also more effective than loratadine, but not fexofenadine, at certain time points after administration. All 3 active treatments were significantly more effective than placebo.[8]

• In 9 evaluable patients with ragweed allergy, wheal and flare responses to ragweed pollen skin prick tests returned to baseline within 2 days of stopping fexofenadine (60mg twice daily) treatment.[9]

2. Pharmacokinetic Profile

• In 24 healthy male volunteers, fexofenadine 60mg twice daily for 5 days produced a steady-state maximum plasma concentration (C_{max}) of 286 μg/L 1.3 hours postdose (t_{max}). The area under the plasma concentration versus time curve (AUC) at steady state was 1521 μg/L · h.[9]

• Steady-state C_{max} and AUC increased in a dose-related manner and t_{max} and steady-state oral clearance values remained relatively static in volunteers receiving multiple 20, 60, 120 or 240mg twice daily doses of fexofenadine.[10]

• An evaluation of the influence of gender on the pharmacokinetic properties of fexofenadine revealed a 33% reduction in oral clearance in female (n = 20) versus male (n = 20) volunteers. However, renal clearance was similar (3.49 *vs* 3.42 L/h) and the drug was equally well tolerated in both groups over the 80 to 800 mg/day dosage range studied.[11]

• Oral clearance was also reduced, and C_{max} and AUC were increased, in elderly (age 65 to 80 years; n = 20) versus younger (19 to 45 years; n = 110) volunteers given a single oral 80mg dose of fexofenadine. However, AUC values in older patients were considered to be within acceptable limits.[12]

• The C_{max} and half-life of fexofenadine were markedly increased (87 to 111% and 59 to 72%, respectively) in patients with mild to severe renal impairment, compared with volunteers, and US dosage guidelines recommend a lower (60 mg/day) starting dose in this patient group.[1] Hepatic impairment did not substantially alter the pharmacokinetic profile of the drug.[13]

• In male volunteers (n = 6) 92% of a 60mg dose of [^{14}C]fexofenadine was recovered, 80% from the faeces and 12% from the urine. More than 85% of recovered radioactivity was in the form of unchanged drug, indicating negligible systemic metabolism.[14]

3. Therapeutic Trials

• Two weeks' randomised double-blind treatment with oral fexofenadine 60 to 240mg twice daily

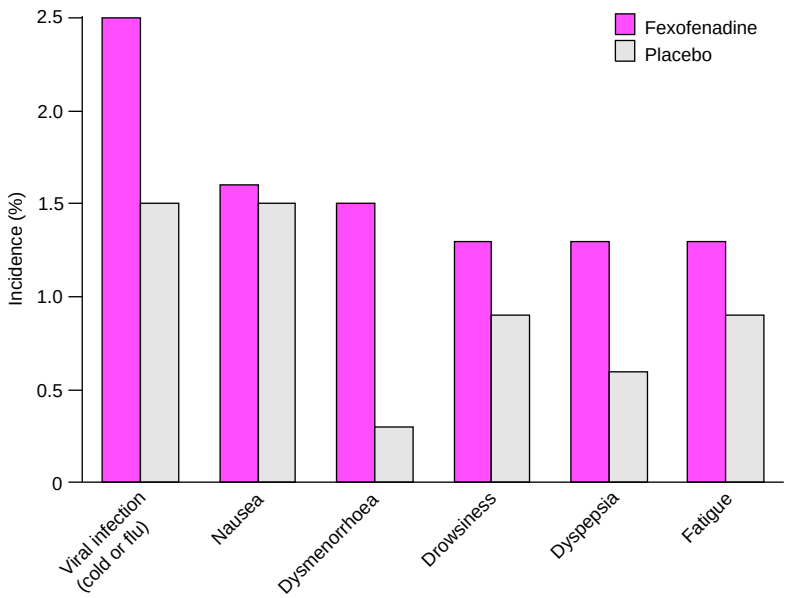


Fig. 2. Adverse events in fexofenadine (n = 679) versus placebo (n = 671) recipients occurring at a rate of >1% in clinical trials. Fexofenadine was administered at a dosage of 60mg twice daily to patients with seasonal allergic rhinitis[1]

was significantly more effective than placebo in 570 patients with seasonal allergic rhinitis. Efficacy was assessed on an intention-to-treat basis according to a patient-assessed 5-point symptom severity rating scale.[15]

