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Cetirizine/Pseudoephedrine

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Contents

Abstract

▲ Cetirizine is the carboxylated metabolite of hydroxyzine, and has high specific affinity for histamine H_1 receptors. Pseudoephedrine is a sympathomimetic drug that acts directly on α-adrenergic receptors.

▲ Cetirizine/pseudoephedrine 5/120mg twice daily was significantly more effective than intranasal budesonide 100μg or placebo at improving nasal obstruction, nasal patency and reducing the volume of nasal secretion, and was significantly more effective than intranasal xylometazoline 0.1% with respect to nasal secretion, during house dust mite faeces challenge in three randomised, crossover studies among volunteers with seasonal or perennial rhinitis. The onset of action of cetirizine/pseudoephedrine was reported to be approximately 30 minutes.

▲ The bioavailability of cetirizine and pseudoephedrine is similar after administration of cetirizine/pseudoephedrine 5/120mg bilayer tablets or coadministration of cetirizine 5mg tablets plus pseudoephedrine sustained-release (SR) 120mg caplets.

▲ Cetirizine 5mg plus pseudoephedrine SR 120mg twice daily for 2 to 3 weeks was significantly more effective than each drug given alone at reducing mean total symptom scores for seasonal or perennial allergic rhinitis in two randomised, double-blind, multicentre trials. In both studies, the mean proportion of days during which the five measured symptoms (nasal obstruction, sneezing, rhinorrhoea, nasal pruritus and ocular pruritus) were absent or mild was significantly greater in recipients of the cetirizine plus pseudoephedrine SR.

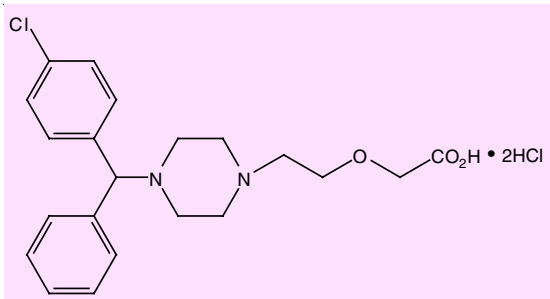
▲ In one study, cetirizine 5mg plus pseudoephedrine SR 120mg was significantly more effective at reducing nasal obstruction than either drug alone.

▲ Cetirizine 5mg plus pseudoephedrine SR 120mg twice daily for 2 to 3 weeks was well tolerated in patients with seasonal or perennial allergic rhinitis. The most common adverse events were dry mouth, insomnia, headache, somnolence, asthenia and nervousness.

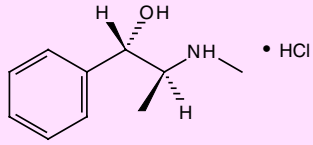
Features and properties of cetirizine/pseudoephedrine

Indication		
Relief of nasal and non-nasal symptoms associated with seasonal and perennial allergic rhinitis in adults and children ≥12 years of age		
Mechanism of action		
Cetirizine is a selective histamine H_1 receptor antagonist; pseudoephedrine is an α-adrenoreceptor agonist		
Dosage and administration		
Usual dose in clinical trials	Cetirizine/pseudoephedrine 5/120mg	
Route of administration	Oral	
Frequency of administration	Twice daily	
Pharmacokinetic profiles of cetirizine and pseudoephedrine [a]		
	Cetirizine	**Pseudoephedrine sustained-release**
Route of elimination	Predominantly renal	Predominantly renal
Time to peak plasma concentration	<1h	3.8 to 6.1h
Elimination half-life	6.5 to 10h	Dependent on urinary pH (3 to 6h at pH 5, 9 to 16h at pH 8)
Adverse events		
Most frequent	Dry mouth, insomnia, headache, somnolence, asthenia and nervousness	

a Data reported for each drug administered alone.



