

Pharmacokinetic and Pharmacodynamic Characteristics of Cyclosporin A in Rats and Rabbits

Yong-Bok Lee

College of Pharmacy and Institute of Bioequivalence and Bridging Study, Chonnam National University, Gwangju, Korea, 500-757

Cyclosporin A (CSA) is a poorly water-soluble cyclic peptide comprising 11 amino acids. It inhibits T-lymphocyte function that plays an important role in the induction of immune response. The potent immunosuppressive activity of CSA has been used for the prevention of rejection following transplantation of liver, kidney and bone marrow, etc. The use of CSA has been often limited by several disadvantages including low bioavailability, narrow therapeutic window, nephrotoxicity, hepatotoxicity and neurotoxicity. Moreover, CSA injection is limited to patients who are unable to take the oral preparations, because it has a risk of anaphylactic shock and nephrotoxicity due to Cremophor EL[®], a solubilizing agent used in the commercial intravenous formulation. Owing to above mentioned disadvantages of commercial products, there is a great interest in the development of the alternative dosage forms.

Several oral and intravenous formulations of CSA including liposome, fat carrier, microsphere, and microemulsion have been investigated to improve the therapeutic efficacy and to reduce the toxicity. It has been reported that CSA-containing microsphere and liposome showed the sustained depot characteristics, but liposome has the several problems during the storage such as phospholipid hydrolysis, decomposition of encapsulated drug, separation of drug from liposome, sedimentation, aggregation and fusion of liposomes. In case of intravenous formulation, nephrotoxicity caused by CSA or Cremophor EL[®] could be avoided by using a soybean oil based fat emulsion carrier.

In this study, we prepared CSA O/W-emulsion that can be used for both intravenous and oral administration using soybean oil. We also evaluated the pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of the prepared CSA O/W-emulsion in rats and rabbits and compared them with those of two commercial products, CIPOL Inj.[®] for intravenous administration and Sandimmun Neoral[®] for oral administration.

Assay: The concentration of CSA in whole blood was assayed by using the TDxFLx[®] (Abott Laboratories, Abott Park, U.S.A.). We performed the count of total lymphocyte population by an automated hemocytometer (Coulter STKS, Coulter Electronics Inc., Northwell, England).

Animal Experiments: Male Sprague-Dawley rats weighing 200-350 g and male white rabbits weighing 1.5-2.5 kg were used. All animals were fasted overnight but were allowed free access to water. In the rats, the oral administration (10 mg/kg) was performed using oral zonde while the left femoral vein was used for intravenous dosing (10 mg/kg). Each rat was randomly subjected to only four blood samplings in order to prevent the over-loss of blood. In the rabbits, the oral doses (10 mg/kg) were administered using catheter while the marginal ear vein was used for intravenous dosing (10 mg/kg). The blood samples (about 1 ml) were withdrawn via the left femoral artery of rat and central ear artery of rabbit with the aid of implanted catheter into the EDTA tube at 0.5, 1, 2, 3, 4, 6, 8, 12 and 24 (36 and 48) hours. The samples were stored at 4°C until assay.

PK/PD evaluation: The PK and PD parameters were evaluated by WinNonlin program on the basis of open two compartment and indirect response model.

Fig. 1 shows the mean whole blood concentration-time profiles of CSA after intravenous administration (A) of O/W-emulsion and CIPOL Inj.[®], and oral administration (B) of O/W-emulsion and Sandimmun Neoral[®] to rabbits at 10 mg/kg (n=3-5). The lymphocyte fraction-time profiles for various CSA formulations are shown in Fig. 2. In rabbits, total clearance (CL_t) was increased after intravenous administration of CSA O/W-emulsion compared with intravenous administration of CIPOL Inj.[®]. In case of oral administration, AUC and bioavailability of O/W-emulsion were not significantly different ($P > 0.05$) from those of Sandimmun Neoral[®], however, MRT and T_{max} of O/W-emulsion were significantly increased ($P < 0.05$). There were no significant differences in the area between the baseline and effect curves (ABEC) among these formulations ($P > 0.05$), but the pharmacodynamic availability (F_{PD}) of CSA O/W-emulsion was 5.51 fold higher than that of CIPOL Inj.[®] and was significantly greater than that of Sandimmun Neoral[®] ($P < 0.05$).

The mean whole blood concentration-time profiles of CSA after intravenous administration (10 mg/kg) of CSA O/W-emulsion and CIPOL Inj.[®], and oral administration (10 mg/kg) of CSA O/W-emulsion and Sandimmun Neoral[®] to rats are shown in Fig. 3. And also, the mean lymphocyte fraction-time curves in rat whole blood following intravenous (10 mg/kg) and oral (10 mg/kg) administration of CSA formulations are shown in Fig. 3. In rats, the area under the concentration-time curve (AUC), terminal half-lives (T_{1/2}), CL_t and relative bioavailability (F) after intravenous administration of CSA O/W-emulsion were not significantly different from those of intravenous administration of CIPOL Inj.[®] ($P > 0.05$). In oral administration, AUC and C_{max} of CSA O/W-emulsion were significantly decreased ($P < 0.05$), while T_{1/2}, MRT, T_{max} and F were not significantly different ($P > 0.05$) from those of Sandimmun Neoral[®]. However, the ABEC and pharmacodynamic efficiency (EFF) of CSA O/W-emulsion were significantly greater than those of references regardless of routes of administration ($P < 0.05$). The F_{PD} of CSA O/W-emulsion was 1.79 fold and 2.13 fold higher than that of CIPOL Inj.[®] and Sandimmun Neoral[®] ($P < 0.05$), respectively.

