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TITLE

EFFECT OF TRUNCATED AUC METHOD ON DRUG BIOEQUIVALENCE IN HUMANS: AN EMEA DRAFT GUIDELINE EVALUATION

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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 (AUC0-t , AUC00), maximum concentration (Cmax) and time to reach maximum concentration (Tmax) 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 Tmax of reference product. No direct correlation was shown between study results due to AUC truncation. The 90 % confidence intervals for log-transformed AUC0 -t, AUC00, and Cmax were not always in agreement with the 90 % confidence intervals for log-transformed truncated AUC. More over, the 90 % confidence intervals for log-transformed AUC0 -t, AUC00 passed in all drugs, while those for Cmax failed in 3 drugs and for truncated AUC failed in seven drugs. This indicates that Cmax, AUC0 -t, AUC00 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 AUC0 -t, AUC00, 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.