- Fexofenadine 40 to 120mg twice daily was also significantly more effective than placebo in this indication. 588 patients with confirmed seasonal allergic rhinitis were enrolled in a 2-week multicentre double-blind trial. Efficacy was again assessed on an intention-to-treat basis according to patient-rated individual symptom severity on a 5-point scale.[16]

- Fexofenadine 120 or 180mg once daily has also been shown to be as effective as cetirizine 10mg once daily in patients (n = 821) with seasonal allergic rhinitis in a double-blind placebo-controlled study. 24-hour reflective total symptom score improved to a significantly greater extent in patients receiving active treatment compared with those given placebo ($p \leq 0.0001$). Nasal congestion, which was not included as a component of the total symptom score, also significantly improved in fexofenadine and cetirizine recipients compared with placebo recipients.[17]

- In patients with chronic idiopathic urticaria (n = 224) fexofenadine 180 and 240mg, but not 60 or 120mg, once daily for 14 days significantly reduced total symptom score (based on patient-assessed rating scales) compared with placebo. All fexofenadine dosages were significantly more effective than placebo in reducing pruritus, and in terms of reducing the interference of the allergy with sleep and normal daily activities.[18]

- Fexofenadine 60mg twice daily was associated with significantly greater improvements in disease-specific quality of life (assessed via the Rhinoconjunctivitis Quality of Life Questionnaire) than placebo in studies involving 1948 patients with seasonal allergic rhinitis. Similarly, patient-reported work and activity impairment was reduced to a significantly greater extent in fexofenadine than placebo recipients.[19]

4. Tolerability

• Clinical trials involving 2461 patients treated with fexofenadine 20 to 240mg twice daily report a similar incidence of adverse events in fexofenadine and placebo recipients. Adverse events occurring at a rate of more than 1% in patients receiving fexofenadine 60mg twice daily (n = 679) or placebo (n = 671) are shown in figure 2. Headache and throat irritation, while occurring at a rate of more than 1%, were more frequent in placebo than in fexofenadine recipients and are not included in figure 2. The incidence of adverse events was not dose related. 2.2% of fexofenadine recipients withdrew from clinical trials because of adverse events compared with 3.3% of placebo recipients.[1]

Laboratory abnormalities occurred at a similar rate and magnitude in fexofenadine and placebo recipients.[1]

• After acute and subchronic dosage tolerability testing of fexofenadine (either as a single 10 to 800mg dose or 20 to 690mg twice daily for 28.5 days) in male volunteers, no dose-related trends or differences with respect to placebo in terms of adverse events or laboratory parameters were noted.[20]

• Administration of fexofenadine 60mg twice daily for 6 months, or 240mg once daily for 12 months, was not associated with significant increases in QT_c relative to placebo.[5]

• In volunteers, coadministration of fexofenadine 120mg twice daily with erythromycin 500mg every 8 hours, or ketoconazole 400mg once daily, was associated with increases in the steady-state C_{max} and $AUC_{(0\text{-}12h)}$ of fexofenadine. However, levels remained below those established in tolerability studies with higher (400mg twice daily) dosages of fexofenadine and the plasma concentrations of erythromycin and ketoconazole were unaffected. Furthermore, no increase in the incidence of adverse events or QT_c abnormalities was observed relative to fexofenadine monotherapy. Dosage adjustment is not considered necessary when fexofenadine is coadministered with these drugs.[1]

5. Fexofenadine: Current Status

The histamine H_1 receptor antagonist fexofenadine has shown clinical efficacy in, and has been approved for, the treatment of seasonal allergic rhinitis and chronic idiopathic urticaria. Notably, QT interval prolongation occasionally seen with the parent compound, terfenadine, does not occur with fexofenadine.

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