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Bioavailability of Dextromethorphan (as Dextrorphan) from Sustained Release Formulations in the Presence of Guaifenesin in Human Volunteers

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ABSTRACT: A multiple dose bioavailability study with six healthy male human volunteers was conducted. The bioavailability of an experimental sustained release tablet containing dextromethorphan hydrobromide (DXP-HBr), was compared with a marketed sustained release DXP-HBr suspension in a three-way crossover study. Plasma samples, collected serially after oral drug administration, were analysed for the major metabolite of dextromethorphan (DXP), dextrorphan (DX), using a specific HPLC method with fluorescence detection. The bioavailability parameters; area under the concentration–time curve (AUC), maximum plasma concentration (C_{max}), and time to peak (T_{max}), were obtained from the plasma concentration–time data. Additionally, pharmacokinetic parameters such as mean residence time (MRT), accumulation factor (R), fluctuation index (F_i), total body clearance (Cl), and the average concentration ($\bar{C}$) were estimated by using model independent kinetics approach. Analysis of variance of the data revealed that the presence of guaifenesin in the test formulation does not appear to have a statistically significant ($p > 0.05$) effect on the bioavailability of dextromethorphan as dextrorphan. The relative bioavailability of the tablet dosage form with respect to the suspension was found to be 113% on Day 1 and 110% on Day 6. © 1998 John Wiley & Sons, Ltd.

Key words: bioavailability; pharmacokinetic; dextromethorphan; dextrorphan; guaifenesin

Introduction

Several sustained release products containing dextromethorphan in combination with guaifenesin exist in the market place. However, little information is available regarding the influence of guaifenesin on the bioavailability of dextromethorphan. The objective of the present investigation was to explore the effect of a presence or absence of guaifenesin on the bioavailability of dextromethorphan as dextrorphan.

Dextromethorphan, methyl ether of the *d*-levorphanol, is a highly potent and commonly used antitussive agent. Unlike its *l*-isomer form, a synthetic analog of codeine, DXP has no narcotic analgesic effect and addictive properties. Its potency is almost equal to codeine's antitussive potency. The usual doses of dextromethorphan are 10–20 mg every 4 h or 30 mg every 6–8 h with a maximum of 120 mg daily [1]. Following oral administration, it exerts its effect in 15–30 min. After oral administration, DXP quickly and extensive metabolized by cytochrome P450IID6 enzyme (after 48 h, an average amount of 86% of the dosage was excreted as dextrorphan in the urine) [2]. Sensitive analytical methods like gas chromatography by means of electron capture detector or radioimmunoassay (with a detection limit of approximately 1 ng mL^{-1} of plasma) have been proven to be insufficient to carry out pharmacokinetic plasma level examinations with unchanged dextromethorphan in humans [3,4]. For this reason the main O-demethylated metabolite, dextrorphan, contained at considerably high concentrations in plasma was used to assess the bioavailability of DXP [5]. However, it has to be kept in mind that 5–10% of the caucasian population are reported to be poor metabolizers on the basis of the formation rate of the O-demethylated metabolite, dextrorphan [6,11].

In this investigation the bioavailability of dextromethorphan was determined in the presence and absence of guaifenesin by measuring the formation of dextrorphan, following oral administration of a sustained release DXP tablet and a sustained release DXP suspension. A validated HPLC method with fluorescence detection was used to simultaneously determine the concentration of guaifenesin and dextrorphan in human plasma [7,8,10]. The data demonstrate that presence of guaifenesin did not appear to have a statistically significant effect on the bioavailability of dextromethorphan from sustained release products.

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Material and Methods

Study Design

Six healthy male volunteers between the ages of 18 and 39 and weight between 145 and 185 lb., after informed consent, were selected for the bioavailability studies. In accordance with a three-way crossover design, each subject received three different treatments. Treatment A was an experimental sustained release tablet containing 30 mg dextromethorphan hydrobromide and 600 mg guaifenesin, Treatment B was a sustained release suspension containing 30 mg/5 mL of dextromethorphan hydrobromide, Delsym®, and Treatment C was a marketed fast acting tablet, containing 200 mg of guaifenesin, Glytuss®.

On Day 1 subjects received only a single oral dose from each treatment (which is two tablets of Treatment A, or 10 mL of Treatment B, or six tablets of Treatment C). On the following 5 days, subjects received two tablets of Treatment A every 12 h, or 10 mL of Treatment B every 12 h, or two tablets of Treatment C every 4 h. All six subjects fasted overnight before the start of each treatment. Each dose was administered with 240 mL of water and no food or fluid (except water) was permitted. A week washout period was maintained between the phases and the subjects did not receive any concurrent medication during the study phases.

