Drug Development and Industrial Pharmacy, 25(4), 529–534 (1999)

COMMUNICATION

Comparative Pharmacodynamic-Pharmacokinetic Correlation of Oral Sustained-Release Theophylline Formulation in Adult Asthmatics

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ABSTRACT

A sustained-release formulation of theophylline with an innovative release mechanism was evaluated in adult asthmatics. The pharmacodynamics and pharmacokinetic behavior of this formulation was compared with a market formulation (Theobid®). The formulations, each containing 200 mg of anhydrous theophylline, were evaluated in six male subjects, 40–55 years of age, 151–169 cm in height, 41–60 kg in weight, who were nonsmokers with moderate chronic obstructive pulmonary disease (COPD); the study was a randomized, single-dose, open, complete crossover study with an interval of 1 week. Written consent was obtained from the patients prior to the trial. Plasma samples were obtained at 0, 1, 2, 4, 6, 8, 10, and 12 hr postadministration. Pulmonary functions were simultaneously recorded using an Erich Jaeger spirometer. Plasma theophylline assays were performed using high-performance thin-layer chromatography (HPTLC). Individual bioavailability parameters were obtained using the S-Inv computer program. Pharmacodynamic-pharmacokinetic correlation was studied using the Excel 95 version 7.0 Regression Statistics program. The test formulation (innovator) was found to be comparable with the marketed product with respect to t_{max}, $t_{1/2}$ *and* K_{el} *(*$p < .05$*). A significant difference in the means of* C_{max} *and* AUC_{0-12} *between the innovator and the market formulation indicated a superior extent of absorption from the innovator formulation. A good pharmacodynamic-pharmacokinetic correlation was observed when plasma theophylline concentration was compared with forced expiratory volume.*

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INTRODUCTION

Theophylline preparations have been used in the therapy of asthma for nearly 50 years (1). The introduction of sustained-release formulations has been regarded by many as a significant improvement on an old and reliable drug (2–4). The use of a sustained-release theophylline formulation reduces dosage frequency; provides more uniform blood levels, which reduces toxicity (5); and enhances patient compliance (6). Although there are many separate reports of comparative pharmacodynamic and comparative pharmacokinetics (7–11) of oral sustained-release theophylline formulations, there is very little data available on a comparative pharmacodynamic-pharmacokinetic correlation in adult asthmatics. The objective of this study was dual: to establish a pharmacodynamic-pharmacokinetic correlation and to assess the innovator formulation comparatively with a commercial product, namely, Theobid®.

EXPERIMENTAL

Materials

Innovator Formulation

Formulation of the innovator was from a 200-mg tablet of anhydrous theophylline, hydroxypropyl methylcellulose, polyvinylpyrrolidone, sodium chloride, magnesium stearate, and talc in a sufficient quantity. Matrices were obtained using standard tableting techniques.

Market Formulation

The market formulation was a 200-mg tablet of anhydrous theophylline dispersed in an inert polymeric matrix (Theobid, batch number AF 5078).

Methods

Subjects

Six male subjects 40–55 years of age, 151–169 cm in height, 41–60 kg in weight, with moderate chronic obstructive pulmonary disease (COPD) and a forced expiratory volume in 1 s (FEV_1) or peak expiratory flow rate (PEFR) less than 70% of predicted normal value were selected. Written informed consent was obtained from each subject prior to entrance into the study. All subjects were nonsmokers without a history of alcoholism or cardiovascular or renal disease.

Drug Administration

A randomized, single-dose, crossover study with an interval of 1 week was performed. Subjects were instructed to refrain from any medication at least 24 hr prior to the study and to abstain from alcohol and xanthine-containing foods or beverages for 24 hr prior to dosing and throughout the study. No other medication was given concomitantly with theophylline. All subjects were fasted with the exception of water at least 12 hr prior to dosing.

The six subjects were divided into two groups, group A and group B. One tablet (innovator formulation or Theobid) equivalent to 200 mg of anhydrous theophylline was administered at 7 A.M. with 200 ml water. A standard breakfast and lunch were provided 2 and 6 hr postdosing, respectively. After an interval of 7 days, the subjects were administered the alternate formulation.

