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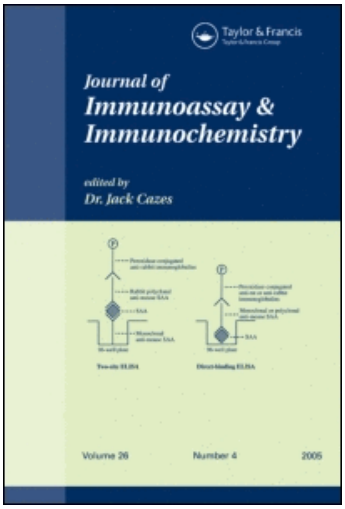

Journal of Immunoassay and Immunochemistry

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597271

Pharmacokinetics of Theophylline after Administration of Suppositories Formulation

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To cite this Article Abou-Basha, L. I. , Wahman, L. F. , Hamza, A. and Aboul-Enein, Hassan Y.(2005) 'Pharmacokinetics of Theophylline after Administration of Suppositories Formulation', Journal of Immunoassay and Immunochemistry, 26: 4, 251 — 258
To link to this Article: DOI: 10.1080/15321810500220670
URL: http://dx.doi.org/10.1080/15321810500220670

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Journal of Immunoassay & Immunochemistry, 26: 251–258, 2005
Copyright © Taylor & Francis, Inc.
ISSN 1532-1819 print/1532-4230 online
DOI: 10.1080/15321810500220670

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Pharmacokinetics of Theophylline after Administration of Suppositories Formulation

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Abstract: Asthma is a public health problem for developed countries. It attacks all age groups but often starts in childhood. Theophylline ethanoate of piperazine in a suppository form is one of the treatments of asthmatic children. The pharmacokinetics of theophylline were evaluated in 24 healthy male subjects after administration of theophylline ethanoate of piperazine suppositories (PR) (Minophylline 500 mg. Alexandria Co.) and single injection intravenous (IV) of theophylline ethanoate of piperazine (Minophylline ampoules 500 mg Alexandria Co.).

The theophylline serum levels were determined by an ELISA method. Peak theophylline plasma concentration, C_{max}, (mean $\pm$ S.D) was $21.5 \pm 2.10\,\mu g/mL$ & $14 \pm 0.90\,\mu g/mL$; $AUC_{(0\text{-}t)}$ values were 80.9 and 67. $4\,\mu g \cdot ml \cdot hr$ for the reference IV preparation and suppositories, respectively. The median peak time, T_{max}, was 0.5 hr for theophylline rectal administration.

The above mentioned results demonstrate the possibilities of using theophylline (Minophylline Suppositories—500 mg Alexandria Co.) in asthmatic children in rural and desert areas away from health care personnel.

Keywords: Theophylline, Bioavailability, Pharmacokinetics, Enzyme immunoassay

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INTRODUCTION

Asthma is one of the commonest chronic diseases worldwide and is increasing in children and, probably, also in adults.

The prevalence of childhood asthma has been reported to vary between 1% and 30% in different populations.[1] According to some reports from Egypt, it affects up to 8% of the children studied.[2] It was recently reported that asthma affects 18% of Egyptian children.

Theophylline ethanoate of piperazine has been known for several decades for its bronchodilator properties. Onset occurs as soon as serum level reaches 5 μg/mL. This can be within minutes after an intravenous dose or 15 to 30 minutes after rapidly absorbed oral liquid or plain uncoated tablets. Theophylline ethanoate of piperazine is commonly administered rectally, particularly in asthmatic children; onset occurs 15 to 30 minutes after a dose of a rapidly absorbed suppository. It has been shown that theophylline can be irregularly absorbed from normal suppository base preparations (in some cases), showing peak serum levels considerably lower than from comparable oral doses. The drug appears to be fully bioavailable from this route. Correlation of serum levels and clinical response is readily achievable.[3–5]

Theophylline is a xanthine derivative that relaxes bronchial smooth muscle, relieves bronchospasm, and has a stimulant effect on respiration.[6]