Cetirizine hydrochloride



Pseudoephedrine hydrochloride

Cetirizine/pseudoephedrine

Allergic rhinitis is a common disease, the symptoms of which include nasal congestion with airflow obstruction, rhinorrhoea, sneezing, nasal and/or ocular pruritus, paranasal pain and/or headache, anosmia or dysosmia, chronic pharyngitis and recurrent infections of the nose or sinuses.[1] Exposure to allergens results in the production of specific IgE antibodies that bind to receptors on mast cells and basophils. Further allergen exposure results in the release of histamine, as well as other inflammatory mediators, from mast cells and eosinophils. This leads to the immediate or early phase of an allergic reaction.[2] Allergic rhinitis may be seasonal or perennial and treatment with oral antihistamines, in conjunction with allergen avoidance, is generally considered the first line of defence.[3] Oral decongestants are also effectively used for the relief of nasal congestion in patients with allergic rhinitis.[4]

Cetirizine, a selective histamine H_1 receptor antagonist,[5] is well established in the treatment of allergic rhinitis.[6-8] It is minimally metabolised and has a rapid onset of action, and, like other newer histamine H_1 receptor antagonists, is associated with fewer sedative or anticholinergic effects at therapeutic dosages than older histamine H_1 receptor antagonists. Pseudoephedrine, an α-adrenoreceptor agonist, is widely used in the relief of nasal congestion.[4] It can also be used as an adjunct to other drugs, such as analgesics, antitussives, expectorants, antibacterials and antihistamines.[9]

This review examines the use of an oral formulation of the antihistamine cetirizine combined with the decongestant pseudoephedrine sustained-release (SR) in a bilayer tablet. This combination is hereafter referred to as cetirizine/pseudoephedrine.

1. Pharmacodynamic Profile

The pharmacodynamics of cetirizine have been previously reviewed in *Drugs*[6] and *Paediatric Drugs*.[7] Therefore, this review provides a brief overview of the pharmacodynamic profile of cetirizine along with a brief summary of the mechanism of action of pseudoephedrine. The pharmacodynamics of cetirizine/pseudoephedrine have been studied in three small studies in atopic volunteers.[10-12]

Mechanism of Action

- Cetirizine is the carboxylated metabolite of hydroxyzine, and has high specific affinity for histamine H_1 receptors [concentration required for 50% inhibition (IC_{50}) = 0.65 μmol/L].[13] The drug's affinity for calcium channel, α-adrenergic, dopamine D_2, serotonin and muscarinic receptors is low (IC_{50} >10 μmol/L); it has no affinity for histamine H_2 receptors.[7]
- Early studies in atopic and nonatopic volunteers demonstrated that a single oral 10mg dose of cetirizine significantly reduced histamine-induced wheal and flare formation compared with baseline and placebo.[14-21] Furthermore, the effect was maintained for ≥24 hours.[22]
- Cetirizine 20 mg/day for 3 to 4 days increased the conjunctival reaction threshold to pollen challenge and reduced the number of inflammatory cells in the conjunctival epithelium in patients with allergic rhinoconjunctivitis.[23] Furthermore, cetir-

izine 10 mg/day for 9 days inhibited the immediate and late responses to allergen challenge in patients with allergic rhinitis.[24]

• Cetirizine 10mg was shown to be more effective than loratadine 10mg and chlorphenamine 8mg at reducing allergen-induced wheal and flare,[14,25,26] and to be similar in efficacy to astemizole 10mg, terfenadine 120mg and ketotifen 1mg; all drugs were administered orally to atopic volunteers.[14,15,26] A 20mg dose of cetirizine was more effective than clemastine 2mg after allergen challenge.[27]

• Cetirizine had no effect on the QT or QT_c interval even at dosages of 20 or 60 mg/day for 14 days, and did not significantly increase heart rate in healthy volunteers.[28,29] Furthermore, unlike terfenadine and astemizole, it has little or no *in vitro* effect on potassium channels (e.g. IC_{50} of cetirizine = 108 μmol/L, compared with 0.096 μmol/L for terfenadine).[30]

• Pseudoephedrine is a sympathomimetic drug that acts directly on α-adrenergic receptors and, to a lesser extent, β-adrenergic receptors. The α-adrenergic effects of pseudoephedrine are considered to be a result of inhibition of adenyl cyclase which leads to the blockade of cyclic adenosine-3′,5′-monophosphate production. The drug acts directly on α-adrenergic receptors in the mucosa of the respiratory tract causing vasoconstriction, the result of which is shrinkage of swollen nasal mucous membranes, reduction of nasal congestion, edema and tissue hyperaemia, and an increase in nasal patency and sinus drainage.[9]