Pulmonary Function Evaluation

Pulmonary function was evaluated by recording FEV_1 and PEFR using an Erich Jaeger TS-11-SB/RAM spirometer. Patients were initially trained to breathe in and out into the spirometer mouthpiece. A pilot reading was taken to ensure that the subject was trained sufficiently. Three sets of readings were taken at intervals of 1 min, and the averages were computed from the spirograms. Pulmonary functions were recorded at 0 (predosing), 1, 2, 4, 6, 8, 10, and 12 hr postdosing.

Blood Sampling

Blood samples were collected in heparinized tubes at 0 (pre dosing), 1, 2, 4, 6, 8, 10, and 12 hr postadministration of the dosage form. Plasma samples were frozen at −20°C until further analysis.

Theophylline Analysis

Plasma theophylline determinations were made using the high-performance thin-layer chromatography (HPTLC) method. Alkaline plasma was treated with 6% w/v perchloric acid (12) to precipitate the plasma proteins. Theophylline was extracted using diethyl ether:dichloromethane:isopropyl alcohol (6:4:1) (13). The organic layer was separated by centrifugation. The organic solvent was vacuum dried, and the residue was reconstituted in HPLC grade methanol. Then, 5 µl of the reconstituted solution was streaked as narrow bands using Linomat IV (Camag) onto (E-Merck) precoated Al-plates of silica gel 60 F-254. These plates were developed in ascending mode using chloroform:methanol (9:1) as the solvent system. The plates were then analyzed densito-

metrically on a Camag scanner II in the absorbance mode at 272 nm.

Pharmacokinetic Analysis

A one-compartment model was used to calculate the pharmacokinetic parameters. Parameters like rate constant for elimination, elimination half-life, and area under the curve (AUC) were calculated form plasma concentration time data using the S-Inv computer program.

Statistical Analysis

Data were analyzed by two-way analysis of variance (ANOVA) and split-plot ANOVA. Pharmacodynamic-pharmacokinetic correlation was studied using the Excel 95 version 7.0 Regression Statistics program. Plasma theophylline concentration versus FEV_1 and plasma theophylline concentration versus PEFR for both the innovator and market formulation were evaluated and the r^2 coefficient of correlation was computed.

RESULTS AND DISCUSSION

Pharmacodynamic Analysis

Both the innovator and the market formulation exhibited significatn improvement in the parameter of airflow obstruction compared to baseline values.

Forced Expiratory Volume at 1 Second

An insignificant increase was obtained in FEV_1 (Fig. 1) from 0 to 2 hr postadministration of the theophylline

