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International Journal of Pharmaceutics 114 (1995) 171–176

international journal of pharmaceutics

Steady-state human pharmacokinetics and bioavailability of guaifenesin and pseudoephedrine in a sustained-release tablet relative to immediate-release liquids

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Received 27 July 1993; modified version received 7 July 1994; accepted 8 July 1994

Abstract

Steady-state human pharmacokinetics and bioavailability were compared for a sustained-release decongestant/expectorant tablet and two coadministered immediate-release liquids that together contained the same active ingredients. In each leg of a randomised, two-leg, complete crossover, multiple-dose study, 15 of the 30 enrolled healthy male subjects received Entex® PSE (600 mg guaifenesin (GGE) and 120 mg pseudoephedrine hydrochloride (PSE · HCl) in a matrix formulation) twice daily on days 1–4 and once daily on day 5. The remaining subjects received the reference dose forms, Robitussin® (300 mg GGE/15 ml) and Sudafed® (60 mg PSE · HCl/10 ml) immediate-release liquids, coadministered four times daily on days 1–4 and twice daily on day 5. Plasma GGE and PSE pharmacokinetic data indicated that steady state was attained by day 5 of dosing for both the tablet and the reference liquids. The sustained drug release from Entex PSE resulted in a significant ($P = 0.0001$) reduction in the GGE fluctuation index (as C_{max} minus C_{min} divided by the average plasma drug concentration) and no difference in the PSE fluctuation index as compared with the corresponding indexes for the reference liquids. Under steady-state conditions, sustained-release GGE and PSE profiles were obtained for Entex PSE. The extents of GGE and PSE absorption were equivalent for the tablet and coadministered immediate-release liquids, and no dose dumping occurred with the sustained-release dosage form.

Keywords: Absorption; Bioavailability; Guaifenesin; Pharmacokinetics; Plasma level; Pseudoephedrine; Urinary excretion

1. Introduction

Pseudoephedrine hydrochloride (PSE · HCl) is an α-adrenergic receptor agonist (sympathomimetic) that produces vasoconstriction by stimulating α-receptors within the mucosa of the respiratory tract. Clinically, pseudoephedrine (PSE) shrinks swollen mucous membranes, increases nasal airway patency, and reduces tissue hyperemia, edema, and nasal congestion. Guaifenesin (guaiacyl glyceryl ether or GGE) is widely used to

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Elsevier Science B.V.
SSDI 0378-5173(94)00235-5

promote lower respiratory tract drainage by thinning bronchial secretions, lubricate irritated respiratory tract membranes through increased mucous flow, and facilitate the removal of viscous, inspissated mucous.

Entex® PSE tablets, formulated with a matrix designed to provide sustained delivery of PSE and GGE, are indicated for the relief of nasal congestion and symptomatic relief of respiratory conditions characterized by dry nonproductive cough. Sudafed® liquid contains PSE · HCl and is indicated for the relief of nasal congestion due to the common cold. Robitussin® liquid contains GGE and helps loosen phlegm and thin bronchial secretions to make coughs more productive.

The purpose of this study was to compare the steady-state in vivo performance of sustained-release Entex PSE tablets and the coadministered immediate-release reference liquids Robitussin and Sudafed.

2. Materials and methods

This randomised, two-leg, complete crossover, multiple-dose study was conducted at Medical Technical Consultants, Inc., Lenexa, KS, USA, under the auspices of Procter & Gamble Pharmaceuticals. Healthy adult men ($n = 30$), 18–39 years of age and weighing 61–90 kg, participated in the study. Written informed consent was obtained from each volunteer. Complete physical examinations and clinical laboratory evaluations were performed on each subject before the study. No subject exhibited overt symptoms or findings of central nervous, cardiopulmonary, gastrointestinal, hepatic, renal, or hemopoietic system disease or clinical laboratory values that might compromise drug absorption, metabolism, or excretion. The test formulation was sustained-release Entex PSE tablets (600 mg GGE and 120 mg PSE · HCl per tablet), and the reference formulation was immediate-release Robitussin (20 mg GGE/ml) and Sudafed (6 mg PSE · HCl/ml) liquids; the liquids were coadministered and the dosing schedule was set up to deliver daily GGE and PSE doses equivalent to those in the tablets.