Blood samples were collected in heparinized vacutainer tubes on Days 1, 4, 5, and 6 just prior to the first daily dose (0 h), and then at 0.33, 0.67, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 16.0, and 24.0 h on Days 1 and 6 and at 12.0 h on Days 4 and 5. No samples were collected on Days 2 and 3. After collection of each sample the vacutainer tubes were gently inverted for mixing and then immersed in chipped ice for rapid cooling. The tubes were then centrifuged at 3000–5000 rpm for 5 min in a refrigerated centrifuge. The plasma from each tube transferred to polypropylene screw cap tubes, labeled, fresh frozen, and kept frozen at $-20°C$ until assayed.

Sample Analysis

A 1 mL plasma sample was mixed with 100 mL of a 2.6 μg mL^{-1} solution of the internal standard, laudanosine, and 500 mL of saturated sodium carbonate solution. A 5 mL aliquot of chloroform was added, and mixed in a rocking mixer for 40 min. After centrifugation for 25 min at 2000 rpm, the aqueous layer was removed by aspiration and the chloroform layer was evaporated to dryness under a stream of nitrogen. The residue was reconstituted with 400 μL of mobile phase and 300 μL was injected into the column of the HPLC system by means of an automated injector.

Chromatographic Conditions

The HPLC system consisted of a solvent delivery pump (Model LC 10 AD, Shimadzu Scientific Corporation, Colombia MD), a stainless steel 5-CN Spherisorb analytical column with 150 × 4.6 mm i.d. (Phenomenex Inc.), a fluorescence detector (Model RF535, Shimadzu), an autosampler (Model Sil-9A, Shimadzu), an integrator (Chromatopac CR501, Shimadzu).

The mobile phase was composed of acetonitrile, triethylamine and distilled water in the ratio of 10/1/89 v/v/v. O-Phosphoric acid was use for the adjustment of pH to 6.01. The flow rate was set at 1 mL min^{-1}. The excitation and emission wavelength of the fluorescence detector were set at 280 and 315 nm, respectively. The sensitivity was set at low, and the response was set at medium.

Chromatograms of a plasma blank, a plasma with dextrorphan, a plasma with internal standard and a plasma sample are illustrated in Figure 1. The concentration–response relationship for dextrorphan in the presence of internal standard, laudanosine, was found to be linear in the concentration range of 23–515 ng mL^{-1} with a lower limit of detection 20 ng mL^{-1} and a lower limit of quantitation 25 ng mL^{-1}. The coefficient of variation for the day-to-day variability was 2.28% and that for the intra-day variability was 5.67%. The mean percentage recovery of dextrorphan from plasma was 92%. Additionally, this method was specific in the presence of guaifenesin [8].

Bioavailability Assessment and Statistical Analysis

The individual subject plasma concentration data on Days 1 and 6 were used to obtained the partial area under the curve for 24 h ($AUC_{0-24\ h}$), the observed peak plasma concentration (C_{max}), and the time at which C_{max} occurred (T_{max}). The area under the plasma concentration–time curve was calculated using the trapezoidal rule.

Attainment of the steady state was assessed by performing an analysis of variance (ANOVA) of the through levels obtained on Days 4 and 5. The $AUC_{0-24\ h}$, C_{max}, and T_{max} were subjected to an analysis of variance using a general linear model (sequence, subject (sequence), period, treatment) to perform bioavailability comparisons between Treatments A and B using the Treatment B as the reference formulation. The relative bioavailability was determined as the ratio of the $AUC_{0-24\ h}$ for Treatment A relative to that for Treatment B. All statistical analyses of the data were performed using BIOPAK, version 2.1 [9].

Pharmacokinetic Parameters

The plasma concentration–time data obtained on Day 6 were used to calculate the model indepen-