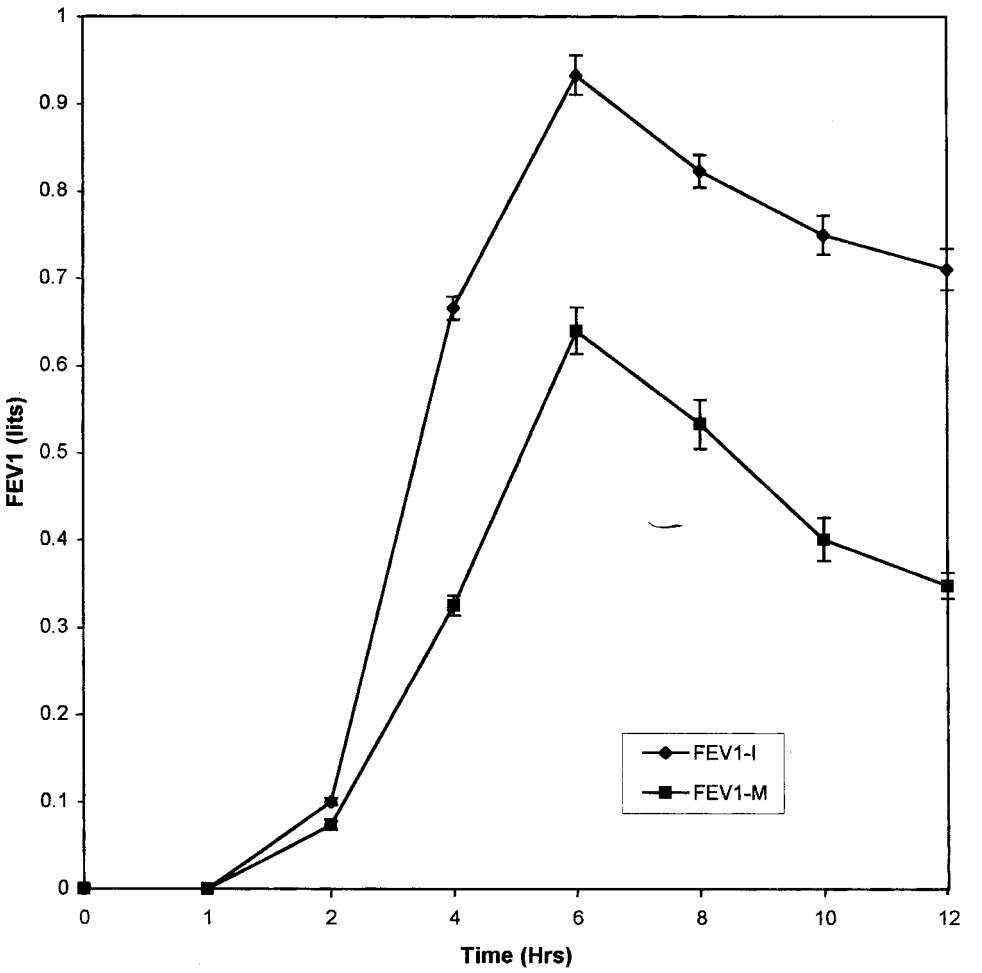

Figure 1. Increase in FEV_1 (L) for innovator (I) and market (M) formulations.

