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Effect of Truncated AUC Method on Drug Bioequivalence 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 different drugs in healthy volunteers. Model drugs used clopidogrel, glimepiride, losartan, carvedilol, carbamazepine, diazepam, donepezil, tramadol and repaglinide. 24 – 38 healthy subjects participated in each study using cross over design. Individual disposition kinetic parameters of areas under plasma concentrations (AUC_{0-t}, AUC_{00}), maximum concentration (C_{max}) and time to reach maximum concentration (T_{max}) were calculated by non-compartmental analysis using Kinetica program V 4.2 using all data points. In addition, truncated AUC was calculated up to median T_{max} of reference product. No direct correlation was shown between study results due to AUC truncation. The 90 % confidence intervals for log-transformed AUC_{0-t}, AUC_{00}, and C_{max} were not always in agreement with the 90 % confidence intervals for log-transformed truncated AUC. More over, the 90 % confidence intervals for log-transformed AUC_{0-t}, AUC_{00} passed in all drugs, while those for C_{max} failed in 3 drugs and for truncated AUC failed in seven drugs. This indicates that C_{max}, AUC_{0-t}, AUC_{00} rather than truncated AUC are more accurate to determine formulation differences, which is the goal of bioequivalence studies. It was shown that intra-subject variability is usually higher in truncated AUC as compared to variabilities of AUC_{0-t}, AUC_{00}, and Cmax. This rendered the sample size to be in adequate for calculation of tuncated AUC parameter, which explained the high failure rate in its limits. These results suggest not using truncated AUC to support the bioequivalence of drugs where rapid absorption is of importance as recommended by the draft EMEA guideline.

Keywords: Truncated AUC; Bioequivalence; EMEA

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 (1). Of special interest are bioequivalence studies of drugs that require rapid absorption and onset of action. Hence, it was recommended by the new draft EMEA guideline that 90 % confidence intervals for log-transformed areas under curve (AUC_{0-t}, AUC_{00}), maximum plasma concentration (C_{max}) and partial AUC, truncated at median time to reach maximum concentration (T_{max}) of the reference product, to fall between 80-125 % (1).

The purpose of this study is to investigate the effect of using truncated area under the curve AUC method on the bioequivalence of high (intra-subject variability > 30%) and low (intra-subject variability < 30%) variable drugs that require rapid absorption and onset of action in healthy volunteers (1). Model drugs used were clopidogrel, glimepiride, losartan, carvedilol, carbamazepine, diazepam, donepezil, tramadol and repaglinide. They were chosen based on clinical opinions about the need for rapid absorption and onset on action.

Materials and Methods

Drugs

Drug formulations were clopidogrel, glimepiride, losartan, carvedilol, carbamazepine, diazepam, donepezil, tramadol and repaglinide.

Subjects and Study Design

24 - 36 healthy adult male volunteers participated in each of a two formulation, two sequence, two period cross-over single oral dose studies. Sample size for each study was calculated based on reported intra-subject variability of pharmacokinetics primary parameters, considering $\alpha = 0.05$, the bioequivalence range (0.8-1.25) and to obtain a statistical power greater than 80%. All subjects had mean age, mean body weight and mean height. 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. Studies were performed according to the revised Declaration of Helsinki for bio-medical research involving human subjects and the rules of Good Clinical Practices. Also, study protocols were approved by Institutional Review Board (IRB) of IPRC.

Experimental and Assay Procedure

In each study, following a ten-hour overnight fast, single oral dose of each drug was administered followed by 240-ml water in each study. Blood samples were collected up to 24 - 240 hour after dosing. Samples were stored at –20°C until analyzed by validated and sensitive hplc or LC-MS methods.