Cetirizine/Pseudoephedrine in Atopic Volunteers

The onset of action and/or efficacy of cetirizine/pseudoephedrine 5/120mg in the relief of nasal congestion has been evaluated in a randomised, double-blind, crossover, placebo-controlled study,[10] as well as in two randomised, nonblind, crossover studies reported as abstracts.[11,12]

• In the double-blind study,[10] 24 adult volunteers (aged 18 to 32 years) with a mean 10.5-year history of perennial rhinitis due to house dust mite allergy were randomised to treatment after house dust mite faeces challenge (at a concentration of 110 ng/m^3) in the Vienna Challenge Chamber (VCC). Sensitivity to house dust mites was confirmed outside the pollen season by anamnesis, radioallergosorbent testing (RAST) and skin prick testing performed during the 5 weeks before randomisation.

• Volunteers received cetirizine/pseudoephedrine 5/120mg or matching placebo twice daily for 1 week, followed by a washout period of at least 2 weeks before crossover to the alternative treatment. The first challenge (7-hour duration) occurred immediately after administration of the first dose, and the second challenge (3-hour duration) took place 12 hours after the last dose.[10]

• Cetirizine/pseudoephedrine was significantly ($p \leq 0.0001$) more effective than placebo at improving nasal obstruction during both challenges; nasal airflows were approximately 30% higher after administration of cetirizine/pseudoephedrine than after placebo. The onset of action of cetirizine/pseudoephedrine was approximately 30 minutes after the first dose. During both challenges, cetirizine/pseudoephedrine was also associated with significantly lower total nasal secretions than placebo. Among recipients of cetirizine/pseudoephedrine during challenge 1, the area under the weight of secretions-time curve from 0 to 7 hours was 508.9 g □h, compared with 924.2 g □h in placebo recipients ($p = 0.0003$). Furthermore, among recipients of cetirizine/pseudoephedrine during challenge 2, the area under the weight of secretions-time curve from 0 to 3 hours was 152.4 g □h, compared with 392.3 g □h in placebo recipients ($p = 0.0035$). Nasal patency was approximately 20% greater among cetirizine/pseudoephedrine recipients than in recipients of placebo during both challenges ($p < 0.05$).[10]

• Symptom scores for nasal obstruction, rhinorrhoea, sneezing and nasal pruritus, as measured by the volunteers every 15 minutes using a 4-point scale (0 to 3, increasing in severity), favoured cetirizine/pseudoephedrine during challenge 1. The total nasal symptom score among cetirizine/pseudoephedrine recipients was 96.3, compared

with 155.1 among placebo recipients (p = 0.0004). During challenge 2, cetirizine/pseudoephedrine was significantly (p < 0.01) more effective than placebo at relieving all nasal symptoms except for nasal pruritus.[10]

• Short-term treatment with cetirizine/pseudoephedrine was significantly more effective than budesonide at relieving nasal congestion, and had a faster onset of action, in a randomised, nonblind, crossover study in 36 volunteers challenged with house dust mite faeces.[12] Volunteers received cetirizine/pseudoephedrine 5/120mg or intranasal budesonide 100μg twice daily for 4 days followed by a ≥2 week washout period before crossing over to the alternative treatment. Nasal congestion and related symptoms were assessed during a 5-hour challenge which started immediately after the first dose of medication.

• Although actual data were not reported in the abstract, cetirizine/pseudoephedrine was significantly more effective than budesonide at improving airflow (p = 0.03) and nasal patency [as assessed by digital imaging (p = 0.04)]. The weight of nasal secretion was also significantly lower in recipients of cetirizine/pseudoephedrine than in budesonide-treated volunteers (12.5 versus 20.8g, respectively, p < 0.01). The onset of action of cetirizine/pseudoephedrine occurred within 30 minutes of administration, compared with 4 days for budesonide.[12]

• Cetirizine/pseudoephedrine was significantly more effective than xylometazoline at relieving nasal obstruction in a randomised, nonblind, crossover study in 36 volunteers challenged with house dust mite faeces.[11] Volunteers received cetirizine/pseudoephedrine 5/120mg or xylometazoline 0.1% nasal spray twice daily. The duration of treatment was not reported in the abstract. Nasal congestion and related symptoms were monitored during the 5-hour challenge which began immediately after the first dose of medication. Although no actual data were reported, cetirizine/pseudoephedrine was significantly more effective than xylometazoline at reducing the volume of nasal secretion (p = 0.0004) and the sum of nasal symptoms (p < 0.0001). However, both drugs showed similar efficacy in improving nasal patency.[11]