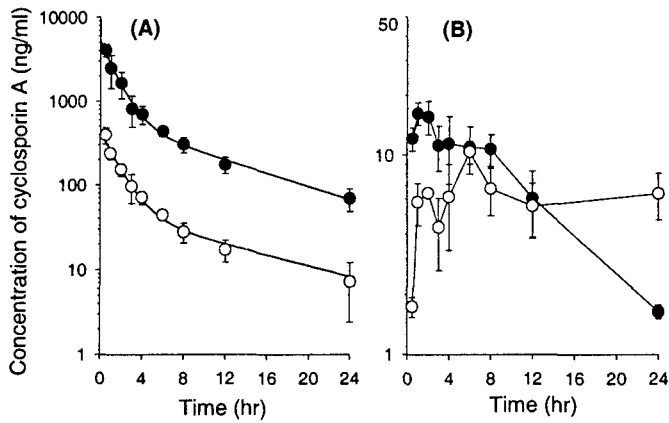


Fig. 1. (A) The whole blood concentration-time profiles of cyclosporin A after intravenous administration (10 mg/kg) of CIPOL Inj.[®] (●) and CSA O/W-emulsion (○) to rabbits. The points are the experimental data (\pm S.E.), the lines are the pharmacokinetic model fitted curves; (B) the whole blood concentration-time profiles of cyclosporin A after oral administration (10 mg/kg) of Sandimmun Neoral[®] (●) and O/W-emulsion (○) to rabbits. Each point represents the mean \pm S.E. (n=3~5).

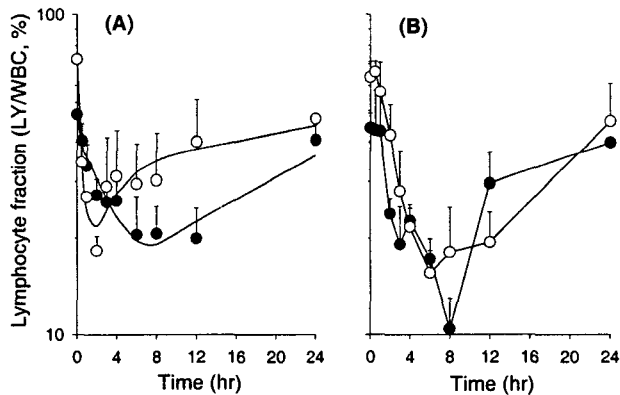


Fig. 2. (A) The pharmacodynamic profiles of cyclosporin A after intravenous administration (10 mg/kg) of CIPOL Inj.[®] (●) and CSA O/W-emulsion (○) to rabbits. The points are the experimental data (\pm S.E.), the lines are the model fitted curves; (B) the whole blood concentration-time profiles of cyclosporin A after oral administration (10 mg/kg) of Sandimmun Neoral[®] (●) and O/W-emulsion (○) to rabbits. Each point represents the mean \pm S.E. (n=3~5).

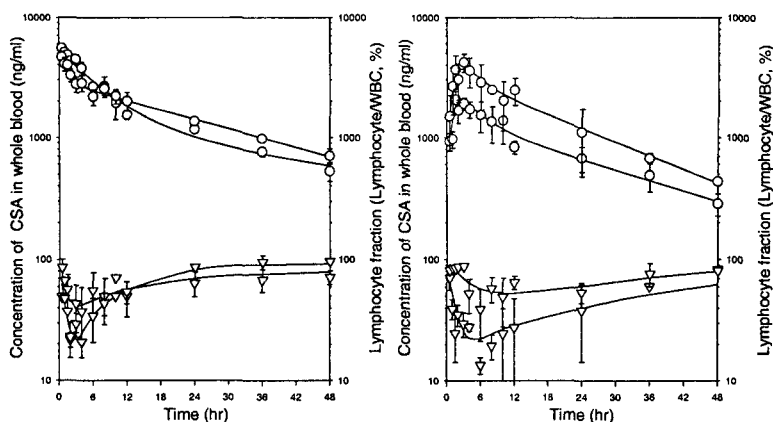


Fig. 3. Mean whole blood concentration of CSA (● for CSA O/W-emulsion and ○ for CIPOL Inj.®) and lymphocyte fraction (▼ for CSA O/W-emulsion and ▽ for CIPOL Inj.® and Sandimmun Neoral®)-time profiles after intravenous administration (10 mg/kg) of CSA O/W-emulsion and CIPOL Inj.® (left panel) and after oral administration (10 mg/kg) of CSA O/W-emulsion and Sandimmun Neoral® (right panel) to rats. The points are experimental data (mean ± S.E., $n=4$) and the lines are pharmacokinetic/ pharmacodynamic model fitted curves in whole blood.

The species-related changes in the PK/PD parameters of CSA between rats and rabbits may be due to differences in their absorption, metabolic capacity and sensitivity of lymphocyte for CSA. Eut, all the results suggest that CSA O/W-emulsion may be used as such formulations for oral or intravenous administration of CSA.

References

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