In each leg of the study, 15 subjects received one Entex PSE tablet twice daily on days 1–4 and once daily on day 5. The remaining 15 subjects received Robitussin (300 mg GGE/15 ml) and Sudafed (60 mg PSE · HCl/10 ml) liquids, coadministered four times daily on days 1–4 and twice daily on day 5. Each tablet dose was followed with a 105 ml water rinse; the liquid doses were followed with an 80 ml water rinse. The initial dose in each test period was administered after an overnight fast and 1 h after a standard high-fat breakfast. A uniform diet and meal schedule was maintained throughout the remainder of each test period. There was a 5 day washout between test periods.

In each test period, blood was collected by venipuncture at 0 h on day 1, at 0 h and 12 h on days 3 and 4, and at 0, 1, 1.5, 2, 2.5, 3, 4, 4.5, 5, 5.5, 6, 7, 7.5, 8, 8.5, 9, 10, 12, and 24 h on day 5. A sample was also collected at 24 h on day 6. The samples were centrifuged immediately to obtain plasma. Voided urine was collected just before the initial drug administration on day 1 and from 0–6, 6–12, 12–18, and 18–24 h on days 3–5. On day 6, a 0–24 h urine sample was collected. Aliquots of plasma and urine were frozen (−20°C) until analysis for GGE (plasma only) and PSE (plasma and urine) at Kansas City Analytical Services (KCAS), Shawnee, KS, U.S.A. Plasma GGE was measured by capillary gas liquid chromatography with electron-capture detection (Freeman et al., 1991); the method had a lower limit of quantitation (LLQ) of 10 ng/ml and linearity to 500 ng/ml. Since GGE is known to be extensively metabolized (Clarke, 1986), urine GGE assays were not conducted for this study. PSE in plasma and urine was assayed by high-performance liquid chromatography (Coyazo et al., 1991a–c). The plasma PSE method had an LLQ of 25 ng/ml and linearity to 750 ng/ml. For urine PSE determinations, samples containing less than 10 μg/ml were assayed by a method standard curve with an LLQ of 0.50 μg/ml and linearity to 10 μg/ml; samples with PSE concentrations greater than 10 μg/ml were assayed by a method with an LLQ of 10 μg/ml and a standard curve that was linear to 500 μg/ml. For both PSE and GGE, samples containing drug concentrations greater than the upper limit of linearity

were diluted and reassayed. KCAS analytical methods reports documented the quality assurance procedures and acceptance criteria used to successfully validate the assays prior to the study. Data obtained for three levels of quality control samples, assayed in duplicate with each batch of study unknowns, provided assurance that the assays were in control on a daily basis. These quality control samples ($n = 581$) yielded overall accuracy (percent of nominal amount added) ranging from 93 to 102% and precision (percent coefficient of variation) ranging from 2.5 to 9.6%.

The pharmacokinetic parameters for PSE and GGE were determined by model-independent methods with the assumption that drug disposition is not concentration dependent. There is no evidence for nonlinearity in the published literature for either compound. Maximum (C_{max}) and minimum (C_{min}) plasma drug concentrations were the highest and lowest levels, respectively, observed during a 12 h interval on day 5. The day 5 profiles were the basis for steady-state comparisons between dosage forms. The area under the plasma drug concentration-time curve for a 0–12 h interval ($AUC_{0-12\ h}$) on day 5 was determined by linear trapezoidal rule. AUC ratios were used to calculate relative fraction of dose absorbed (F_{rel}) for Entex PSE as compared with Robitussin and Sudafed.

Fluctuation index (I_{fluct}) was determined as C_{max} minus C_{min} divided by the average plasma drug concentration for a 12 h interval, with the average plasma concentration estimated as the $AUC_{0-12\ h}$ divided by 12 h. Urine PSE dose recovery was calculated from mg PSE excreted and mg PSE administered during a 12 h interval. Pharmacokinetic variables were evaluated by analysis of variance (ANOVA; model = subject, days) at the 5% level of significance ($P = 0.05$), performed by SAS GLM procedure. A Duncan test was applied to test for differences between the 0 h plasma concentrations of both GGE and PSE on different days and similarly between the 12 h concentrations of each active ingredient on different days. A two one-sided tests procedure (Schuirmann, 1987) was performed to determine 90% confidence intervals for each parameter ratio. A linear regression model was used to evaluate plasma concentrations of GGE and PSE vs time (with day 3, 0 h as 0 h and day 5, 12 h as 60 h) for individual subjects on days 3–5.