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DRUG (N)	AUC_{0-t}	AUC_{00}	Result	C_{max}	Result	$^{\$}T_{max}$	AUC*	Result**
Clopidogrel (33 subjects)	97 88 – 107 (24%)	98 89 – 109 (23%)	Pass	92 82 – 104 (31%)	***Fail***	82-97 (16%)	88 – 140 (56%)	***Fail***
{ HYPERLINK "http://www.ncbi.nlm.nih.gov/sites/?te	101 94-108 (17%)	99 92-105 (17%)	Pass	123 111- 134 (23%)	***Fail***	43-72 (115%)	134-174 (32%)	***Fail***
Losartan (36 subjects)	102 99-108 (12%)	102 98-107 (11%)	Pass	87 74-102 (40%)	***Fail***	101-153 (99%)	50-144 (128%)	***Fail***
{ HYPERLINK "http://www.ncbi.nlm.nih.gov/sites/?te	104 89-104 (19%)	104 91-105 (18%)	Pass	103 87-107 (26%)	Pass	86-109 (36%)	75-128 (66%)	***Fail***
Carbamazepine (24 subjects)	98 94-104 (10%)	-	Pass	105 100-109 (9%)	Pass	90-109 (99%)	104-124 (17%)	Pass
Diazepam (24 subjects)	94 83-105 (22%)	*102* 95-109 (13%)	Pass	*91* 81-103 (24%)	Pass	99-126 (16%)	55-81 (40%)	***Fail***
Donepezil (24 subjects)	*99* 94-101 (7%)	-	Pass	*101* 95-106 (10%)	Pass	76-107 (92%)	95-117 (20%)	Pass
Tramadol (24 subjects)	*96* 90-103 (12 %)	*97* 91-103 (12 %)	Pass	*102* 95-108 (12 %)	Pass	56-94 (57%)	102-133 (27 %)	***Fail***
Repaglinide (36 subjects)	*107* 99-116 (20 %)	*106* 97-115 (21 %)	Pass	*98* 86-111 (31 %)	Pass	51-90 (99%)	119-183 (54 %)	***Fail***

*AUC Truncated at Median Tmax of Reference Product.
**Truncation Result
- No AUC_{00} calculated since study truncated at 72 hours.
$ Tmax parameter was not log transformed.

Table 1: Point estimates and 90 % confidence intervals (% Intra-subject variability) of primary pharmacokinetic parameters after log-transformation.

Data Analysis

Analysis were done on parent drugs only not on metabolites. Areas under plasma concentrations (AUC_{0-t}, AUC_{00}), maximum concentration (C_{max}), time to reach maximum concentration (T_{max}) and truncated AUC were calculated by non-compartmental analysis for all subjects using Kinetica® software (2). Confidence interval analysis for log-transformed AUC_{0-t}, AUC_{00}, C_{max} and partial AUC, truncated at median T_{max} of the reference product were calculated using Kinetica® software (2).

Results and Discussion

Confidence interval analysis results were summarized in Table 1. Per the new draft EMEA guideline, the 90 % confidence intervals for log-transformed AUC_{0-t}, AUC_{00}, C_{max} and partial AUC, truncated at median T_{max} of the reference product, are to fall between 80-125 % (1). In this research, we investigated the effect of using truncated area under the curve method on the bioequivalence of different drugs in healthy volunteers. T_{max} is a good indicator of continued absorption of a drug from the GIT, though absorption may continue afterwards. However and as shown in table 1, T_{max} variability was high in most drugs with confidence limits felled outside acceptance range. Yet, T_{max} is secondary parameter and final bioequivalence conclusion is not based on T_{max}.

As shown in table 1, the 90 % confidence intervals for log-transformed AUC_{0-t}, AUC_{00}, and C_{max} were not always in agreement with the 90 % confidence intervals for log-transformed truncated AUC. Intra-subject variability of primary original parameters were as expected, indicating adequate sample size. However, point estimates and confidence intervals of C_{max} for the first 3 drugs indicated formulation differences. More over, the 90 % confidence intervals for log-transformed AUC_{0-t}, AUC_{00} passed in all drugs, while those for Cmax failed in 3 drugs and for truncated AUC failed in seven drugs. This indicates that C_{max}, AUC_{0-t}, AUC_{00} rather than truncated AUC are more accurate to determine formulation differences, which is the goal of bioequivalence studies. It was shown that intra-subject variability is usually higher in truncated AUC as compared to variabilities of AUC_{0-t}, AUC_{00}, and C_{max}. This rendered the sample size to be in adequate for calculation of tuncated AUC parameter, which explained the high failure rate in its limits. Actually, truncated AUC parameter is not mandatory but only recommended according to US FDA guideline (3). These results suggest not using truncated AUC to support the bioequivalence of drugs where rapid absorption is of importance as recommended by the draft EMEA guideline.

Conclusion

C_{max}, AUC_{0-t}, AUC_{00} rather than truncated AUC are more ac-

curate to determine formulation differences, which is the goal of bioequivalence studies, due to higher intra-subject variability in truncated AUC. These results suggest not using truncated AUC to support the bioequivalence of drugs where rapid absorption is of importance as recommended by the draft EMEA guideline.

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