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Population pharmacokinetics of oral cyclosporin in Iranian bone marrow transplant patients: comparison of different absorption models

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Background and Aims: Substantial inter- and intra-individual pharmacokinetic variability and narrow therapeutic index of cyclosporin justify its dose individualization through AUC-based monitoring. Population pharmacokinetic parameters need to be determined before limited sampling strategies by Bayesian estimation of AUC could be developed. Usually cyclosporin absorption kinetics could not adequately be described by first-order absorption model. In the current study population pharmacokinetics of cyclosporine was assessed using different absorption models in Iranian bone marrow transplant patients.
Methods: Steady-state cyclosporine blood concentrations were measured using direct radioimmunoassay method within a dosing interval (12 hours post administration) in 35 allogeneic bone marrow transplant patients receiving 238(±117) mg of cyclosporine twice daily. A one-compartment disposition with different absorption models (zero and first order with and without lag time, gamma distribution and Erlang) was fitted to blood concentration data using non-linear mixed effect modeling approach with Monolix 4.1.2 software. A proportional error model was used to describe residual variability. Comparison of different models was carried out by checking diagnostic plots and goodness-of-fit factors.
Results: Gamma absorption model best described the data with estimated (CV%) trough concentration (C0), one-compartment disposition parameter(A), absorption parameters (b and a) and elimination constant (k) of 109 ng/mL (12%), 0.0040 (L-1) (10%), 2.84 (h-1) (7%), 2.94 (7%) (dimensionless) and 0.336 (h-1) (3%), respectively. The corresponding inter-individual variabilities for the parameters were 68, 54, 25, 23 and 12%. The estimated residual variability was 13%.
Conclusions: Pharmacokinetics of oral cyclosporine in bone marrow transplant patients at steady-state can be adequately described by a one-compartment model with gamma distribution absorption.

Keywords: Cyclosporin; Bone marrow transplantation; Population pharmacokinetics; Absorption models