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Research paper

Biopharmaceutical characterization of oral theophylline and aminophylline tablets. Quantitative correlation between dissolution and bioavailability studies

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Abstract

Considering the narrow therapeutic index of theophylline and the low range between the safe and toxic serum concentrations of this drug, the study of its pharmacokinetic properties is necessary. However, considering the time consuming and expensive in vivo tests, quantitative correlation between in vivo bioavailability and in vitro dissolution tests can be used routinely in quality control tests of these drug products to predict the in vivo pharmacokinetic parameters. For this reason healthy human volunteers were used for in vivo studies and serum samples were analyzed by a fluorescence polarization immunoassay analysis (FPIA) method. The results showed that an open one compartmental model could best describe the pharmacokinetic properties of orally administered theophylline and aminophylline tablets. Linear regression analysis by least-square method showed a good correlation between some in vivo and in vitro parameters obtained from dissolution studies by rotating basket and paddle methods. D_{30}% (percentage of drug dissolved in vitro after 30 min) and $F_{0.5}$% (drug absorbed in vivo after half an hour calculated by Wagner–Nelson equation) showed best correlation ($r = 0.99036$). C_{max} (maximum serum concentration) of this drug also correlates well with $t_{25\%}$ (time required to dissolve 25% of the drug). The calculated correlation coefficients could best predict the actual values of some pharmacokinetic parameters; $AUC_{0\rightarrow\infty}$, $AUC_{0\rightarrow1}$, $F_{0.5}$% and C_{max}.

Keywords: Bioavilability; Theophylline; Asthma; Pharmacokinetics; Dissolution

1. Introduction

Theophylline is a methylxanthine derivative with a narrow therapeutic index [1,2] and a serum concentration between 10–20 μg/ml is too effective and safe in controlling the signs of asthma and bronchospasms caused by other diseases.

As the induced bronchodilation is diminished by reducing its serum concentration and on the other hand its toxicity risk is increased above 20 μg/ml, the fluctuations of its serum concentrations produce some clinically important problems. In other words, there is a very close relationship between plasma concentration of this drug, its toxic and therapeutic effects [3,4]. Therefore, it seems that plasma drug monitoring is quite necessary for different dosage forms of theophylline.

Since drug release pattern from each dosage form is significantly affected by the special design used in manufacturing the formulations, planning an in vitro dissolution method corresponding to the in vivo drug absorption rate, will facilitate the development of the drug formulations and quality control tests. From the economic, technical, and ethical perspectives of bioavailability studies, it is necessary to establish an in vitro test method that can predict the progress of drug release and the absorption of products in vivo [5].

El-Yazigi and Sawchuk [6] found good correlations between bioavailability parameters and dissolution characteristics of theophylline sustained-release dosage forms in rabbit. Ritschel et al. [7] also reported such correlations in beagle dog. Brockmeir [8], Hwan Chung and Shim [9] also compared in vitro dissolution rates with in vivo parameters in human using theophylline saliva concentrations.

The objective of this study was to correlate logically the rapid simple and practical in vitro dissolution methods of theophylline tablets with its in vivo human pharmacokinetic parameters. This correlation will be able to predict the bioavailability of theophylline dosage forms instead of difficult, time-consuming and expensive in vivo tests routinely.

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2. Materials and methods

2.1. Materials

All studied dosage forms were purchased commercially; 100 mg enteric coated tablet of aminophylline (ethylenediamine salt of theophylline) (Iran Hormone, Iran) with code A, 100 mg sugar coated tablets of aminophylline (Abidi laboratories, Iran) with code B, 100 mg tablets of aminophylline (Artezan, Germany) with code C, and 200 mg tablets of theophylline (Abidi Laboratories, Iran) with code D, anhydrous theophylline and aminophylline powder (Bohringer, Germany).

2.2. Methods

2.2.1. Bioavailability studies

Six healthy male volunteers, ranging 21–24 years old and weighing 58–75 kg, participated in this study. The subjects were not smokers and had not taken any drugs during the preceding 2 months. They were found to be normal on physical examination, a blood screen and urinalysis. None of them had a history of any serious or chronic disease. They were allowed no xanthine-containing beverages for 3 days before each administered dose and for the duration of the sampling schedule. No food was permitted for 3 h after taking the tablets. Each volunteer received a 200 mg single dose of products A, B, C and D in a complete cross-over design. The interval between each studied dosage form was 2 weeks. The respective dose of the drug was given with 200 ml of water.