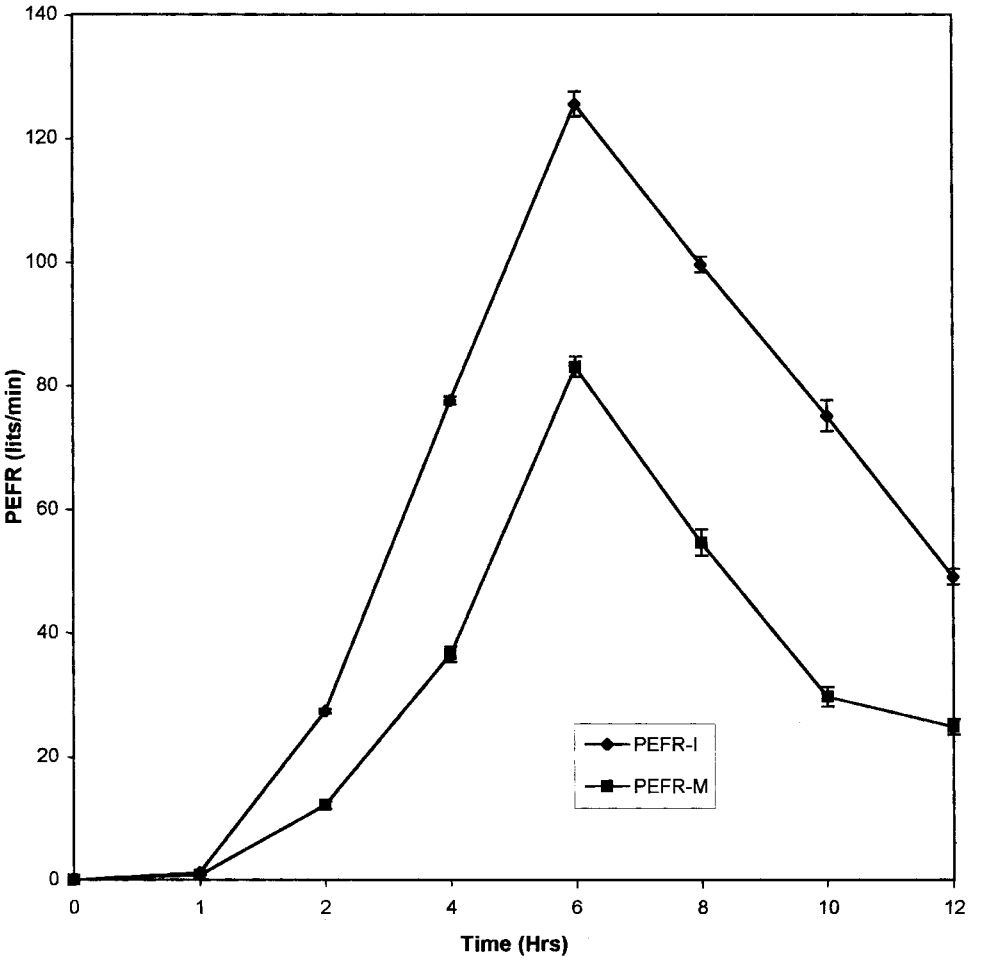

Figure 2. Increase in PEFR (L/min) for innovator (I) and market (M) formulations.

dose. The improvement in FEV_1 after the fourth hour was significantly different for the innovator. Analysis of the increase in FEV_1 from the baseline by split-plot ANOVA revealed the innovator to be superior to the market formulation F value of 9.925 for 1 and 10 degrees of freedom ($F_{table} = 4.96$, $p < .05$). The maximum improvement in FEV_1 was evident at the sixth hour postadministration of the dose.

Peak Expiratory Flow Rate

From 0 to 1 hour postadministration of the dose, no significant change in PEFR was observed (Fig. 2). From the second hour postadministration of the dose onward, a significant improvement in PEFR was observed with both formulations. Maximum improvement was evident at the sixth hour postadministration of the dose.

Of the two formulations, the innovator was superior to the market formulation in improving the PEFR F test for 1 and 10 degrees of freedom (5.118, $p < .05$ for split-plot ANOVA).

Pharmacokinetic Analysis

Plasma theophylline was analyzed using HPTLC. The calibration curves of theophylline from plasma were linear in the range 20–100 ng. The mean values of intercept, slope, and correlation coefficient (±SD) were 0.618 (±0.034), 0.443 (±0.0017), and 0.99547 (±0.00031).