2. Pharmacokinetic Profile

The pharmacokinetics of cetirizine and pseudoephedrine have been investigated after administration of either drug alone or as the combination formulation. There has also been a study comparing the bioavailability of cetirizine and pseudoephedrine after administration of cetirizine/pseudoephedrine bilayer tablets or the coadministration of cetirizine tablets and pseudoephedrine SR caplets.[31]

Absorption and Distribution

• Cetirizine is rapidly absorbed from the gastrointestinal tract. After oral administration of a 10 or 20mg dose of cetirizine to healthy adults, maximum plasma concentrations (C_{max}) are dose-proportional and are reached within 1 hour, with a mean C_{max} of 257 and 580 μg/L, respectively. The area under the concentration-time curve (AUC) values after 10 or 20mg doses of cetirizine were 2.87 and 5.80 mg/L □h, respectively, and the volume of distribution was 33.2 and 40.8L.[6] Administration of cetirizine with food may slow the rate of absorption but does not affect the extent of absorption. Cetirizine is extensively bound to plasma proteins (93% at plasma concentrations of 25 to 1000 μg/L), and steady-state concentrations are reached within 3 days.[32]

• Pseudoephedrine is also rapidly absorbed from the gastrointestinal tract, and there is no evidence of first-pass metabolism.[9] After oral administration of a solution of pseudoephedrine 120mg, a C_{max} of between 397 and 422 μg/L is reached within 2 hours. After administration of pseudoephedrine SR, absorption is slower, with C_{max} being achieved in approximately 3.8 to 6.1 hours. Although food delays absorption of the drug when administered as a solution, it does not affect the absorption of the SR preparation.[9]

• The bioavailability of cetirizine/pseudoephedrine 5/120mg when administered with food has been studied in 24 volunteers in a randomised, crossover study, the results of which are available in an ab-

stract.[33] Mean AUC and half-life ($t_{1/2}$) values for cetirizine were similar under fed or fasted conditions after administration of a single dose of cetirizine/pseudoephedrine. However, the C_{max} of cetirizine was decreased by 30% and the mean time to C_{max} (t_{max}) was delayed by 1.8 hours after administration with food. Values for the AUC, C_{max}, t_{max} and $t_{1/2}$ for pseudoephedrine under fed or fasted conditions were not significantly different.[33]

Metabolism and Elimination

- About 60% of an oral 10mg dose of cetirizine is excreted in the urine within 24 hours, >80% of which is unchanged drug. Total urinary recovery is 70% and faecal recovery is 10% (predominantly as unchanged drug).[6] Small amounts of a metabolite derived from oxidative *O*-dealkylation appear in the plasma at 10 hours and in the faeces from 24 to 48 hours.[32] The mean terminal elimination half-life ($t_{1/2\beta}$) after administration of a 10mg dose of cetirizine to healthy adults is between 6.5 and 10 hours, and renal excretion involves an active transport system.[6]
- 55 to 96% of a dose of pseudoephedrine is excreted unchanged in the urine. A minimal amount of the drug is converted in the liver to an inactive metabolite by *N*-demethylation; this is also excreted in the urine. The $t_{1/2\beta}$ of pseudoephedrine is dependent on urinary pH; at pH 5 or 8, the $t_{1/2}\beta$ is 3 to 6 or 9 to 16 hours, respectively. Renal clearance in adults is approximately 0.44 to 0.46 L/h/kg (7.3 to 7.7 ml/min/kg).[9]
- In patients with moderate renal dysfunction [creatinine clearance 0.66 to 1.86 L/h (11 to 31 ml/min)], $t_{1/2}$ is increased 3-fold and clearance is decreased by 70%; similar results were obtained in patients on haemodialysis.[5]