2.2.2. Sample collection

Three milliliters of blood was taken from the forearm vein just prior to dosing and at 0.5, 1, 2, 3, 5, 7, and 9 h after dosing. Each blood sample was allowed to stand for about 1 h and then serum was separated by centrifugation. The serum samples were kept frozen (−20°C) until the time of analysis.

2.2.3. Assay

The serum theophylline concentrations were determined by a TD_x analysis ($TD_x^{®}$ System Analyzer Abbott™ Laboratories, Dallas, TX) based on a fluorescence polarization immunoassay analysis (FPIA) method [10].

2.2.4. Bioavailability parameters

The area under the serum concentration-time curve from time zero to time t ($AUC_{0\rightarrow t}$) was calculated using the linear trapezoidal rule. The area from time t to infinity was estimated by C_t/K_{el}, where C_t is the serum theophylline concentration observed at time t, and K_{el} is the apparent elimination rate constant of theophylline obtained from the slope of log-linear portion of the curve by least square regression analysis. Moreover, the area from time zero to infinity was calculated by:

$$AUC_{0\rightarrow\infty} = AUC_{0\rightarrow t} + C_t/K_{el} \quad (1)$$

The fraction of the dose absorbed in time t (F_t) was calculated from the Wagner-Nelson equation [11].

$$F_t = \frac{(C_t + K_{el}.AUC_{0\rightarrow\infty})}{K_{el}.AUC_{0\rightarrow\infty}} \quad (2)$$

2.2.5. Statistical analysis

A one-way ANOVA post hoc multiple comparison LSD test with $P < 0.05$ was used for statistical analysis using SPSS computer software. The correlation coefficients of the regression lines between in vitro dissolution parameters and in vivo parameters were obtained by the linear least square method. The correlation coefficients were examined for their significance with the t-test.

3. Results

3.1. Bioavailability results

The results of bioavailability and pharmacokinetic studies of four theophylline and aminophylline tablets; A, B, C and D in six volunteers are shown in Table 1. Fig. 1 indicates that an open one compartmental model best describes the disposition of oral theophylline and its ethylenediamine derivative in human body [9,12–14]. A great difference can be seen between the absorption (K_a) and elimination rate (K_{el}) of this drug (Table 1). The average elimination half life ($T_{1/2}$) in six volunteers showed no significant difference between different studied products (Table 1). The differences between bioavailability (expressed as the area under the time-concentration curve until infinity, i.e. $AUC_{0\rightarrow\infty}$) of products A and C ($P < 0.01$) and also between C and D ($P < 0.05$) were significant so that C was greater than A and D (Table 1). The results of in vitro dissolution tests also showed that the dissolution rate of C is faster than others [15].

4. Discussion

The great difference between K_a and K_{el} of the studied products shows that theophylline absorbs rapidly from the studied dosage forms while its elimination happens slowly. However, as it shows a one-compartmental pharmacokinetic model (Fig. 1), it may be concluded that its elimination rate from the central compartment (i.e. blood) is slow [9,12]. This suggests the necessity of constant monitoring of this drug in the blood of the patients under long treatment with theophylline to prevent any intoxication.

However, the great variations between $T_{1/2}$ in different subjects probably indicates the interindividual differences in hepatic metabolism rate of theophylline [14,16–19]. Different types of sustained release theophylline dosage forms also show a great interindividual variation in extent and absorption rate [20].

