Cyclosporine therapeutic window evaluation by Chebyshev's inequality method in kidney recipients

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Inadequate cyclosporine blood levels may cause acute rejection in transplanted renal graft, and its increase is accompanied with graft toxicity. These reasons settle that many years cyclosporine was monitored by determining through level, latter 2-hour peak level which was determined as not a suitable method (1). And mostly through level and 2-hour peak are used for counting area under the concentration time curve as the single points (2). The aim of this study was to identify cyclosporine therapeutic range for kidney recipients using 3-point limited sampling strategy.

Methods. The cyclosporine exposure level was based on the calculation of the mean area under the concentration-time curve AUC $_{(0\text{-}12).}$ The AUC $_{(0\text{-}12)}$ was estimated using a Bayesian estimator and a 3-point limited sampling strategy. Cyclosporine exposure levels were obtained from 3 blood samples: 0, 1, and 3 hours post–dose; and analyses were performed using a liquid chromatography-tandem mass spectrometry method. The therapeutic window of cyclosporine was calculated by the Chebyshev's inequality method with a 99% guarantee (α=0.01) using the IBM SPSS Statistics 20 software.

*Results.*It was found that the therapeutic window of cyclosporine estimated by the Chebyshev's inequality method and put on the AUC $_{(0\text{-}12)}$ exposure lies in the ranges from 2.84–3.13 mg h/L with the 99% confidence (the average AUC $_{(0\text{-}12)}$ exposure is 2.99 mg h/L, maximum 5.43 mg h/L, and minimum 1.39 mg h/L) for the patients with the target AUC $_{(0\text{-}12)}$ exposure of 3.8 mg h/L (post-transplantation time >1 year). The therapeutic window of cyclosporine differs in different post-transplantation time groups: the estimated AUC exposure range in the group of patients who have a graft longer than 5 years is 2.70–2.98 mg h/L (the average AUC $_{(0\text{-}12)}$ exposure is 2.84 mg h/L, maximum 4.38 mg h/L. and minimum 1.39 mg h/L), and the estimated AUC exposure range in the group of patients who have a graft for 1–5 years is 3.05–3.75 mg h/L (the average AUC $_{(0\text{-}12)}$ exposure is 3.60 mg h/L, maximum 5.43 mg h/L, and minimum 1.65 mg h/L).

Conclusions. Chebyshev's inequality could be an appropriate and more precise method to determine the therapeutic window for CsA in kidney recipient**s** than the target AUC $_{(0\text{-}12)}$ value, but further studies should be conducted to evaluate patients with postoperative time < 1 year.

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