Considerable inter-individual difference in the rate of hepatic metabolism of theophylline results in large variations in clearance, serum concentration, and half lives. Hepatic metabolism is further affected by factors such as age, smoking, disease, diet, and drug interactions.[5]

Serum theophylline concentration was originally measured by spectrophotometry, but this is subject to considerable interference from other drugs. High performance liquid chromatography is now the method of choice when extreme accuracy is important.[7,8] The enzyme multiplied immunoassay technique (EMIT) used in this study has become popular because of its rapidity and adaptability for processing large batches.[3]

The study was performed to compare the pharmacokinetic parameters of theophylline in two pharmaceuticals preparations produced by Alexandria Co.: minophylline suppositories, 500 mg; and minophylline ampoules, 500 mg.

EXPERIMENTAL

Protocol and Subjects

The protocol of the study was reviewed by NODCAR's Ethical Committee. The protocol and information on theophylline were discussed with a group of volunteers who met all of the inclusion criteria and have no exclusion criteria. The volunteers who participated in the study underwent laboratory

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tests and physical examination. Twenty-four male volunteers were included in this study; age, body weight, and height are presented in Table 1.

Drug Administration

This was a randomized, open level, two period cross over design (single dose). Subjects were fasted after 10 P.M. the day before the drug was administered. On the first day (phase I), half the subjects received, rectally, 500 mg theophylline ethanoate of piperazine (minophylline suppositories). To the remainder, was administered 500 mg theophylline ethanoate of piperazine (IV ampoules) diluted in 10 mL saline and were injected slowly at the rate of 2 mL/min (in the right forearm while a cannula was

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Table 1. Subject characteristics

Subject				Treatment (date)	
Volunteer no.	Age (year)	Ht (cm)	Wt (Kg)	Treatment phase I	Treatment phase II
1	41	156	70	T	R
2	35	171	75	R	T
3	31	160	67	T	R
4	29	169	70	T	R
5	34	174	82	R	T
6	29	162	69	R	T
7	22	169	80	R	T
8	40	160	60	T	R
9	39	175	82	T	R
10	25	165	72	R	T
11	32	165	78	R	T
12	31	164	62	T	R
13	26	160	64	T	R
14	36	168	75	T	R
15	28	177	74	T	R
16	23	166	67	R	T
17	34	171	71	R	T
18	29	177	79	T	R
19	22	165	67	R	T
20	31	170	79	R	T
21	40	175	76	R	T
22	22	166	65	T	R
23	29	172	78	T	R
24	34	167	78	R	T

Treatment T: Theophyliine PR "Alexandria Co."
Treatment R: Theophylline IV "Alexandria Co."

fixed in the left hand for blood sampling). Blood samples (2 mL) were collected at the following time intervals after drug administration 0.08, 0.16, 0.25, 0.33, 0.41, 0.50, 0.66, 0.83, 1.0, 1.25, 1.50, 1.75, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 10.0, 12.0, and 24 hours post dose. Zero blood sample was withdrawn immediatyely before drug administration, Blood samples were collected in polypropylene tubes. The cannula was thoroughly flushed with sodium heparin solution (100 u/mL) after each sample collection. The blood samples were centrifuged and serum samples were kept at $-20^{\circ}C$ until time of analysis. After a wash out period of two weeks, an alternative formulation was given (phase II).

Method of Analysis

The determination of theophylline in serum samples was performed in one day with enzyme immunoassay kits manufactured by Boehringer Mannheim Corp., Indianapolis, IN, USA.

The principle of the method is the CEDIA Theophylline II assay which uses recombinant DNA technology (US Patent No 4,708,929) to produce a unique homogenous enzyme immunoassay system. The assay is based on the bacterial enzyme β-galactosidase which has been genetically engineered into two inactive fragments. These fragments spontaneously reassociate to form fully active enzyme that, in the assay format, cleaves substrate, thereby generating a color change that can be measured spectrophotometrically.