3. Results and discussion

In vitro testing of the Entex PSE tablets was conducted by the USP paddle method. The sustained-release profiles obtained for both PSE and GGE are shown in Table 1.

Plasma PSE and GGE concentrations determined at 0 h and 12 h after Entex PSE tablet and after coadministered Robitussin and Sudafed liquid doses on days 3–5 were used to assess time to achieve steady state. Statistical evaluations by ANOVA followed by a Duncan test showed no consistent trends for differences in 0 or 12 h PSE or GGE concentrations between days. Linear regressions of plasma PSE and GGE concentrations vs time for individual subjects on days 3–5 yielded PSE regression line slopes not significantly different from zero in 29 of 30 subjects after Entex PSE dosing in the study and in 29 of 30 subjects after liquid dosing. No GGE regression line slopes were significantly different from zero. Based on these evaluations, it was concluded that steady state was attained by day 5 of dosing for both the Entex PSE tablets and the coadministered Robitussin and Sudafed liquids.

Plasma PSE and GGE steady-state concentration-time profiles for a 12 h interval on day 5 are

Table 1
Cumulative percent pseudoephedrine and guaifenesin dissolved from Entex PSE tablets

Drug	n	Cumulative percent dissolved Mean (% C.V.)		
		1.5 h	4 h	8 h
Pseudoephedrine	6	41.6 (1.3)	66.0 (0.5)	84.6 (2.9)
Guaifenesin	6	26.5 (1.7)	48.9 (1.3)	66.1 (3.2)

C.V., coefficient of variation.Dissolution was tested by the USP XXII dissolution method, Apparatus 2 (pp. 1578–80). Paddle speed was 50 rpm; medium (at 37°C) was simulated gastric fluid without enzymes (USP XXII, sodium chloride and hydrochloric acid buffer) from 0 to 1.5 h and simulated intestinal fluid without enzymes (USP XXII, phosphate buffer) from 1.5 to 8 h.

shown in Fig. 1. Consistent with the concept of steady state, the plasma GGE and PSE profiles for both Entex PSE tablets and the Robitussin and Sudafed reference liquids each begin and end the 12 h period at essentially the same plasma concentrations. Evaluation of data for individual subjects showed that sustained-release plasma drug profiles, with delayed t_{max} and no evidence of dose dumping, were apparent for both GGE and PSE following the single Entex PSE dose on day 5. The plasma GGE and PSE concentrations rose relatively slowly to a broad C_{max} and then gradually declined during the remainder of the 12 h interval. In contrast, after each of the two coadministered doses of reference liquids on day 5, the plasma PSE and GGE concentrations increased rapidly to a more distinct C_{max} before declining.

Table 2 presents steady-state plasma PSE pharmacokinetics. No significant differences between Entex PSE tablets and the Robitussin and Sudafed reference liquids were noted, and 90% confidence intervals for plasma PSE C_{max}, C_{min}, and AUC were well within the limits necessary to establish equivalence. Equivalence in PSE I_{fluct} was also shown for the two dosing regimens, although the 90% confidence interval was marginally above 100%. F_{rel} (based on AUCs) for Entex PSE as compared with the liquids was 105%, supporting a conclusion of equivalent extents of PSE absorption.

Urine PSE dose recoveries determined for five consecutive 12 h intervals on days 3–5 (Table 3) show that most of the PSE from Entex PSE tablets and the Robitussin and Sudafed reference liquids was excreted unchanged in the urine. Urine PSE recoveries in corresponding time periods were not significantly different between the Entex PSE tablets and the reference liquids, providing further evidence of equivalent extents of absorption for the two dosing regimens.

Table 4 presents steady-state plasma GGE pharmacokinetics. C_{max} for Entex PSE tablets was significantly ($P = 0.0001$) lower and C_{min}, significantly ($P = 0.0001$) higher than the corresponding values determined for the Robitussin and Sudafed reference liquids, resulting in a significantly ($P = 0.0001$) smaller I_{fluct} for Entex