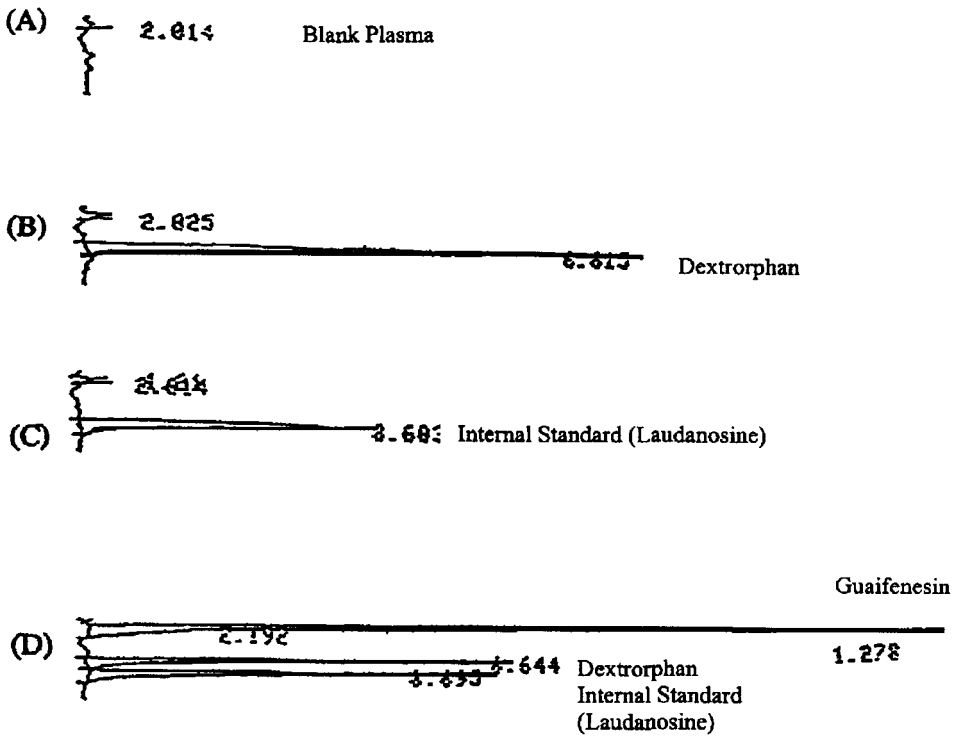

Figure 1. Chromatograms of a plasma blank (A), a plasma with dextrorphan (B), a plasma with internal standard (C) and a plasma standard (D)

dent pharmacokinetic parameters, such as; the individual average dextrorphan plasma concentration at steady state ($\bar{C}$), accumulation factor (R), mean residence time (MRT), volume of distribution (V), total body clearance (Cl); these were calculated by using the raw data and model-independent kinetic approach. Equations used to calculate the accumulation factor (R), fluctuation index (F_i) and $\bar{C}$ are presented below:

$$R = \frac{C^{ss}_{max}}{C^{sd}_{max}} \quad (1)$$

where C^{ss}_{max} is the maximum concentration at steady state and C^{sd}_{max} is the maximum concentration after a single dose;

$$F_i = \frac{C_{max} - C_{min}}{\bar{C}} \quad (2)$$

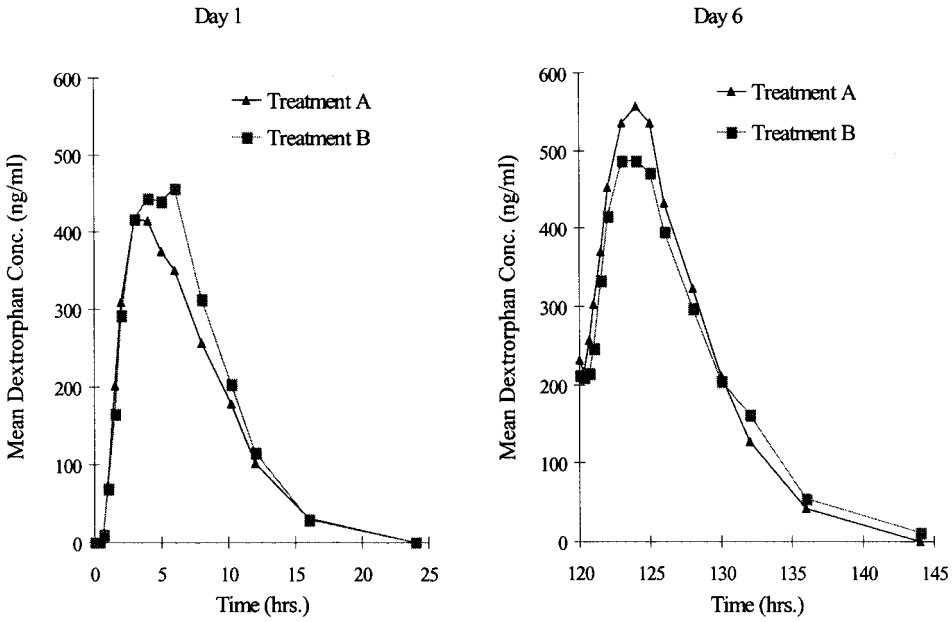

Figure 2. Mean plasma concentration of dextrorphan after oral administration of Treatments A and B

Table 1. Mean bioavailability parameters ($\pm$S.D.) on Days 1 and 6 for Treatments A and B