Table 1
Pharmacokinetic data (mean ± SD) of four commercial products of theophylline[a]

Product	C_{max}[b] (μg/ml)	T_{max}[c] (h)	$T_{1/2}$[d] (h)	K_a[e] (h^{-1})	K_a[f] (h^{-1})	$AUC_{0\rightarrow0.5}$[g] (μg/ml·h)	$AUC_{0\rightarrow1}$[h] (μg/ml·h)	$AUC_{0\rightarrow9}$[i] (μg/ml·h)	$AUC_{0\rightarrow\infty}$[j] (μg/ml·h)	$F_{0.5}$%[k]
A	6.364 ± 0.587	2.213 ± 0.447	7.985 ± 0.769	1.532 ± 0.853	0.087 ± 0.008	0.771 ± 0.339	2.714 ± 1.040	40.944 ± 3.786	80.687 ± 4.945	44.48 ± 17.44
B	7.045 ± 0.771	2.000 ± 0.707	8.176 ± 1.680	1.484 ± 0.819	0.088 ± 0.018	0.425 ± 0.495	2.110 ± 1.420	44.639 ± 3.576	90.707 ± 18.114	21.96 ± 24.43
C	6.886 ± 0.970	1.900 ± 0.894	8.448 ± 1.420	1.689 ± 0.811	0.084 ± 0.012	0.939 ± 0.719	3.397 ± 1.654	45.227 ± 2.774	93.982 ± 6.965	47.46 ± 31.35
D	6.040 ± 0.509	2.000 ± 0.707	7.308 ± 2.683	1.192 ± 0.459	0.105 ± 0.037	0.562 ± 0.336	2.354 ± 1.014	36.512 ± 6.443	70.907 ± 26.595	32.90 ± 16.73

[a] Aminophylline tablets (A–C) and theophylline tablet (D) (n =6).
[b] Maximum serum concentration.
[c] Time required to reach maximum serum concentration.
[d] Elimination half life.
[e] Absorption rate constant.
[f] Elimination rate constant.
[g] Area under the serum concentration-time curve from zero time to 0.5 h.
[h] Area under the serum concentration-time curve from zero time to 1 h.
[i] Area under the serum concentration-time curve from zero time to 9 h.
[j] Area under the serum concentration-time curve from zero time to infinity.
[k] Percentage of drug absorbed after half an hour.

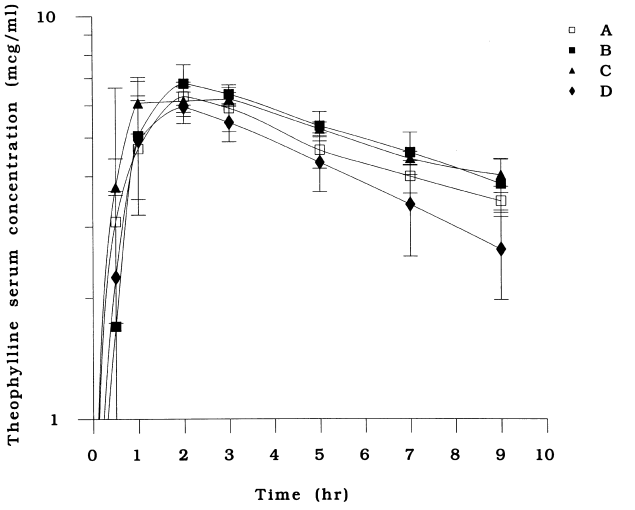

Fig. 1. Mean log of theophylline serum concentrations of human healthy volunteers after oral administration of a single dose (equal to 200 mg of pure theophylline) from aminophylline (A–C) and theophylline (D) tablets ($n = 6$).

Similar results for T_{max} of the studied products suggests that there may be a problem in the formulation of product A. As this tablet is an enteric coated form, it needs a 3.61 ± 1.47 h to be evacuated from the stomach [13]. In vitro dissolution studies also showed the rapid release of the drug from tablet A [15].

