Fexofenadine Hydrochloride – A New Anti-Histaminic Drug

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Fexofenadine hydrochloride (TELFAST®, Israel and Europe. ALLEGRA®, USA), $C_{32}H_{39}NO_4HCL$, is a new non-sedating anti-histamine with rapid and long-acting activity. Fexofenadine is the active derivative of terfenadine produced in the body and is responsible for terfenadine's anti-histaminc effects. Fexofenadine is a highly selective peripheral histamine H_1-receptor antagonist with no anti-cholinergic or alpha1-adrenergic receptor-blocking effects and without the severe cardiac side effects of terfenadine [1–4].

Pharmacology

Pharmacodynamics

Fexofenadine does not cross the blood-brain barrier. Unlike terfenadine, fexofenadine does not block potassium channels in animal [1,2] and human [5] cardiocytes and does not affect the cardiac interval (QT_C) [1–3]. This lack of propensity to cause QT_C abnormalities was confirmed in healthy volunteers taking fexofenadine 120 mg/day for 6 months or 240 mg/day for 12 months [6].

In vitro, fexofenadine significantly attenuated expression of the adhesion molecule ICAM-1 in human epithelial cells [1]. Fexofenadine was found to have some anti-inflammatory properties by modulating the release of pro-inflammatory mediators and adhesion molecules from human nasal epithelial cells [7,8].

In human histamine skin wheal and flare studies, the anti-histaminic effect of fexofenadine on the skin can be detected within one hour of ingestion, with maximum effect after 2 to 3 hours. The drug effect is seen even 12 hours after administration, and can be used for long periods without evidence of intolerance [1–3,9].

Pharmacokinetics

Fexofenadine is rapidly absorbed after oral administration and is not affected by food [10]. Plasma concentrations reach a peak in about 2.6 hours. In the plasma, about 60–70% of fexofenadine is bound to plasma proteins, mainly albumin and alpha1-acid glycoprotein. The metabolism of fexofenadine is not dependent on cytochrome P450 activity [11]. Approximately 5% of the total dose is metabolized in the liver and only 0.5–1.5% is converted by cytochrome P450. The rest is excreted in the feces (80%) and urine (12%), with an elimination half-life of 14.4 hours [1–3]. The pharmacokinetics of fexofenadine in adolescents and children is similar to that in adult patients without significant sex-induced differences. In 14 children with a mean age of 9.8 years treated with fexofenadine 30 or 60 mg/day the drug was found to be effective and safe in suppressing wheals and flares [6]. In older subjects peak plasma levels of fexofenadine were greater than in adults, but the mean elimination half-time was similar [2]. Renal disease with diminished renal function slows elimination of the drug. Hepatic disease does not interfere significantly with the pharmacokinetics of fexofenadine [1–3].

Safety and side effects

Although shown to be effective in children, additional studies of the drug's efficacy and safety are needed. In geriatric patients receiving 20–240 mg of fexofenadine twice daily, adverse effects were similar to those seen in patients under the age of 60. Patients with diminished renal function should start with 60 mg/day [1–3]. There was no evidence of teratogenicity, carcinogenicity, mutagenicity or impairment of fertility in animals treated with fexofenadine. Fexofenadine is classified as Category C in the Risk factors A to D and X, and should be given during pregnancy only if the potential benefit justifies the potential risk to the fetus. There is insufficient data regarding excretion of fexofenadine in breast milk [2].

Fexofenadine was well tolerated in clinical trials, with an adverse event profile similar to that seen with placebo. The most common adverse events were headache, throat irritation, symptoms of viral infection, nausea, dyspepsia, dysmenorrhea, drowsiness and fatigue [1–3].

Fexofenadine is reported to be free of adverse central nervous system effects. It is non-sedating and has no effect on driving performance after being taken in the recommended dosage of 60 mg twice daily [12]. Fexofenadine may also be potentially useful and safe for aircrews [13].

Cardiovascular safety of fexofenadine

In view of the known severe arrhythmias induced by terfenadine, the cardiovascular safety profile of fexofenadine was studied carefully. Several clinical studies have shown that fexofenadine does not have any major cardiovascular side effects, although palpitations, chest pain, chest tightness and

arrhythmia were found during treatment, albeit rarely, and were resolved on stopping fexofenadine. The effect of fexofenadine on QTc was evaluated in dose tolerance, safety, and drug-interaction studies with healthy volunteers, and in clinical studies in patients with seasonal allergic rhinitis. Fexofenadine has no significant effect on QTc, even at doses up to tenfold higher than the daily recommended dose. Longer term studies indicated no statistically significant QTc increases compared with placebo in patients receiving fexofenadine up to 240 mg/day for 12 months. Interaction studies showed no significant increases in QTc when fexofenadine was co-administered with erythromycin or ketoconazole. In controlled trials with approximately 6,000 persons, no case of fexofenadine-associated torsades de pointes was observed [14–16]. Recently a case of QT lengthening and life-threatening arrhythmia associated with fexofenadine was reported. This patient, who had a known cardiac disease, was treated with fexofenadine and developed severe arrhythmia. Rechallenge test with fexofenadine confirmed the drug etiology [17].

No significant changes in laboratory values were seen between fexofenadine and placebo [18]. Information concerning overdosage is limited, but in normal volunteers receiving up to 690 mg twice daily for one month no significant adverse reactions were noted. In animals no deaths occurred at oral doses of up to 330 times the recommended human daily doses [2].

Drug interactions

Since fexofenadine does not undergo extensive hepatic metabolism, concomitant administration with drugs that are metabolized by cytochrome P450 is safe. Co-administration of fexofenadine 120 mg twice daily with erythromycin 500 mg every 8 hours, or ketoconazole 400 mg/day was associated with increases in steady-state plasma concentrations of fexofenadine without affecting plasma concentrations of erythromycin or ketoconazole. However, the increase in plasma levels of fexofenadine did not lead to an increase in the incidence of side effects or QTC abnormalities when compared to patients on fexofenadine monotherapy, and dosage adjustment is not considered necessary when fexofenadine is co-adminisered with these drugs. It seems that concomitant administration of fexofenadine with anti-fungal agents (such as fluconazole and terbinafine), anti-depressants (tricyclics, sertraline, paroxetine), H_2-blockers (cimetidine, ranitidine, famotidine, nizatidine), or alcohol is safe [1–3,12,19].

Clinical trial in patients

In double-blind controlled studies, fexofenadine 60 mg twice daily or 120 mg once daily was found to be more effective than 10 mg daily of loratadine in wheal inhibition [20] and significantly better than loratadine in improving quality of life [21]. Fexofenadine was also shown to be as effective and safe as 10 mg daily of cetirizine in patients with seasonal allergic rhinitis [22]. In patients with chronic urticaria, fexofenadine 180 or 240 mg/day reduced the total symptom score, including pruritus, compared with placebo [23].

Indications

In cases of seasonal allergic rhinitis the recommended dosage of fexofenadine is 120 mg daily in a single dose or in two divided doses for patients 12 years of age and older [20,21,24,25]. In cases of chronic idiopathic urticaria once-daily doses of 180 mg fexofenadine is recommended [26,27].

Pretreatment with fexofenadine during venom immunotherapy reduces local allergic reactions and generalized symptoms of the urticaria and angioedema type [28].

With the approval of fexofenadine, an alternative effective and safe anti-histaminic drug in the treatment of allergic rhinitis and chronic urticaria is now available. The anti-inflammatory effect of fexofenadine may also be beneficial, but more research is required.

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