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Effect of Truncated AUC Method on the Bioequivalence of High and Low Variable Drugs in Humans

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Abstract

The purpose of this study is to investigate the effect of using truncated area under the curve (AUC) method on the bioequivalence of high and low variable drugs with long half lives in healthy volunteers. Model low and high variable drugs used are Tamoxifen (CV < 30 % , with mean half live of > 100 hr) and Flouxitine Tamoxifen (CV > 30 % , with mean half live of > 45 hr) respectively. 24 healthy subjects participated in each study using cross over design. Individual disposition kinetic parameters of AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max} and half life were calculated by non-compartmental analysis using Kinetica program for both studies using all data points and using truncated AUC method. No statistical significant differences were obtained between parameters C_{max} and T_{max} suggesting similar rate of drug absorption in both methods, which is expected. However, AUC_{0-t}, $AUC_{0-\infty}$ and half life values were statistically lower ($P < 0.05$) in the truncated AUC method for both drugs, which is also expected since shorter time interval was used for calculations. In addition, the 90 % confidence intervals for log-transformed AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} falled within the accepted 80 – 125 % in both methods. These results are in agreement with the US FDA guidelines that recommend using truncated AUC method for long half life drugs, which saves time and money.

Keywords: truncated AUC, bioequivalence, tamoxifen, fluoxitine.

Introduction

Studies to measure bioavailability and/or establish bioequivalence of a product are important elements in support of the different drug applications and their supplements (Anon. 2003). Of special interest to generic drug companies are bioequivalence studies of long half live drugs that require sampling to long time intervals that can reach weeks. This adds more time and cost to generic drug companies, in addition to having human volunteers committed in longer studies.

Hence, it was recommend by US FDA that sample collection time be shortened but adequate to ensure completion of gastrointestinal transit (approximately 2 to 3 days) of the drug product and absorption of the drug substance. Cmax and a suitably truncated AUC can be used to characterize peak and total drug exposure, respectively (Anon. 2003). So, for drugs that demonstrate low intrasubject variability in distribution and clearance, an AUC truncated at 72 hours (AUC0-72 hr) can be used in place of AUC0-t or AUC0-∞. However, for drugs

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demonstrating high intrasubject variability in distribution and clearance, AUC truncation warrants caution (Anon. 2003).

The purpose of this study is to investigate the effect of using truncated area under the curve AUC) method on the bioequivalence of high and low variable drugs with long half lives in healthy volunteers as compared to total AUC method. Model low and high variable drugs used are Tamoxifen (intrasubject CV < 30 % , with mean half live of > 100 hr) and Fluoxitine (intrasubject CV > 30 % , with mean half live of > 45 hr) respectively (Nagip et al., 2005; Nagip et al., 2004; DiLiberti, 2004).

Material and Methods

1. Drugs and Reagents

Tests products: Flutin and Tamophar - Fluoxetine 20mg capsules and Tamoxifen 10 mg tablets respectively, Gulf Pharmaceutical Industries - Julphar, United Arab Emirates. Reference Products: Prozac capsules and Nolvadex tablets- Eli Lilly, UK. and Zeneca,UK respectively. All reagents used were obtained from Sigma Chemical Company, St. Louis, USA (Nagip et al., 2003; Anon. 2004).

2. Subjects and Study Design

Twenty-four healthy adult male volunteers participated in each of the two treatment, two sequence, two period cross-over studies. In Fluoxitine study, the mean age was 25.25±3.49 years, mean body weight 74.33±9.60 kg and mean height was 172.13±5.38 cm . In tamoxifen study, the mean age was 24.3±4.21 years, mean body weight 72.8±9.93 kg and mean height was 171.3±4.72 cm (Nagip et al., 2003; Anon. 2004).

The volunteers were instructed to abstain from taking any drug including over-the-counter (OTC) for 2 weeks prior to and during the study period. The study was performed according to the revised Declaration of Helsinki for bio-medical research involving human subjects and the rules of Good Clinical Practices. The study protocol was approved by Institutional Review Board (IRB) of Al-Mowasah Hospital, Amman, Jordan (Nagip et al., 2003; Anon. 2004).