4.1. Quantitative correlation of bioavailability and dissolution parameters

Some bioavailability parameters showed a good degree of correlation with some dissolution parameters. For example, Fig. 2 shows a very high correlation ($r = 0.990$, $P < 0.05$ for paddle method and $r = 0.984$, $P < 0.05$ for rotating basket method) between the fraction absorbed in 0.5 h calculated by Wagner–Nelson Eq. ($F_{0.5}$%) and the percentage dissolved in 30 min (D_{30}%) for four products. Some

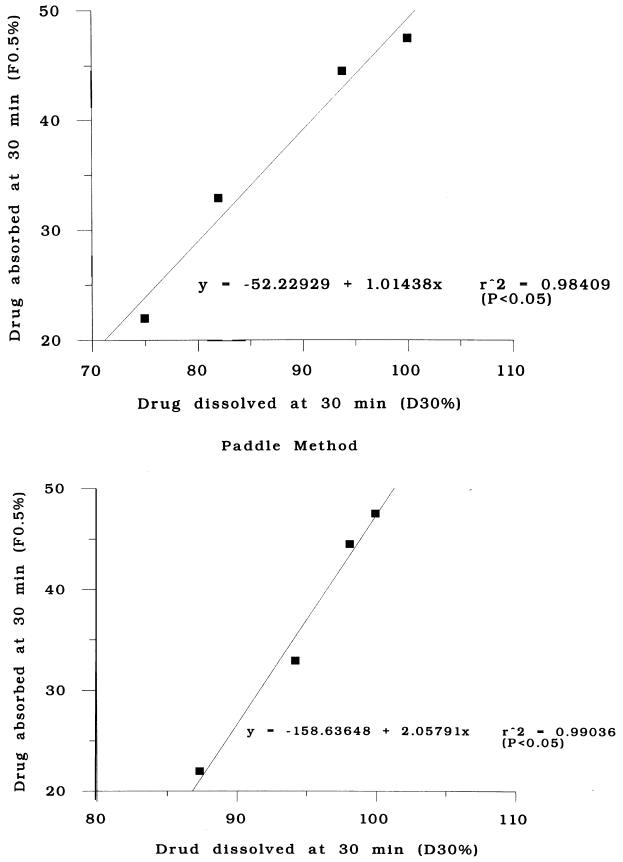

Fig. 2. Quantitative correlation between percentage of theophylline absorbed ($F_{0.5}$%) and dissolved (D_{30}%) after 30 min by two methods of dissolution studies (Rotating Basket and Paddle Method).

pairs of parameters showed significant correlations, as shown in Table 2. The percentage of dissolved drug from studied dosage forms by rotating basket method showed better correlations with some serum bioavailability parameters than did paddle method, except in one case, i.e. the correlation coefficient between $F_{0.5}$% and D_{30}% which was greater by the paddle method (Table 2). Using the equations

Table 2
Correlation coefficients between in vitro dissolution and in vivo pharmacokinetics parameters

Dissolution test method	In vitro parameter	In vivo parameter	Correlation coefficient (r)	Slope	y-Intercept
I[a]	D_{30}%	$F_{0.5}$%	0.984	1.014	−52.229
II[b]	D_{30}%	$F_{0.5}$%	0.990	2.058	−158.636
I	D_{30}%	$AUC_{0\rightarrow1}$	0.956	0.047	−1.504
II	D_{30}%	$AUC_{0\rightarrow1}$	0.882	0.880	−5.707
I	D_{60}%	$AUC_{0\rightarrow1}$	0.797	0.079	−4.853
II	D_{60}%	$AUC_{0\rightarrow1}$	0.669	0.137	−10.788
I	D_{60}%	$AUC_{0\rightarrow\infty}$	0.693	1.287	−37.492
II	D_{60}%	$AUC_{0\rightarrow\infty}$	0.680	2.598	−170.327
I	$t_{25\%}$	C_{max}	0.699[c]	0.053	6.255
II	$t_{25\%}$	C_{max}	0.701[c]	0.061	6.254

[a] Rotating Basket method.
[b] Paddle method.
[c] Not significantly different.

