Influence of cyclosporin dosing schedule on receptor occupancy in bone marrow transplantation: analysis with a PBPK-PD model

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Introduction and objectives

In bone marrow transplantation, cyclosporin is administered to prevent graft-versus-host disease (aGVHD), which occurs mainly in three organs (skin, intestines and liver).

This immunosuppressant drug acts on T lymphocytes and has some nephrotoxicity. Because its disposition depends on several sources of nonlinearity [1], organ exposure may be higher after intermittent infusions (II) than after continuous infusions (CI).

Methods

A physiologically-based pharmacokinetic model was developed in order to estimate cyclosporin exposure in interstitial fluid (space of T lymphocytes) of the target organs of aGVHD and in intracellular space of kidneys, because of nephrotoxicity (figure 1).

These simulations were used to compare exposures and receptor occupancies (RO) of pediatric patients that received cyclosporin either by II or CI. The fractional receptor occupancy (RO) was calculated as:

$$RO(t) = \frac{Cu(t)}{IC_{50} + Cu(t)}$$

where Cu(t) is the unbound concentration of cyclosporin, and IC_{50} its half-maximal inhibitory unbound concentration.

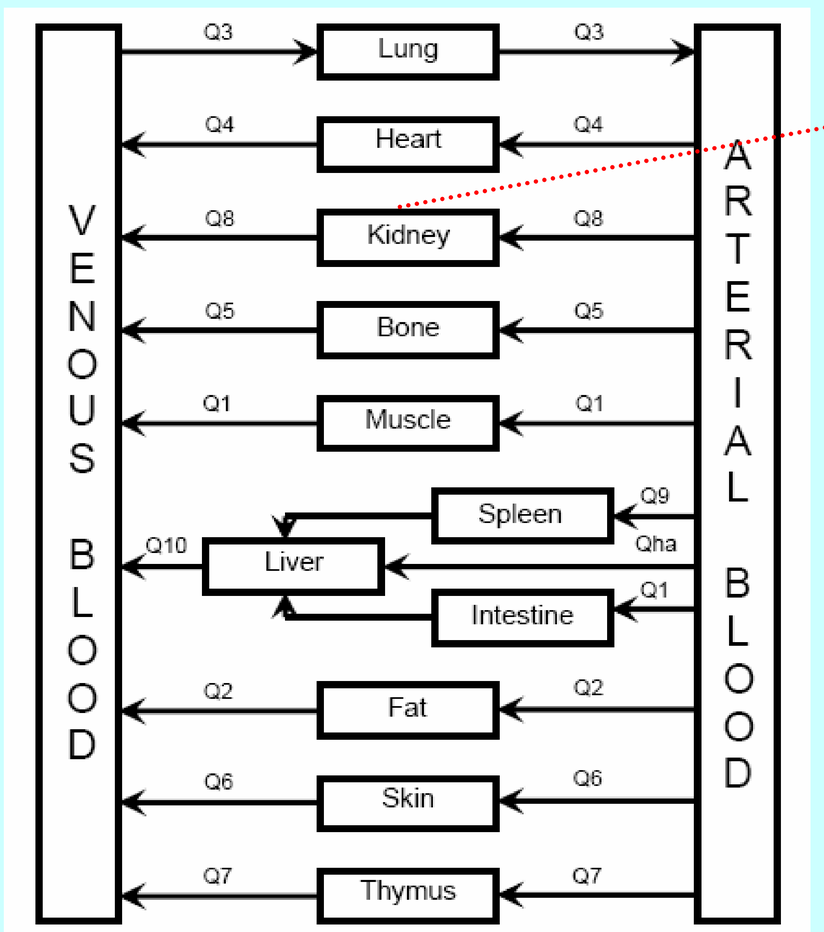
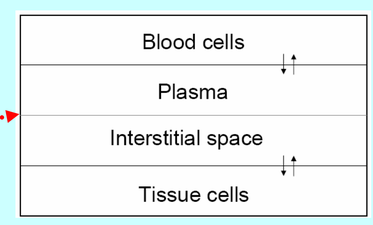


Figure 1. Global PBPK model of cyclosporin



The typical value of total IC_{50} is 200 µg/L (depending on the measured effect, the estimates of total IC_{50} varies from 40 to 440 µg/L), while the typical value of blood unbound fraction of cyclosporin is 0.05. Therefore, the IC_{50} of unbound concentration of cyclosporin in blood was fixed at 10 µg/l.

The area under the receptor occupancy versus time curves (AUC_{RO}; from 0 to 24 h after the onset of treatment and at steady state) was calculated. The relevant biological parameters and their interindividual variability were based on a clinical study in 2 groups of pediatric patients that received cyclosporin either by II (n = 31) or CI (n = 30) at an initial dose of 3 mg/kg/day.

Results

Simulations showed that the exposure to cyclosporin in the interstitial fluid of aGVHD target organs was greater at day 1 after II than after CI (mean area under the curve (AUC) of 2.65 *vs* 2.39 h.mg/l). At steady state, there was no difference.