3. Experimental and Assay Procedure

In each study, following a ten-hour overnight fast, oral dose of drug was administered orally followed by 240-ml water in parallel study. Blood samples were collected up to 360 and 480 hour after dosing of Fluoxitine and tamoxifen respectively. Samples were stored at –20 ^{0}C until analyzed by validated and sensitive HPLC methods (Nagip et al., 2003; Anon. 2004).

4. Data Analysis

4.1. Disposition Kinetics

Areas under plasma concentration-time curves (AUC_{0-t} , AUC0-∞), maximum concentration (C_{max}), time to reach maximum concentration (T_{max}) , elimination rate constant (Kel) and elimination half life were calculated by non-comparmental analysis for all subjects using Kinetica® software (Anon. 2000).

4.2. Statistical analysis

Descriptive statistics and confidence interval analysis for all disposition parameters were calculated using Microsoft Excell and Kinetica® software (Anon. 2000).

Results

Mean plasma concentrations for the two studies were shown in Figures 1 and 2. Disposition parameters and statistical analysis results were summarized in Tables 1 and 2.

Discussion

Per US FDA recommendation that for long half life drug products, sample collection time can be shortened but adequate to ensure completion of gastrointestinal transit (approximately 2 to 3 days) of the drug product and absorption of the drug substance. Hence, Cmax and a suitably truncated AUC can be used to characterize peak and total drug exposure, respectively (Anon. 2003). So, for drugs that demonstrate low intrasubject variability in distribution and clearance, an AUC truncated at 72 hours (AUC0-72 hr) can be used in place of AUC0-t or AUC0-∞ . However, for drugs demonstrating high intrasubject variability in distribution and clearance, AUC truncation warrants caution (Anon. 2003).

In this research, we investigated the effect of using truncated area under the curve AUC method on the bioequivalence of high and low variable drugs with long half lives in healthy volunteers as compared to total AUC method. Model low and high variable drugs used are Tamoxifen (intrasubject CV $<$ 30 % , with mean half live of $>$ 100 hr) and Fluoxitine (intrasubject CV $>$ 30 % , with mean half live of $>$ 45 hr) respectively (Nagip et al., 2005; Nagip et al., 2004; DiLiberti, 2004).

As shown in Tables 1 and 2 and according to t-test results at 0.05 level of significance, no statistical significant differences were obtained between parameters C_{max} and T_{max} suggesting similar rate of drug absorption in both methods, which is expected. However, AUC_{0-t} , $AUC_{0-\infty}$ and half life values were statistically lower ($P < 0.05$) in the truncated AUC method for both drugs, which is also expected since shorter time interval was used for calculations.

On the other hand, both methods yielded similar conclusions: bioequivalence of the test and reference products in both methods and for both low and high variable drugs.

These results are in agreement with the US FDA guidelines that recommend using truncated AUC method for long half life drugs, which saves time and money. It is therefore recommended to use truncated AUC instead of total AUC in bioequivalence studies of drugs with long half live, especially those showing low intrasubject variability.

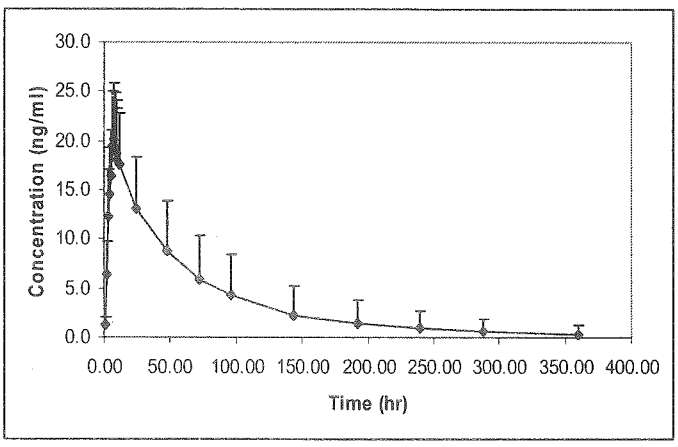

Figure 1. Fluoxitine Mean Plasma Profiles (⊦ SD) after 20 mg oral dose capsules to 24 healthy volunteers.