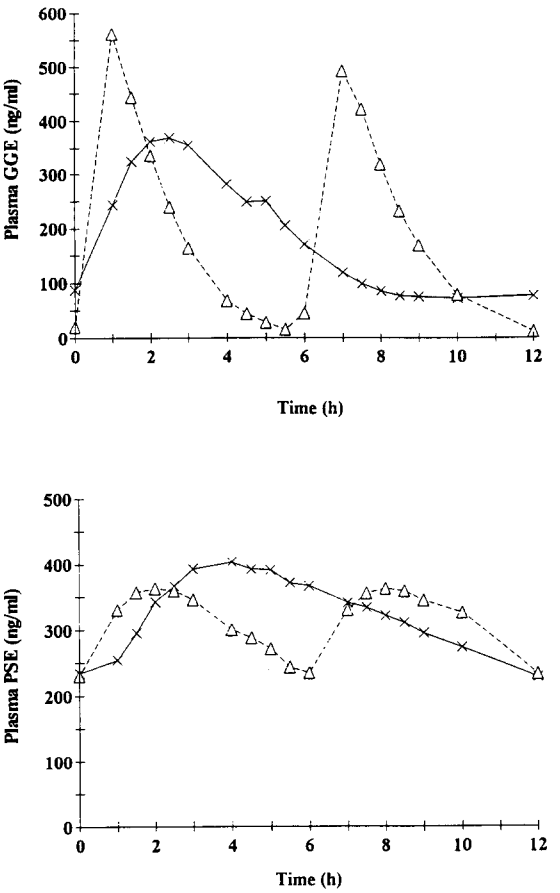

Fig. 1. Mean steady-state plasma guaifenesin (GGE) and pseudoephedrine (PSE) concentration-time profiles ($n = 30$) on day 5 following a single dose of Entex PSE tablets (×) and two doses of coadministered Robitussin and Sudafed liquids (△). On days 1–4, Entex PSE tablets were administered twice daily and Robitussin and Sudafed liquids, coadministered four times daily for total daily doses of GGE and PSE equivalent to those of Entex PSE.

PSE. These findings emphasize the sustained-release characteristics of Entex PSE. The plasma GGE AUC of Entex PSE was not significantly different from that of the liquids, and the 90% confidence interval was within the limits necessary to establish equivalence. F_{rel} (based on AUCs) for GGE from Entex PSE was 95%, supporting a conclusion of equivalent extents of absorption for GGE from Entex PSE tablets and the reference liquids.

Table 2
Plasma pseudoephedrine pharmacokinetic data (day 5) in 30 subjects

Parameter		Entex PSE tablets (T) [a]	Robitussin and Sudafed liquids (R) [b]	Ratio (%) (T/R)	90% CI	*P* value [c]
C_{max} (ng/ml)	mean	428	403	109	99.6–112.7	NS
	(% C.V.)	(25)	(21)	(25)		
C_{min} (ng/ml)	mean	211	213	102	91.5–107.3	NS
	(% C.V.)	(41)	(24)	(33)		
AUC 0–12 h (ng ml^{-1} h)	mean	3857	3732	105	98.0–108.7	NS
	(% C.V.)	(30)	(21)	(25)		
I_{fluct} [d]	mean	0.7	0.6	118	100.5–122.8	NS
	(% C.V.)	(21.4)	(34.9)	(29)		

T, test formulation (Entex PSE tablet); R, reference formulation (Robitussin and Sudafed liquids). C.V., coefficient of variation; NS, not statistically significant. Ratio (%) was calculated as the relative fraction of the value obtained for the test formulation as compared with the reference formulation.

[a] Entex PSE tablets (600 mg GGE and 120 mg PSE hydrochloride) were administered twice daily on days 1–4 and once daily on day 5.

[b] Robitussin liquid (300 mg GGE/15 ml) and Sudafed liquid (60 mg PSE hydrochloride/10 ml) were coadministered four times daily on days 1–4 and twice daily on day 5, for total daily GGE and PSE doses equivalent to those of Entex PSE.

[c] By analysis of variance at the 5% level of significance, for treatment differences.

[d] I_{fluct} (fluctuation index) was calculated as C_{max} minus C_{min} divided by the average plasma drug concentration for a 12 h interval, with the average plasma concentration estimated as the $AUC_{0-12\,h}$ divided by 12 h.