Bioequivalence

- The bioavailability of cetirizine and pseudoephedrine after administration of cetirizine/pseudoephedrine 5/120mg bilayer tablets has been compared with that after the coadministration of cetirizine 5mg tablets and pseudoephedrine SR 120mg caplets in a randomised, crossover study in 24 volunteers, reported as an abstract.[31] After a single dose or at steady state, the mean AUC, C_{max}, t_{max} and $t_{1/2}$ values for cetirizine and pseudoephedrine were similar. At steady state, the 90% confidence intervals for the geometric mean ratios of the C_{max} (87 to 97%) and $AUC_{(0\text{-}12h)}$ (94 to 101%) for cetirizine after administration of cetirizine/pseudoephedrine compared with coadministration of cetirizine plus pseudoephedrine SR met the criteria for bioequivalence; corresponding intervals for pseudoephedrine were 103 to 116% and 99 to 111%, respectively.

Drug Interactions

- No drug interactions were observed after concomitant administration of cetirizine with pseudoephedrine, antipyrine, ketoconazole, erythromycin or azithromycin in adults.[5] A 16% decrease in the clearance of cetirizine was observed after administration of cetirizine 20 mg/day and theophylline 400 mg/day for 3 days; the disposition of theophylline was not altered.[5]

3. Therapeutic Efficacy

The efficacy of cetirizine 5mg plus pseudoephedrine SR 120mg in the relief of nasal congestion in patients with seasonal allergic rhinitis has been evaluated in two randomised, double-blind, parallel-group, multicentre studies of similar design.[34,35]

- Cetirizine plus pseudoephedrine SR was more effective than each drug given alone at relieving overall symptoms of allergic rhinitis in two trials, one in 687 patients aged 9 to 66 years,[34] and the other in 210 patients aged 10 to 68 years.[35] Patients included in both studies had a documented history of perennial or seasonal allergic rhinitis for ≥1 year, and had positive skin prick or RAST tests. In the larger trial,[34] all patients presented with nasal obstruction and ≥2 of the following symptoms of rhinitis: sneezing, rhinorrhoea, nasal pruritus or ocular pruritus. In the other trial,[35] all patients presented with nasal obstruction, sneezing and rhinorrhoea. In both studies, symptoms were scored on a 4-point scale (0 to 3, increasing in