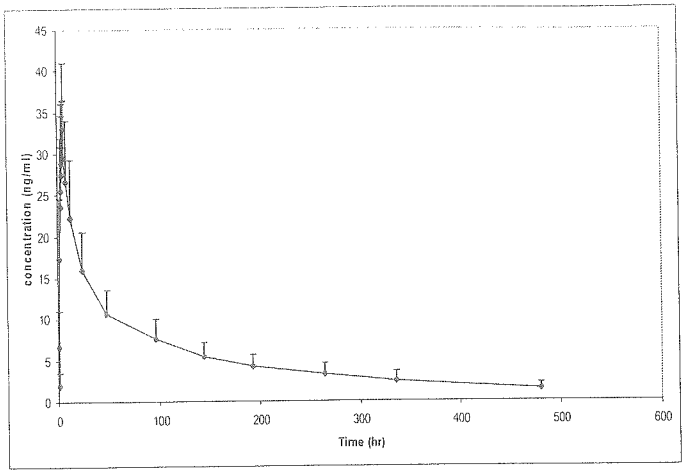

Figure 2. Tamoxifen Mean Plasma Profiles (+ SD) after 2X10 mg oral dose tablets to 24 healthy volunteers.

Table 1. Fluoxitine pharmacokinetic parameters (mean ± SD of untransformed data) and the 90 % confidence intervals of log-transformed data

AUC Method	Truncated AUC	Truncated AUC	Truncated AUC	Total AUC	Total AUC	Total AUC
Treatment	Test	Reference	T/R % limits	Test	Reference	T/R % limits
* AUC 0-t (ng/ml.hr)	761.00 ± 289.49	744.24 ± 286.32	96.5 - 108.9	1008.11 ± 416.98	1020.08 ± 440.87	94.6 - 106.4
* AUC 0-∞ (ng/ml.hr)	1125.72 ± 709.92	1073.78 ± 690.31	96.2 - 114.8	1098.92 ± 439.13	1101.46 ± 463.10	94.6 - 108.1
Cmax (ng/ml)	21.68 ± 5.40	22.56 ± 6.98	91.9 - 103.7	21.68 ± 5.40	22.56 ± 6.98	91.9 - 103.7
Tmax (hr)	6.83 ± 2.06	6.67 ± 2.35	-	6.83 ± 2.06	6.67 ± 2.35	-
* T 1/2 (hr)	37.32 ± 15.97	35.35 ± 14.84	-	46.27 ± 21.56	46.39± 22.61	-

* Significantly lower in truncated AUC method ($P < 0.05$)

Table 2. Tamoxifen pharmacokinetic parameters (mean ± SD of untransformed data) and the 90 % confidence intervals of log-transformed data.

AUC Method	Truncated AUC	Truncated AUC	Truncated AUC	Total AUC	Total AUC	Total AUC
Treatment	Test	Reference	T/R % limits	Test	Reference	T/R % limits
* AUC 0-t (ng/ml.hr)	1237.48 ± 336.45	1200.52 ± 293.41	98.1 - 106.5	2497.20 ± 684.16	2408.54 ± 684.46	100.1 - 107.6
* AUC 0-∞ (ng/ml.hr)	1992.85 ± 671.66	2044.43 ± 652.19	90.4 - 103.4	2664.10 ± 746.21	2556.77 ± 726.78	99.8 - 108.7
Cmax (ng/ml)	34.01 ± 8.26	32.27 ± 6.84	99.9 - 109.6	34.01 ± 8.26	32.27 ± 6.84	99.9 - 109.6
Tmax (hr)	5.63 ± 0.92	5.54 ± 0.62	-	5.63 ± 0.92	5.54 ± 0.62	-
* T 1/2 (hr)	67.16 ± 22.88	76.32 ± 25.62	-	114.88 ± 25.44	116.26± 20.12	-

* Significantly lower in truncated AUC method ($P < 0.05$)

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