Parameters	Treatment A		Treatment B	
	Day 1	Day 6	Day 1	Day 6
AUC (ng·h mL^{-1})	3883.6 $\pm$ 1198.2	4330.3 $\pm$ 1406.3	3449.6 $\pm$ 1773.8	3962.8 $\pm$ 1857.7
C_{max} (ng mL^{-1})	465.8 $\pm$ 112.8	580.4 $\pm$ 142.9	436.6 $\pm$ 174.7	528.6 $\pm$ 243.6
T_{max} (h)	5.2 $\pm$ 0.98	3.7 $\pm$ 0.82	3.7 $\pm$ 0.82	3.9 $\pm$ 1.05

Table 2. Comparison of the bioavailability parameters of Treatment A with Treatment B

Statistics	Day 1			Day 6		
	AUC	C_{max}	T_{max}	AUC	C_{max}	T_{max}
F-value	0.7540	0.3718	27.0000	0.8139	0.8944	0.2000
p-value	0.4491	0.5851	0.0138	0.4335	0.4141	0.6850

where $\bar{C}$ is the average concentration of dextromethorphan at steady state, C_{min} is the average of the minimum three concentrations at steady state and C_{max} is the average of the maximum three concentrations at steady state;

$$C = \frac{\int_0^{TAU} C_t \cdot dt}{TAU} \quad (3)$$

where TAU is the dosing interval and C_t is the dextrorphan plasma concentration at time t during the dosing interval at steady state.

Results and Discussion

All six subjects completed the study and no signs or symptoms attributable to the drug were seen after administration of either formulations. Conjugated dextrorphan was prevailing in the plasma of the six volunteers with the average half-life of 3.67 h for Treatment A and 3.02 h for Treatment B following a single dose administration. The mean plasma level of dextrorphan curves on Days 1 and 6 are presented in Figure 2. The mean $AUC_{0-24\ h}$, C_{max}, and T_{max} values for Treatments A and B on Days 1 and 6 are presented in Table 1.

Table 3. Model independent pharmacokinetic parameters of dextrorphan (values $\pm$ S.D.)

Parameters	Treatment A	Treatment B
Half-life (h)	3.67 $\pm$ 0.82	3.02 $\pm$ 0.83
Mean residence time (MRT) (h)	6.61 $\pm$ 0.67	6.32 $\pm$ 1.00
Volume of distribution (V_d) (L)	109.0 $\pm$ 30.9	134.8 $\pm$ 67.2
Cl/*F* (L h^{-1})	16.6 $\pm$ 4.75	23.0 $\pm$ 15.9
Accumulation factor (*R*)	1.25 $\pm$ 0.17	1.19 $\pm$ 0.28
Fluctuation index (F_i)	1.06 $\pm$ 0.34	0.80 $\pm$ 0.35
$\bar{C}$ (ng mL^{-1})	361.5 $\pm$ 117.2	330.2 $\pm$ 154.8

Steady state concentrations were achieved in all subjects by Day 6 based on analysis of variance of the morning predose dextrorphan concentrations of samples drawn on Days 4 and 5. The relative bioavailability of Treatment A with respect to Treatment B was found to be 112.6 and 109.5% for Days 1 and 6, respectively. The model independent pharmacokinetic parameters of dextrorphan were estimated from the data obtained on Day 6 (Table 3).

Analysis of variance of the dextrorphan data, obtained on Days 1 and 6, using the linear model described, revealed no statistically significant differences between Treatments A and B when the AUC and C_{max} were compared ($p > 0.05$). However, comparison of the T_{max} by ANOVA revealed a statistically significant difference ($p = 0.0138$). This is expected because we are comparing a suspension with a tablet dosage form and may be attributed to a slower dissolution time for the tablet (Table 2).

Conclusions

Analysis of variance of the plasma concentration–time data on Days 1 and 6 data revealed no statistically significant differences ($p > 0.05$) between Treatments A and B when the AUC and C_{max} were compared in the presence of guaifenesin. The observed statistical difference, on Day 1 for T_{max} values between treatments may be the result of a slower dissolution process for the tablet dosage form, Treatment A. The relative bioavailability of the sustained release tablet, Treatment A (test), with respect to a sustained release suspension, Treatment B (reference), were found to be 113% on Day 1 and 110% on Day 6.

In conclusion, the presence of guaifenesin in formulation does not appear to have a statistically significant ($p > 0.05$) effect on the bioavailability of dextromethorphan from sustained release formula-

tions. Dextrorphan and guaifenesin were cleared very rapidly from the systemic circulation. No drug accumulation was observed after multiple dose administration for 6 days.

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