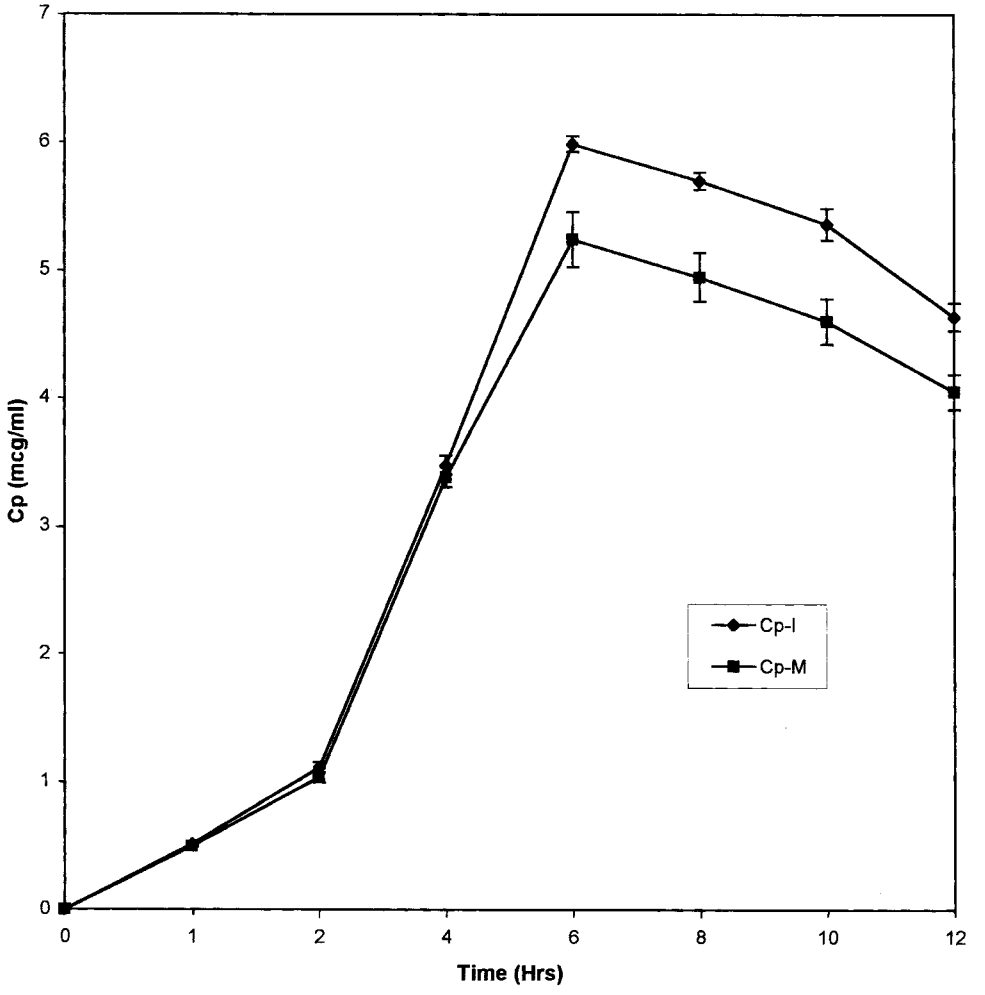

Figure 3. Mean plasma theophylline concentration of innovator (I) and market (M) formulations.

Mean plasma level profiles of theophylline obtained following administration of a controlled-release oral dose of innovator and market formulations are graphically represented in Fig. 3.

Split-plot ANOVA revealed a significant difference in the overall average efficiency of the two formulations, suggesting the superiority of the innovator, with $F = 9.474$ (1 and 10 degrees of freedom, $p < .05$). This result was confirmed by the significant difference in C_{max} and AUC_{0-12} of the two formulation ($p < .05$). The average values of the pharmacokinetic parameter for the two formulations are summarized in Table 1. T_{max} was seen to be at 6 hr postadministration for both the products and correlated with the time of maximum pharmacodynamic response. The enhancement in the bioavailability of theophylline by the innovator formulation was by a factor of 1.142. No significant difference was observed in $t_{1/2}$ and K_{el} ($p > .05$) for the two products.

Pharmacodynamic-Pharmacokinetic Correlation

A good correlation was observed between plasma theophylline concentration and FEV_1 for both the innovator ($r^2 = 0.968639$) and market ($r^2 = 0.94970$) formulations. However, such a correlation was not observed between plasma theophylline concentration and PEFR (innovator $r^2 = 0.85063$; market formulation $r^2 = 0.740574$).

Table 1

Pharmacokinetic Parameters of Controlled-Release Innovator and Market Formulation

Pharmacokinetic Parameter	Innovator Formulation	±SD	Market Formulation	±SD	ANOVA
C_{max} (mcg)	5.990	0.153	5.242	0.522	S
T_{max} (hr)	6	0.0	6	0.0	NS
K_{el} (hr^{-1})	0.0703	0.0041	0.0633	0.00818	NS
$T_{1/2}$ (hr)	9.85	0.56	10.94	1.278	NS
AUC_{0-12} (mcg/ml)	48.24	1.740	42.23	3.92	S

NS, not significant; S, significant, $n = 6$, $p = 0.5$

CONCLUSION

A good pharmacodynamic-pharmacokinetic correlation between plasma theophylline concentration and FEV_1 was obtained ($> .9$) in comparison with plasma theophylline concentration and PEFR ($< .9$). This suggests that FEV_1 could be used as an alternative to plasma concentration measurements to assess antiasthmatic formulations.

The bioavailability of the innovator was enhanced by a factor of 1.142 compared to the market formulation. The superior overall effectiveness of the innovator in improving pulmonary functions strongly suggests the potential for the innovative release mechanism as a novel sustained-release technology.

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