Table 3
Urine pseudoephedrine dose recoveries in 30 subjects

Urine Recovery (%)		Entex PSE tablets (T) [a]	Robitussin and Sudafed liquids (R) [b]	Ratio (%) (T/R)	90% CI	*P* value [c]
Day 3						
0–12 h	mean	70.3	69.3	122	85.2–117.8	NS
	(% C.V.)	(33.5)	(35.3)	(67)		
12–24 h	mean	83.0	81.1	111	92.4–112.3	NS
	(% C.V.)	(21.8)	(23.3)	(46)		
Day 4						
0–12 h	mean	67.4	67.7	110	86.6–111.2	NS
	(% C.V.)	(38.9)	(36.8)	(49)		
12–24 h	mean	79.3	82.1	106	85.4–107.8	NS
	(% C.V.)	(24.4)	(24.0)	(51)		
Day 5						
0–12 h	mean	84.6	78.3	114	97.5–118.4	NS
	(% C.V.)	(21.2)	(25.2)	(33)		

T, test formulation (Entex PSE tablet); R, reference formulation (Robitussin and Sudafed liquids). C.V., coefficient of variation; NS, not statistically significant. Ratio (%) was calculated as the relative fraction of the value obtained for the test formulation as compared with the reference formulation.

[a] Entex PSE tablets (600 mg GGE and 120 mg PSE hydrochloride) were administered twice daily on days 1–4 and once daily on day 5.

[b] Robitussin liquid (300 mg GGE/15 ml) and Sudafed liquid (60 mg PSE hydrochloride/10 ml) were coadministered four times daily on days 1–4 and twice daily on day 5, for total daily GGE and PSE doses equivalent to those of Entex PSE.

[c] By analysis of variance at the 5% level of significance, for treatment differences.

Table 4
Plasma guaifenesin pharmacokinetic data (day 5) in 30 subjects

Parameter		Entex PSE tablets (T) [a]	Robitussin and Sudafed liquids (R) [b]	Ratio (%) (T/R)	90% CI	P value [c]
C_{max}	mean	429	596	72	65.2– 78.6	0.0001
(ng/ml)	(% C.V.)	(42)	(35)	(25)		
C_{min}	mean	49	8	420	491.4–671.9	0.0001
(ng/ml)	(% C.V.)	(59)	(106)	(29)		
AUC 0–12 h	mean	2178	2305	95	87.9–101.1	NS
(ng ml^{-1} h)	(% C.V.)	(41)	(34)	(24)		
I_{fluct} [d]	mean	2.1	3.1	69	62.8– 74.1	0.0001
	(% C.V.)	(21.7)	(14.6)	(23)		

T, test formulation (Entex PSE tablet); R, reference formulation (Robitussin and Sudafed liquids). C.V., coefficient of variation; NS, not statistically significant. Ratio % was calculated as the relative fraction of the value obtained for the test formulation as compared with the reference formulation.

[a] Entex PSE tablets (600 mg GGE and 120 mg PSE hydrochloride) were administered twice daily on days 1–4 and once daily on day 5.

[b] Robitussin liquid (300 mg GGE/15 ml) and Sudafed liquid (60 mg PSE hydrochloride/10 ml) were coadministered four times daily on days 1–4 and twice daily on day 5, for total daily GGE and PSE doses equivalent to those of Entex PSE.

[c] By analysis of variance at the 5% level of significance, for treatment differences.

[d] I_{fluct} (fluctuation index) was calculated as C_{max} minus C_{min} divided by the average plasma drug concentration for a 12 h interval, with the average plasma concentration estimated as the $AUC_{0-12\,h}$ divided by 12 h.

4. Conclusions

When sustained-release Entex PSE tablets, each containing 600 mg GGE and 120 mg PSE · HCl, were administered twice daily and Robitussin and Sudafed liquids were coadministered four times daily at equivalent total daily doses of GGE and PSE · HCl, steady state was achieved for both dosing regimens by day 5. At steady state, sustained-release plasma GGE and PSE concentration-time profiles were obtained for Entex PSE, with no evidence of dose dumping. The extents of absorption from Entex PSE tablets and from the reference liquids were equivalent. Entex PSE sustained the release and absorption of GGE and PSE to yield equivalent plasma PSE C_{max}s for Entex PSE and the liquids, without a meaningful difference in the fluctuation of plasma PSE, and a significantly lower plasma GGE C_{max} for Entex PSE with a corresponding reduction in plasma GGE fluctuation.

Acknowledgments

The authors gratefully acknowledge Kansas City Analytical Services personnel, particularly W.D. Mason, for data analysis and calculations for this study and P.J. (Cilla) Davis, E.L.S., Procter & Gamble Pharmaceuticals, for editorial support in the preparation of the manuscript.

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