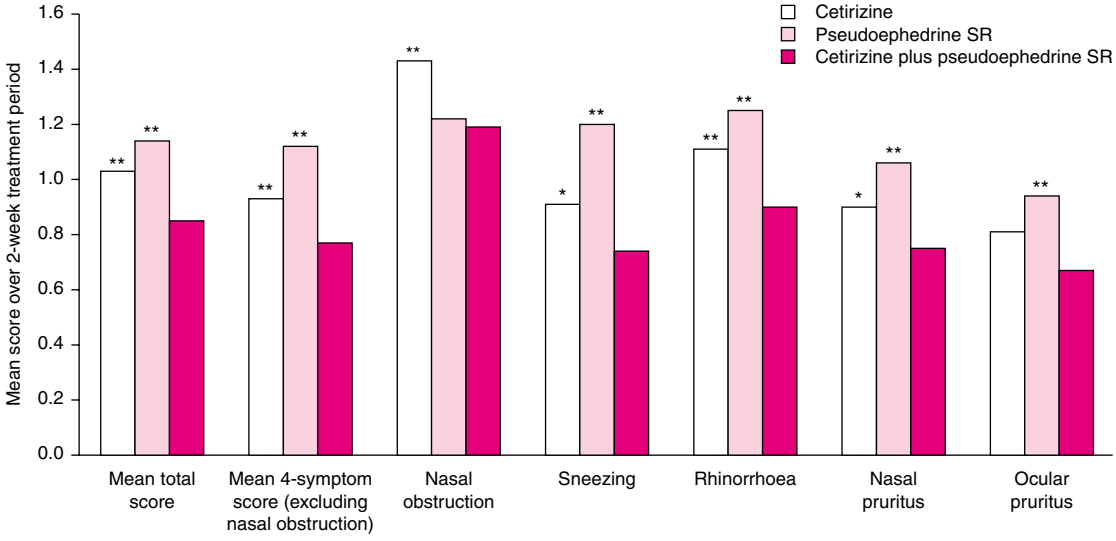


Fig. 1. Efficacy of cetirizine 5mg plus pseudoephedrine sustained-release (SR) 120mg in the relief of symptoms of seasonal allergic rhinitis. 687 patients with pollen-associated allergic rhinitis received cetirizine 5mg plus placebo (n = 231), pseudoephedrine SR 120mg plus placebo (n = 226) or cetirizine 5mg plus pseudoephedrine SR 120mg (n = 230) twice daily for 2 weeks in a randomised, double-blind, multicentre trial. Patients assessed five symptoms of allergic rhinitis (nasal obstruction, rhinorrhoea, sneezing, nasal pruritus and ocular pruritus) daily using a 4-point scale; 0 = absent, 1 = mild, 2 = moderate and 3 = severe. Mean baseline total symptom scores, as rated by patients, ranged from 1.92 to 1.99 in the three groups. Individual symptom scores ranged from 1.68 to 2.29.[34] * $p \leq 0.01$, ** $p < 0.001$ *vs* cetirizine plus pseudoephedrine SR.

severity), and were moderate to severe at baseline. The larger study took place during spring and summer; pollen-sensitive patients were excluded during the pollen season in the smaller trial.

- Patients were excluded from both studies if they had obstructive nasal polyposis or significant septal deviation, were using systemic or inhaled corticosteroids at a dosage of >400 μg/day or they were being treated with antibacterials. In the larger trial,[34] exclusion criteria also included treatment with antihistamines or corticosteroids for atopic dermatitis or urticaria, upper respiratory tract infection, renal, hepatic or cardiovascular disease requiring treatment, hypertension, hyperthyroidism, diabetes mellitus, glaucoma, prostatic hypertrophy, urinary retention or hypersensitivity to cetirizine or pseudoephedrine. Additional exclusion criteria in the smaller trial included infectious rhinitis or any serious medical disorder.[35]

- In the larger study,[34] patients received cetirizine 5mg plus placebo (n = 231), pseudoephedrine SR 120mg plus placebo (n = 226) or cetirizine 5mg plus pseudoephedrine SR 120mg (n = 230) twice daily with meals for 2 weeks. Symptoms of rhinitis were evaluated by the investigators at baseline and at week 1 and 2 using the 4-point scale. The primary efficacy analysis was based on the patients' assessment of the five symptoms recorded daily over the 2-week treatment period. Mean baseline total symptom scores, as rated by patients in diaries, ranged from 1.92 to 1.99 in the three groups.
- Based on the patients' assessment of the five symptoms of allergic rhinitis measured over the 2-week treatment period, cetirizine plus pseudoephedrine SR was significantly more effective than cetirizine or pseudoephedrine SR alone (figure 1).[34] After excluding nasal obstruction from the analysis, mean combined scores for the remaining

four symptoms also significantly ($p < 0.001$) favoured the combination (figure 1).

- The median proportion of days during which the five symptoms were absent or of mild severity was significantly ($p < 0.001$) higher among recipients of cetirizine plus pseudoephedrine SR (53.3%) than in patients who received cetirizine (30.8%) or pseudoephedrine SR (33.3%) alone. Cetirizine plus pseudoephedrine SR was as effective as pseudoephedrine SR alone at relieving nasal obstruction, but was significantly ($p < 0.001$) more effective than cetirizine alone (figure 1). Conversely, the combination was as effective as cetirizine at relieving ocular pruritus, but significantly ($p < 0.001$) more effective than pseudoephedrine SR alone (figure 1).[34]
- At endpoint, 69, 56 and 58% of the patients in the cetirizine plus pseudoephedrine SR, cetirizine ($p = 0.001$ versus cetirizine plus pseudoephedrine SR) and pseudoephedrine SR groups ($p = 0.007$ versus cetirizine plus pseudoephedrine SR), respectively, rated the treatment response as either excellent or good.[34]
- 71 of the 687 patients (10.3%) discontinued treatment prematurely. Of these, 30 patients discontinued because of a lack of efficacy; 11 of 231 cetirizine recipients (4.8%), 13 of 226 pseudoephedrine SR recipients (5.8%) and 6 of 230 recipients of the combination (2.6%).[34]
- In the other study,[35] patients received cetirizine 5mg plus placebo (n = 70), pseudoephedrine SR 120mg plus placebo (n = 70) or cetirizine 5mg plus pseudoephedrine SR 120mg (n = 70) twice daily for 3 weeks. The primary efficacy variable, as in the previously discussed study, was based on patient assessment of nasal obstruction, sneezing, rhinorrhoea, nasal pruritus and ocular pruritus. The most severe daily symptom score, as recorded by the patients, was also used as an efficacy variable. Symptoms of rhinitis were evaluated by the investigators three times during the treatment period (on day 1, between days 5 and 9, and at endpoint) using the 4-point scale.
- The mean proportion of days during which the five measured symptoms of allergic rhinitis were either absent or of mild severity was significantly greater in recipients of combined cetirizine plus pseudoephedrine SR (64.8%) than in patients who received cetirizine (45.5%, $p < 0.003$) or pseudoephedrine SR (40.6%, $p < 0.0001$) alone (figure 2). Furthermore, the percentage of days when nasal congestion was absent was significantly ($p \leq 0.025$) higher in recipients of cetirizine plus pseudoephedrine SR than in patients who received either drug alone (figure 2). Cetirizine plus pseudoephedrine SR was significantly more effective at reduc-

