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Comparative Pharmacokinetics of Cyclosporine and NVa^2-Cyclosporine in Dogs

R. Venkataramanan, **S. Todo**, **I. Zaghloul**, **S. Lynch**, **I. Kam**, **R.J. Ptachcinski**, **G.J. Burckart**, and **T.E. Starzl**
Schools of Pharmacy and Medicine, University of Pittsburgh

NVA^2-Cyclosporine (NVa^2-CsA) is a structural analogue of cyclosporine (CsA) with marked immunosuppressive activity.[1–3] NVa^2-CsA appears to be less nephrotoxic when compared with CsA in rodent models.[4] During efficacy studies in canine orthotopic liver allografts, equal doses of NVa^2-CsA and CsA produced significantly different blood concentrations. This observation prompted us to evaluate the comparative pharmacokinetics of NVa^2-CsA and CsA in dogs.

Methods

Male beagle dogs weighing between 11 to 15 kg received in a sequential manner CsA or NVa^2-CsA intravenously as an infusion over one hour (2 mg/kg) or orally (20 mg/kg) as an olive oil solution on four separate occasions. Drug solutions were administered after an overnight fast while water was allowed at libitum. Heparinized blood samples were obtained at 0, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, and 72 hours after drug administration. Whole blood concentrations of NVa^2-CsA and CsA were measured by high-performance liquid chromatography (HPLC) as described earlier.[5,6] Pharmacokinetic parameters were calculated according to standard procedures.

Results

Following intravenous administration, the blood levels of CsA and NVa^2-CsA declined in a multiexponential manner. The mean terminal disposition rate constant of NVa^2-CsA (0.073 hours^{-1}) was not significantly different from the mean disposition rate constant of CsA (0.119 hours^{-1}). There were also no significant differences in the steady state volume of distribution of these two compounds. However, the mean (±SD) clearance of NVa^2-CsA (5.9 ± 0.7 mL/min/kg) was significantly smaller compared with the clearance of CsA (8.4 ± 1.7 mL/min/kg). There was also less variability in the clearance of NVa^2-CsA as compared with the clearance of CsA.

Following oral administration of equal doses, the blood concentrations of CsA were consistently higher than that of NVa^2-CsA. The time for peak blood concentrations was not significantly different for the two compounds. However, the mean (±SD) oral bioavailability of NVa^2-CsA was 8.4 ± 2.6% as compared with 18.2% ± 3.3% for CsA.

Address reprint requests to R. Venkataramanan, PhD, Clinical Pharmacokinetics Laboratory, 807 Salk Hall, University of Pittsburgh, Pittsburgh, PA 15261.

Discussion

NVa^2-CsA and CsA are produced by the fungus *Tolypocladium inflatum Gams*. NVa^2-CsA differs from CsA in its structure in that the amino acid norvaline replaces the α-aminobutyric acid in position 2 of the cyclic polypeptide. This small change in the structure has preserved the immunosuppressive activity of the compound in rats.[3] Recently, we have shown that in canine orthotopic liver allografts NVa^2-CsA has similar immunosuppressive properties as CsA, with no functionally detectable toxicity affecting the liver or kidney. NVa^2-CsA has been reported to lack the nephrotoxicity, a limiting side effect of CsA in rats.[4]

Since structural changes have been reported to alter the pharmacokinetic profiles of drugs, we investigated the kinetics of CsA and NVa^2-CsA in the same group of animals. From our results it appears that small changes in the structure of CsA result in significant alterations in certain pharmacokinetic parameters. NVa^2-CsA is more lipophilic than CsA and is cleared from the dogs less readily as compared with CsA. It is also absorbed to a lesser extent compared with CsA after a single oral dose. The blood levels of NVa^2-CsA after chronic oral dosing is a function of both the absorption and elimination. Although decreased absorption will tend to produce lower blood levels, decreased elimination will tend to keep the levels higher as compared with CsA.

Our studies also indicate that the extent of absorption of NVa^2-CsA is highly variable between dogs. This is similar to the observations made with CsA. It is therefore essential to monitor the blood or plasma concentrations of NVa^2-CsA in future efficacy and toxicity studies.

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