Cyclosporine, metabolites and calcineurin phosphatase

Clinical and experimental studies

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ABSTRACT

The calcineurin inhibitors, cyclosporine and tacrolimus, have been the cornerstone of immunosuppression for over 20 years. However, the major drawback of these drugs is primarily related to their variable and unpredicted pharmacokinetics and narrow therapeutic index. Consequently, therapeutic drug monitoring became a necessity. In the first study we compared the pharmacokinetic properties of the two drugs under equivalent dosing. It was generally believed that part of the observed differences between drugs could be attributed to the fact that in clinical settings tacrolimus is administered at doses up to 50-fold lower than cyclosporine. However, this was not supported from our results. Despite the equivalent dosing no similarities or correlations could be identified between the two drugs. The second clinical study of this thesis focused on cyclosporine and the potential immunosuppressive action of its metabolites. We utilized a novel pharmacodynamic assay that estimates the inhibition of calcineurin phosphatase. We studied the role of metabolites and calcineurin inhibition in relation to the new monitoring trend of C2 (two-hours post-dose). Additionally, we determined the concentration of cyclosporine (plus/minus metabolites) with three different assay methods and how they correlate with calcineurin phosphatase inhibition. The most interesting of our findings was the fact that CaN inhibition displayed stronger negative correlation with assays which take metabolites into consideration, in comparison with the more drug-specific ones. Until conclusive evidence is available, we cannot exclude that metabolites monitoring could potentially contribute to more precise therapeutic drug monitoring of CsA. Additionally, we confirmed that regardless the assay employed, at two-hours post-dose the relative metabolites influence is less, making this time-point more assay-independent compared with trough levels.

Minimum information is available about the "behaviour" of calcineurin during allograft transplantation and acute rejection in non-immunosuppressed organisms. A deeper insight on the enzyme's course during the rejection process can provide us with more knowledge towards a better understanding of the immune response and subsequently more optimal immunosuppressive strategies. The experimental studies of this thesis consisted of the development and establishment of the heterotopic-cervical-heart transplantation-rat-model and subsequently study of calcineurin's temporal profile during acute rejection. We have shown that the activity of calcineurin is not significantly altered during acute allograft rejection in peripheral blood and in spleen-isolated mononuclear cells.

This thesis has tried to shed light on a number of problematic issues regarding cyclosporine, its metabolites and calcineurin phosphatase. We have performed pharmacokinetic and pharmacodynamic studies during various clinical and experimental settings. We believe we have gained a number of new and interesting insights and at the same time raised a number of intriguing questions which warrant further investigation.