If analyte is not present in the sample, antibody binds to analyte conjugated with the inactive fragments, and no active enzyme is formed.[9,10] The basic technology of CEDIA assays has a number of inherent advantages, the most important of these being a linear calibration curve with high precision over the whole assay range, lack of endogeneous enzyme activity and minimal serum interference, chemically defined conjugates, and flexibility in assay design. These provide significant advantages in comparison with other homogeneous immunoassay techniques. The calibration curves and volunteers' serum samples are processed in a BM-Hitachi 912 Autoanalyzer.

Pharmacokinetic Parameters

The pharmacokinetic characteristics for theophylline ethanoate piperazine were determined from the serum concentration-time data. The maximum plasma concentration (C_{max}) and time (T_{max}) to reach maximum plasma concentration were obtained directly from the serum concentration-time data and used as measures of rate of absorption. The area under the serum concentration-time curve was determined by using the linear trapezoidal rule. The apparent elimination rate constant (K_{el}) was calculated by the technique of least squares regression from the data of the last 4–5 points of each serum concentration-time curve.

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The $AUC_{(0-\infty)}$ values (express the magnitude of absorption) were determined by adding the quotient of $^{\wedge}C_1$ and the appropriate K_{el} to the corresponding $AUC_{(0-t)}$, i.e.,

$$AUC_{(0-\infty)} = AUC_{(0-t)} + {}^{\wedge}C_1/K_{el}$$

where $^{\wedge}C_1$ is the estimated last serum concentration.

The apparent elimination half-life ($t_{1/2}$) for theophylline ethanoate piperazine in serum was calculated by using the following equation:

$$T\ 1/2 = (\ln 2)/K_{el}$$

Statistical Analysis

The two-way analysis of variance (ANOVA) for crossover design was used to assess the effect of formulations, periods, sequences, and subjects within sequence on logarithmically transformed data of $AUC_{(0-\infty)}$, $AUC_{(0-1)}$, (C_{max}), K_{el}, and $t_{1/2}$. The ANOVA of T_{max} was carried out on the untransformed data. Sequence effects were tested against the mean square term for subjects within sequence. All other main effects were tested against the mean square error term. Parametric 90% confidence intervals based on the ANOVA of the mean T/R ratios of AUC parameters and C_{max} was computed under the assumption of a multiplicative model.

Non parametric confidence interval was also performed.[11] In addition, the bioequivalence between the two formulations was also assessed by Schliemann's 2 1–sided *t*–tests.[11] All analyse of the data were performed with the statistical software package, NODCAR.

RESULTS AND DISCUSSION

The subject characteristics of those participating in this study are presented in Table 1. The mean serum concentration of theophylline after IV and rectal administration to 24 subjects are listed in Table 2 and in Fig. 1.

The pharmacokinetic parameters of theophylline after IV and rectal administration are presented in Table 3.

Asthma attacks all age groups, but often starts in childhood. The increase in prevalence of asthma over the past two to three decades, worldwide, have urged both the WHO and the local health authorities in various countries to have a minimum standard of health care for people with asthma.

Theophylline is a xanthine derivative which relaxes bronchial smooth muscle, relieves bronchospasm, and has a stimulant effect on respiration.[6] Therapeutic effects are observed in some patients, initially, at a theophylline level of 5 μg/mL.[3–5]

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Table 2. Mean serum thyeophylline concentrations (μg/mL) after administration of treatment T and R

