PHARMACOKINETICS AND BIOEQUIVALENCE EVALUATION OF TWO PRODUCT OF DIGOXIN 0.25mg TABLETS AFTER A SINGLE DOSE ADMINISTRATION IN HEALTHY VOLUNTEERS: AN OPEN, CROSSOVER RANDOMISED BIOEQUIVALENCE CLINICAL TRIAL.

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Introduction: Digoxin is a cardiotonic drug used as an antiarrhythmic, in atrial fibrillation. The main aims of our study were to evaluate the pharmacokinetic of two different formulations of digoxin 0.25 mg and to assess the bioequivalence.

Settings: This was a randomized, single-centre, single-dose, crossover study. Forty young healthy volunteers were enrolled. Each participant received a single oral dose of digoxin 0.25 mg, and the wash-out period was 14 days. Two market formulations containing digoxin were studied and designed as: product test, which is Digoxina test tablets 0.25 mg and product reference was Digoxina Teofarma reference tablets 0.25 mg, both of Laboratorios Teofarma S.r.L. Digoxin serum concentrations were determined by HPLC.

Methods: The pharmacokinetic parameters $C_{\text{max}}$ and $T_{\text{max}}$ were obtained directly from digoxin serum concentrations; AUC $0-\infty$ (as the addition of $AUC_{[0-t]} + Ct/k$) was calculated by the linear trapezoidal rule for both digoxin. The pharmacokinetics parameters AUC $0-\infty$ and $C_{\text{max}}$ were tested for bioequivalence after log transformation of data.

Results: Following administration of product test and product reference, the mean maximum serum concentration ($C_{\text{max}}$) was 1.64 ± 0.56 ng/ml and 1.76 ± 0.54 ng/ml respectively. These values were similar in both formulations (p < 0.05). The mean ratio of $C_{\text{max}}$ “test over reference” was calculated as of 92.07 with 90% confidence intervals of 84.82-99.93, that is within the 80 to 125% interval proposed by the current regulations of the EMEA for bioequivalence. There was no significant difference in time to maximum concentration median $T_{\text{max}}$, it was 1h for both formulations. 90% confidence intervals of Tmax calculated according to the Hauschke non parametric method were 83.5 to 116. The overall bioavailability judged from AUC $0-72h$ was found mean value (±SD) of Digoxina test was 21.06 (±3.96) ng/mL and Digoxina reference was 20.49 (±3.98). The ratio between logarithmically transformed means of Digoxina test and Digoxina Teofarma reference was 103.04 with a 90% CI of 97.36-109.06, that is within the 90 to 111% interval proposed by the current regulations of the EMEA for bioequivalence for drugs with narrow therapeutic range.

Conclusion: Both formulations of digoxin were found to be bioequivalents and therefore interchangeable.