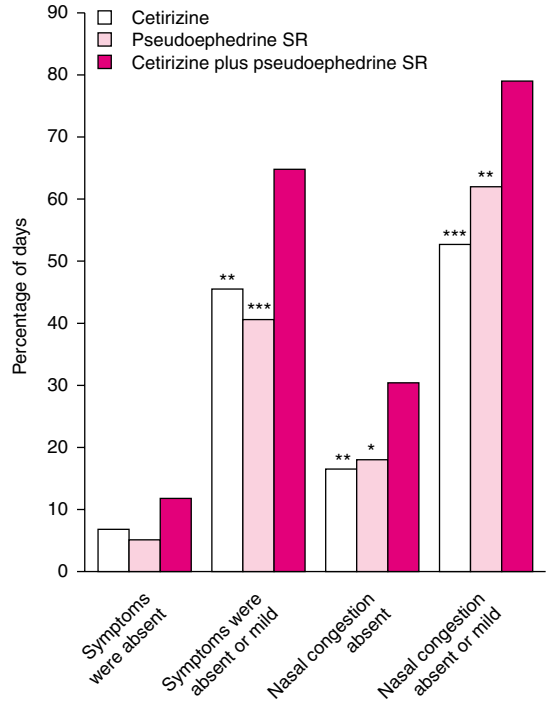


Fig. 2. Comparison of the efficacy of cetirizine plus pseudoephedrine sustained-release (SR) with cetirizine or pseudoephedrine SR alone. 210 patients with perennial allergic rhinitis received cetirizine 5mg plus placebo (n = 70), pseudoephedrine SR 120mg plus placebo (n = 70) or cetirizine 5mg plus pseudoephedrine SR 120mg (n = 70) twice daily for 3 weeks in a randomised, double-blind, multicentre trial. Patients assessed five symptoms of allergic rhinitis (nasal obstruction, rhinorrhoea, sneezing, nasal pruritus and ocular pruritus) daily using a 4-point scale; 0 = absent, 1 = mild, 2 = moderate and 3 = severe.[35] * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ *vs* cetirizine plus pseudoephedrine SR.

ing mean scores for rhinorrhoea than pseudoephedrine SR alone ($p < 0.001$) but was equivalent in efficacy to cetirizine alone; similar results were obtained for sneezing. Cetirizine plus pseudoephedrine SR had similar efficacy, as measured by mean symptom scores, to either cetirizine or pseudoephedrine SR alone at relieving nasal or ocular pruritus.[35]

• At baseline, the mean score for the most severe symptom was similar in the three treatment groups (data not reported). Although cetirizine plus pseudoephedrine SR was associated with a significant ($p = 0.001$) reduction in this mean score compared with the other two treatment groups at the second assessment (recorded between days 5 and 9), there was no significant between-group difference at endpoint. However, the investigators rated the treatment response at endpoint as either excellent or good in 66, 53 and 42% of the patients in the combination, cetirizine ($p = 0.028$ versus combination) and pseudoephedrine SR groups ($p = 0.018$ versus combination), respectively.[35]

