South African National Essential Medicine List
Adult Hospital Level Medication Review Process
Component: Ear, nose and throat conditions

EVIDENCE SUMMARY:

Executive Summary

Date: 23 November 2017
Medicine (INN): Antihistamines for systemic use (non-sedating)
Medicine (ATC): R06A
Indication (ICD10 code): Persistent allergic rhinitis (J30.0-4)
Patient population: Adult patients
Level of Care: Secondary level
Current standard of Care: Cetirizine, oral
Efficacy estimates: n/a
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Author affiliation and conflict of interest details
University of Western Cape, Adult Hospital Level Committee (2017-2020); no conflicts declared.

Objective: Comparison of Second Generation Antihistamines

Evidence review

In a two-week multicenter, double-blind, randomized study, 495 patients with moderate-to-severe seasonal allergic rhinitis (SAR) received once-daily fexofenadine 180 mg or cetirizine 10 mg. Baseline Total symptom score (TSS) and individual symptoms scores were statistically equivalent in the two treatment groups. End points included change from baseline of SAR symptoms and total symptom score (TSS), drowsiness, and daily motivation. The reductions in morning instantaneous TSS were statistically equivalent between fexofenadine and cetirizine: -1.27 (95% CI, -1.64 to -0.90) and -1.44 (95% CI, -1.83 to -1.06), respectively, with a between-treatment difference of -0.18 (95% CI, -0.55 to 0.20). Additionally, the two treatment groups had similar improvements in 24-hour reflective TSS. Overall improvement for patients treated with fexofenadine and cetirizine was -1.56 (95% CI, -1.92 to -1.20) and -1.78 (95% CI, -2.15 to -1.40), with a between-treatment difference of -0.22 (95% CI, -0.59 to 0.15). The treatments were concluded to be statistically and clinically similar. Overall, patients in the fexofenadine treatment group consistently reported less drowsiness with a change from baseline in VAS scores of 2.70 (95% CI, 0.62 to 4.77). As for motivation, there was a trend toward greater improvements from baseline in motivation VAS with fexofenadine compared with cetirizine (-6.2% vs -1.0%; P=.0504). Adverse effects were observed in 16.9% of patients who received fexofenadine and 16.6% who received cetirizine.[1]

In a multicenter, double-blind, parallel-group, placebo controlled trial compared the efficacy of fexofenadine 120 and 180 mg and cetirizine 10 mg daily in the treatment of seasonal allergic rhinitis. Similarly, there were no significant differences among the three active treatment groups. The difference in change from baseline TSS for fexofenadine 120 mg, fexofenadine 180 mg, and cetirizine 10 mg versus placebo was 1.1, 1.4, and 1.4, respectively. The most commonly reported adverse effects were headache and drowsiness. The frequency of headache was similar for all treatments: placebo 7%, fexofenadine 8%, and cetirizine 8%. However, drowsiness occurred more frequently in the cetirizine group (6%) than with placebo (3%) or fexofenadine (3%).[2]

As for loratadine versus fexofenadine, a double-blind, double-dummy, randomized, 2-phase, multicenter study compared the therapeutic responses to loratadine and fexofenadine in patients who had failed initial therapy with the other drug. For the 659 patients who completed phase 1, mean decreases in TSS were significantly greater with loratadine than with fexofenadine (-12.7 vs -10.2, respectively; P =0.019; patient assessment) and for the 389 patients who responded to initial therapy (-6.6 vs -6.1, respectively; P=0.037; investigator assessment.) Of the 389 patients who responded to initial therapy, 61.0% received loratadine and 57% received fexofenadine. More nonresponders to initial therapy had moderate, marked, or complete relief of symptoms after switching to loratadine than after switching to fexofenadine (62.4% vs 51.2%, respectively; P =0.005) and treatment failure in 10.6% vs 21.7%, respectively (P =0.011). As for adverse events, 22.1% of those receiving fexofenadine and 18.2% receiving loratadine experienced one or more adverse events. The most frequent adverse event was headache, which occurred in 8.8% of patients treated with fexofenadine and 4.2% treated with loratadine.[3]

When comparing cetirizine 10 mg to loratadine 10 mg, cetirizine's onset of action was faster at one hour, versus loratadine's onset of 3 hours. Cetirizine produced a 25.4% mean reduction in Total Symptom Complex (TSC), which was greater than the 11.2% reduction with loratadine (P =0.006). Cetirizine also produced greater absolute reductions in TSC scores overall and at each treatment period and endpoint period versus placebo (P <0.001), and overall, at each treatment period, and at endpoint 2 versus loratadine (P = 0.038 to P = 0.003). Changes in Major Symptom Complex (MSC) scores were consistent with those observed for TSC. The incidence of treatment-emergent adverse events of all causality was similar among treatment groups: 15% cetirizine, 18.3% loratadine, 15.0% placebo. Headache was the most common event and was reported in 6.7% of patients that received cetirizine, 5.8% of patients that received loratadine, and 9.2% of patients receiving placebo.[4]

The recommendation to use new generation oral H1-antihistamines that cause some sedation and/or interact with cytochrome P450 places a relatively high value on a reduction of symptoms of AR and a relatively low value on side effects of these medications.[5]

Effects of potassium channel blockade and QT interval prolongation are not a class effect, but result from the action of only a few antihistamine drugs (astemizole and terfenadine specifically). In most cases arrhythmias were reported in cases of high overdose far beyond the suggested doses. It is recommended to monitor for cardiovascular effects in certain patient groups that are at risk, e.g patients with inherited long QT syndrome, the elderly and patients with cardiovascular diseases. In such cases, high dose antihistamines should not be combinedwith CYP3A4 inhibitors (e.g. anti-fungal drugs and macrolides), or with any agents that prolong QT intervals.[6]

For cetirizine prolonged of QT intervals were observed, neither during rest, nor after physical exertion, having administered a therapeutic dose of 10 mg to the patients or 50 mg doses to the healthy volunteers. Loratadine is metabolized by CYP3A4 and CYP2D6 isoenzymes, thus interactions with their inhibitors are possible. No substantial influence on the prolongation of QT intervals or ventricular arrhythmia was found. Potential experimental possibility of potassium channel blockade and QT prolongation exists. Desloratadine is a metabolite of loratadine and no QT interval prolongation was found.[6,7]

In conclusion, fexofenadine and cetirizine appear to be statistically and clinically similar in regard to SAR symptom reduction, but fexofenadine improves drowsiness and motivation compared to cetirizine. Loratadine had a greater reduction in TSS compared to fexofenadine, and loratadine produced a greater effect in nonresponders compared to fexofenadine. Loratadine also had less side effects compared to fexofenadine. Cetirizine has a faster onset and greater reduction in symptom scores versus loratadine, but also a higher incidence of headache. Desloratadine has no QT prolongation.

Recommendation

Fexofenadine and cetirizine appear to be statistically and clinically similar in regards to SAR symptom reduction. Fexofenadine has less drowsiness, but this is not statistically significant. Based on this review recommendations should be guided by availability of agents based on price.

Prices

Medicine	Source	Price
Cetirizine 10 mg tablets (30)	Contract circular HP06-2016SD	R 2.80
Fexofenadine 120 mg tablets (30)	SEP database (60% of average price)	R 88.56

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7. Olasińska-Wiśniewska A , Olasiński J, Grajek S. Cardiovascular safety of antihistamines. PostepDermAlergol. 2014, 3: 182–186 DOI: 10.5114/pdia.2014.43191
8. SEP database, 27 May 2017.
9. Contract circular HP09-2016SD.