Table 3
Relationship between in vivo and in vitro parameters (I, Rotating Basket and II, Paddle method) of theophylline products to predict some pharmacokinetic parameters

Product	D_{30}%[a]		Actual $F_{0.5}$%[b]	Predicted $F_{0.5}$%		Actual $AUC_{0\rightarrow1}$[c] (μg/ml·h)	Predicted $AUC_{0\rightarrow1}$ (μg/ml·h)		D_{60}%[d]		Actual $AUC_{0\rightarrow\infty}$[e] (μg/ml·h)	Predicted $AUC_{0\rightarrow\infty}$ (μg/ml·h)		$t_{25\%}$[f] (min)	Actual C_{max}[g] (μg/ml)	Predicted C_{max} (μg/ml)
	I	II		I	II		I	II	I	II		I	II	I		
A[h]	93.78	98.14	44.48	42.90	43.33	2.71	2.93	2.93	97.79	100	80.69	88.41	89.53	4.8	6.36	6.51
B[h]	74.94	87.32	21.96	23.96	21.05	2.11	2.04	1.97	92.41	97.37	90.71	81.49	82.69	15	7.04	7.06
C[h]	100	100	47.46	49.21	47.16	3.40	3.23	3.09	100	100	93.98	91.26	89.53	3.1	6.89	6.42
D[h]	81.96	94.22	32.9	30.90	35.26	2.35	2.37	2.58	87.48	94.26	70.91	75.13	74.61	1.6	6.04	6.34

[a] Percentage of drug dissolved after 30 min.
[b] Percentage of drug absorbed after half an hour.
[c] Area under the serum concentration-time curve from zero time to 1 h.
[d] Percentage of drug dissolved after 60 min.
[e] Area under the serum concentration-time curve from zero time to infinity.
[f] Time required to dissolve 25% of the drug.
[g] Maximum serum concentration.
[h] Aminophylline tablets (A–C) and theophylline tablet (D).

obtained from the linear regression quantitative correlation between in vitro and in vivo parameters denoted in Table 2, the amount of in vitro parameters obtained by each dissolution study method were fitted in each equation of Table 2 and the amount of in vivo parameters were predicted (Table 3). For example, the mean amounts of $D_{30}\%$ for product A by rotating basket method and paddle method were 93.778 and 98.142%, respectively, which were fitted in the equations obtained from the correlation studies between $F_{0.5}\%$ and $D_{30}\%$ (Table 2 and Fig. 2), i.e. $y = 1.014\ x - 52.229$ (rotating basket method) and $y = 2.058\ x - 158.636$ (paddle method), and the amount of $F_{0.5}\%$ was predicted by each of the two methods. This gives 42.90% for rotating basket method and 43.33% for paddle method (Table 3). As the studied products are immediate release and not sustained-release products, it is not surprising that about 44% of the administered dose is absorbed during the first 30 min of the administration. Chung and Shim [9] also reported a T_{max} of 1.30 ± 0.98 h for a commercial rapid release theophylline dosage form in which 87% of the drug was absorbed after 1 h.

In this way as shown in Table 3, $D_{30}\%$ was used for prediction of $F_{0.5}\%$ and $AUC_{0\rightarrow1}$, $D_{60}\%$ for prediction of $AUC_{0\rightarrow\infty,}$ and $t_{25\%}$ for prediction of C_{max}. The amount of $D_{30}\%$, $D_{60}\%$, and $t_{25\%}$ for each product are shown in Table 3. The predicted amounts were too close to the actual values (Table 3). Therefore, it seems that the two methods of in vitro dissolution tests of theophylline solid dosage forms i.e., rotating basket and paddle method [15] are capable in predicting the in vivo pharmacokinetic parameters in human.

5. Conclusions

In conclusion, it was found that some blood bioavailability parameters of theophylline dosage forms, like $F_{0.5}\%$, $AUC_{0\rightarrow1}$, $AUC_{0\rightarrow\infty}$ and C_{max} may be predicted from in vitro dissolution data, like $D_{30}\%$, $D_{60}\%$ and $t_{25\%}$, by considering the correlation among in vitro and in vivo studies. It seems convenient and advantageous to use $D_{30}\%$ or $D_{60}\%$ instead of blood data, which needs frequent venepuncture for sampling, in the development, evaluation and quality control of theophylline dosage forms.

Both methods of dissolution studies of four commercial tablets of theophylline and aminophylline, i.e. rotating basket and paddle method were capable to predict the pharmacokinetic parameters of this drug in human blood which may be routinely used in quality control laboratories to omit the time consuming and difficult in vivo bioavailability studies in human. This correlation was best shown between the drug absorbed after 30 min ($F_{0.5}\%$) and the drug dissolved after the same time.

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