• 39 of the 210 (18.6%) patients discontinued treatment prematurely. Of these, only three patients discontinued because of a lack of efficacy; none of the recipients of cetirizine plus pseudoephedrine SR discontinued because of therapeutic inefficacy.[35]

4. Tolerability

• There were no significant between-group differences in the total incidence of adverse events among recipients of cetirizine 5mg plus pseudoephedrine SR 120mg, cetirizine 5mg or pseudoephedrine SR 120mg in the two clinical studies in patients with seasonal or perennial allergic rhinitis.[34,35] However, statistical analyses concerning the incidence of particular adverse events were not reported in either trial. In the trial involving 687 patients,[34] adverse events were reported by 29.6% of patients who received cetirizine plus pseudoephedrine SR twice daily for 2 weeks, compared with 23.4 and 30.1% of cetirizine and pseudoephedrine SR recipients, respectively. In the other trial,[35] which involved 210 patients, 50.0% of patients treated with cetirizine plus pseudoephedrine SR twice daily for 3 weeks reported adverse events, compared with 44.3 and 54.3% of cetirizine and pseudoephedrine SR recipients, respectively.

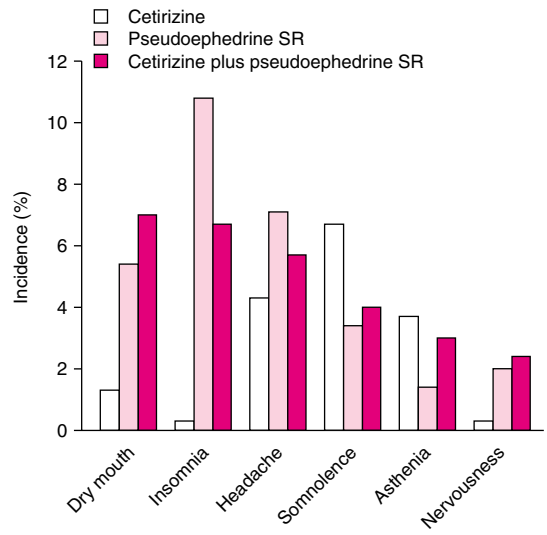


Fig. 3. Most frequent adverse events in patients with seasonal or perennial allergic rhinitis during treatment with cetirizine plus pseudoephedrine sustained-release (SR) or either drug alone. Patients received cetirizine 5mg plus pseudoephedrine SR 120mg (n = 300), cetirizine 5mg plus placebo (n = 301) or pseudoephedrine SR 120mg plus placebo (n = 296) twice daily for 2 to 3 weeks in two randomised, double-blind, multicentre studies.[34,35]

• Across the two trials, the most frequently reported adverse events in 300 patients who received cetirizine plus pseudoephedrine SR were dry mouth (7.0%), insomnia (6.7%), headache (5.7%), somnolence (4.0%), asthenia (3.0%) and nervousness (2.4%). Corresponding values among the 301 cetirizine and 296 pseudoephedrine SR recipients are illustrated in figure 3.[34,35] Pharyngitis was reported by 7.1% of the 70 patients who received cetirizine plus pseudoephedrine SR in the smaller trial,[35] but was not reported in the larger trial.[34]

• In the trial in 687 patients, 3.2% of patients discontinued treatment prematurely because of adverse events; 3.9, 2.6 and 3.1% of patients in the cetirizine plus pseudoephedrine SR, cetirizine or

pseudoephedrine SR groups, respectively.[34] In the other trial, 7.1% of patients discontinued because of adverse events; 5.7, 2.9 and 12.9% of cetirizine plus pseudoephedrine SR, cetirizine or pseudoephedrine SR recipients, respectively.[35] Neither trial reported which events led to discontinuations.

5. Cetirizine/Pseudoephedrine: Current Status

The combined oral formulation of cetirizine/pseudoephedrine has been approved in the US for the relief of nasal and non-nasal symptoms associated with seasonal and perennial allergic rhinitis in adults and children ≥12 years of age. Administration of cetirizine plus pseudoephedrine SR has shown greater efficacy compared with administration of either drug alone in two randomised, double-blind studies. A bioequivalence study has demonstrated that the bioavailability of cetirizine and pseudoephedrine after administration of the combined bilayer tablet is similar to that after the coadministration of the two drugs.

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