



EVALUATION BY ANCOVA OF COMPARATIVE BIOAVAILABILITY OF TWO ORAL FORMULATIONS OF CLOZAPINE IN STEADY STATE IN SCHIZOPHRENIC VOLUNTEERS UNDER A DIFFERENT DOSES REGIME.

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The objective of the study was to evaluate the relative bioavailability of two oral formulations of clozapine (test and reference) in steady state in schizophrenic volunteers under a doses regime between 200 and 800 mg.

The study was conducted in an open, randomized, multiple dose, crossover balanced design in steady state.

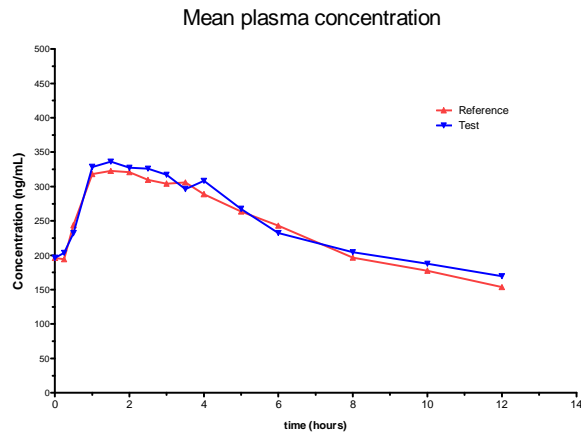
24 hours-confinements were made at the facilities of a psychiatric institution, in 3 separate confinement units with a difference of two weeks. Total running time was 28 days.

17 patients affected by refractory schizophrenia finished the study. They were receiving a stable daily dose of clozapine administered in equally divided multiples of 100 mg doses at 12-hour intervals for at least 3 months and were stabilized.

Administration of clozapine was done orally during 15 days for each period of the study. Pharmacokinetic samples were taken during steady state (3 samples) and during confinement (15 samples).

Plasma samples were obtained over a 12-hour interval for PK curves. Clozapine concentrations were analyzed by combined liquid chromatography and tandem mass spectrometry (LC-MS-MS) using a selected ion monitoring method.

Parameter	Ratio (T/R)	90% CI	ISV(%)	Power
C_{max}	107.198	(99,1725; 115,8721)	12.79	98.9%
ASC_{0-t}	101.694	(93,4996; 110,6061)	13.82	97.7%
C_{max}*	107.198	(99,2088; 115,8297)	12.73	98.9%
ASC_{0-t}*	102.682	(94,3768; 111,7185)	13.87	97.6%



For each patient, two linear regression curves were adjusted: one for each steady state period.

Based on results we can conclude that it exists bioequivalence in terms of the rate and extension of absorption of the two clozapine formulations, and that both products can be considered equally effective in medical practice.