By contrast, the exposure to cyclosporin in the intracellular space of kidney was greater at day 1 and at steady-state after CI than after II (mean AUC of 129 *vs* 112 h.mg/l, figure 2).

Regarding RO, AUC_{RO} in interstitial fluid of aGVHD target organs and in kidney cells at day 1 and at steady state were greater after CI than after II (mean AUC AUC_{RO} of 14.7 *vs* 12.9 h.mg/l, figure 3).

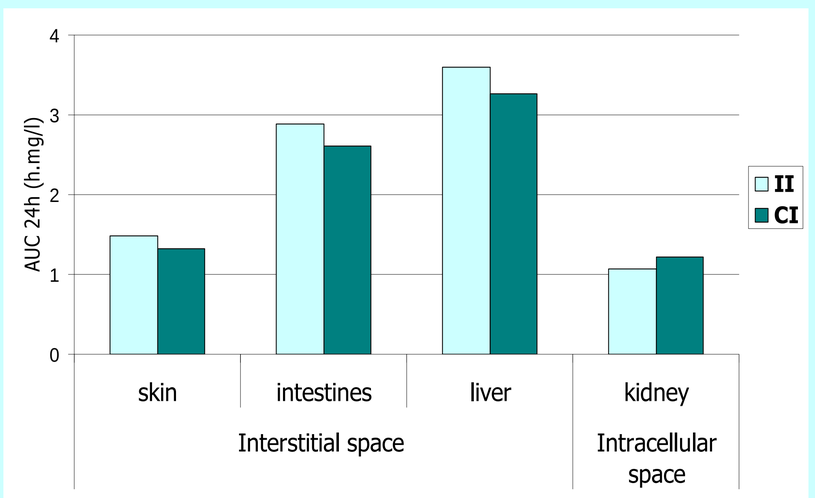


Figure 2. Exposure to cyclosporin at day 1 after II and after CI

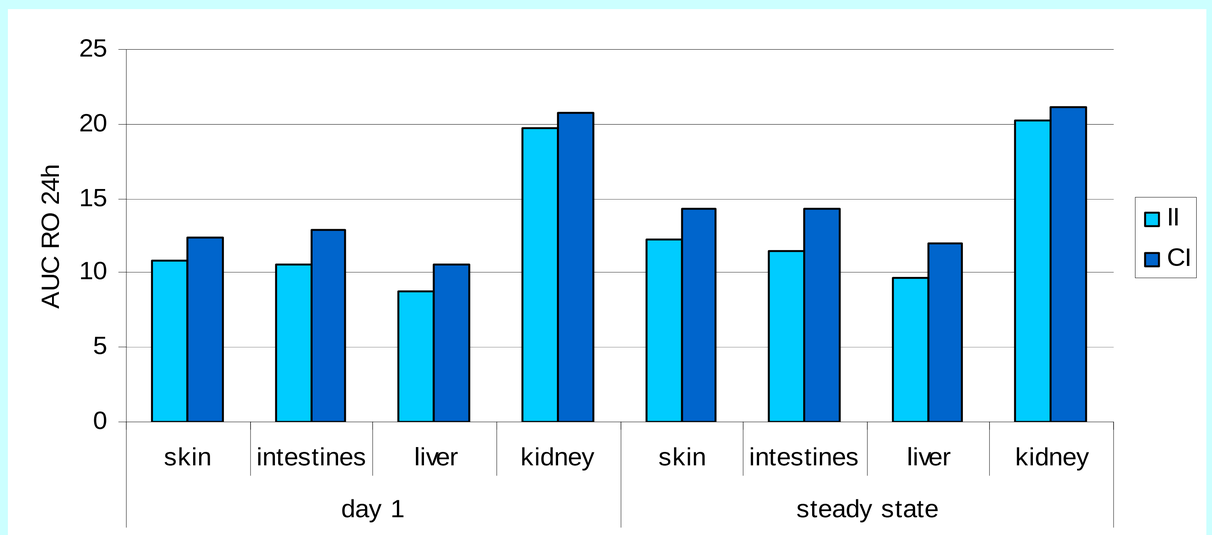


Figure 3. AUC_{RO} after II and after CI

The therapeutic index, estimated as :

$$\frac{AUC_{RO\,blood}}{AUC_{RO\,kidney}}$$

was 0.62 with CI *versus* 0.52 with II.

Conclusion

Regarding organ exposure, II may be more favorable than CI because of a greater exposure in target organs of GVHD and a lower exposure in kidney cells. However, concerning the receptor occupancies, the therapeutic index was slightly better after CI than after II.

Further analyses are required to determine whether cyclosporin efficacy and toxicity depends on the average concentration or on the entire concentration profile in the interstitial or intracellular space of target organs. Ultimately, this information will contribute to determinine the optimal mode of cyclosporin administration.

Reference

[1] Tanaka C, Kawai R, Rowland M. J Pharmacokinet Biopharm 1999;27(6):597-623.