Time (hr)	Test (T) (rectal)	Reference® (IV)
0.0	0.0	21.5 ± 2.10
0.08	5.16 ± 0.67	20.3 ± 1.84
0.17	7.12 ± 0.78	19.2 ± 1.58
0.25	9.55 ± 0.98	18.4 ± 1.46
0.33	10.9 ± 0.78	17.4 ± 1.27
0.41	12.1 ± 0.83	17.1 ± 1.45
0.5	13.80 ± 0.78	16.2 ± 1.57
0.66	12.7 ± 1.32	15.4 ± 1.47
0.83	11.1 ± 0.99	14.5 ± 1.42
1.00	10.2 ± 0.79	13.3 ± 1.35
1.25	9.36 ± 0.56	12.0 ± 1.10
1.50	8.70 ± 0.61	11.0 ± 0.93
1.75	7.97 ± 0.72	10.1 ± 0.75
2.00	7.35 ± 0.54	9.03 ± 0.74
3.00	6.83 ± 0.42	7.9 ± 0.59
4.00	6.35 ± 0.36	5.68 ± 0.51
6.00	5.91 ± 0.47	4.25 ± 0.52
8.00	4.74 ± 0.52	2.71 ± 0.41
10.00	3.09 ± 0.42	0.87 ± 0.15
12.00	0.91 ± 0.07	—
24.00	N.D	—

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Optimum therapeutic serum concentrations generally range from 10–20 μg/mL,[12,13] but should not be regarded as a rigid barrier; clinical decisions should never be based solely on the serum concentrations.[14]

Several reports were published dealing with food effects on the pharmacokinetics of theophylline.[15–18] However, in this study, the pharmacokinetic

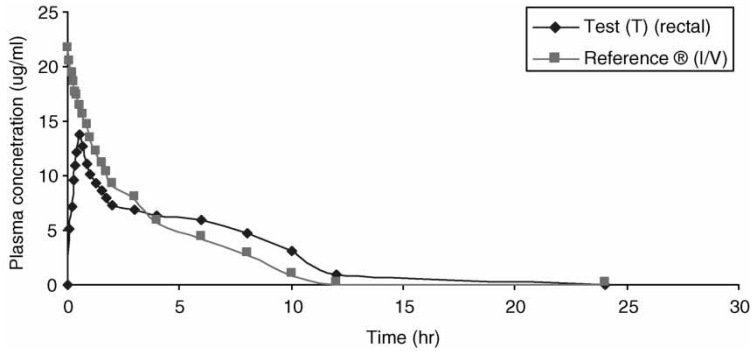

Figure 1. Mean theophylline concentration (mg/mL) fillowing IV and rectal administration of 500 mg minophylline.

Table 3. Pharmacokinetic parameters of theophylline after IV and rectal administration

Parameter	Test (T) Rectal	Reference (R) (I/V)
Dose (mg)	500 mg	500 mg
C_{max} ($\mu g/mL$)	14.0 ± 0.90	21.5 ± 2.10
T_{max} (hr)	0.5	—
AUC_{0-24}($\mu g \cdot ml/hr$)	67.4 ± 2.87	80.9 ± 4.805
$AUC_{(0-\infty)}$ ($\mu g/ml/hr$)	81.6	84.4
MRT (h)	4.5	—
$T_{1/2}$ el (hr)	1.934	1.726
K_{el}	0.358	0.4
$T_{1/2}$ ab (hr)	0.129	—

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of the rectally administered theophylline formulations is studied, so the food effects are not essential.

In this study, the peak theophylline serum concentration C_{max} (mean ± S.D) were 21.5 ± 2.10 $\mu g/mL$ for IV theophylline ampoules and 14.0 ± 0.9 $\mu g/mL$ for the test product theophylline suppository, as shown in Table 3.

The median peak time T_{max} was 0.5 hr (30 minutes) for theophylline PR (minophylline suppositories), which falls within the specified reported value for theophylline PR.[19]

The AUC (0–24 hr) value averaged 80.9 $\mu g \cdot hr/mL$ for the IV product and 67.4 $\mu g \cdot hr/mL$ for theophylline suppositories (Table 3). Although theophylline has a narrow therapeutic range and serum concentration should be monitored during therapy, the pharmaceutical product tested in this study, theophylline ethanoate of piperazine in a suppository form (minophylline supp. 500 mg, Alexandria Co.) could be used safely in asthmatic children in rural and desert areas, away from primary health care personnel.

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Received December 20, 2004
Accepted January 14, 2005
Manuscript 3153

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