MPC-6827, A Small Molecule Inhibitor of Microtubule Formation; Pharmacokinetics in Nu/+ Mice, Sprague Dawley Rats and Beagle Dogs Following Intravenous Administration

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ABSTRACT

MPC-6827 is a drug candidate being developed by Myriad Pharmaceuticals, Inc. for the treatment of primary or metastatic tumors, including those of the central nervous system that have progressed despite best standard treatment. The objectives of these studies were to evaluate the pharmacokinetics of MPC-6827 after intravenous administration to mice, rats and dogs and to provide a pharmacokinetic basis for selection of the initial starting dose for human clinical studies. MPC-6827 was administered as a single 2.5 mg/kg intravenous injection in male Nu/+ mice, a repeated-dose intravenous infusion of 0.1, 0.5 or 1.0 mg/kg in male and female Sprague-Dawley rats, and a single intravenous infusion of 0.1, 0.3 or 0.6 mg/kg in male and female dogs. The study in mice was designed to describe the expected exposure level of MPC-6827 at doses shown previously to inhibit tumor growth *in vivo* (Abstract LB252 AACR 2004 Annual Meeting). These data demonstrate that the average steady state concentration of MPC-6827 achieved over a 24 hour period exceeds the *in vitro* concentrations known to activate caspase and induce apoptosis by approximately two orders of magnitude. In mice, MPC-6827 crossed the blood brain barrier (BBB) and distributed rapidly into the central nervous system (CNS). When areas under the concentration-time curves were compared, exposure in the brain was approximately 14 times higher than in plasma. In rats, increase in $AUC_{(0\text{-inf})}$ was approximately linear with increasing dose. Exposure was higher and clearance was lower in males than in females at each dose level. Clearance of MPC-6827 decreased and terminal elimination half-life increased with increasing dose in both male and female rats. Similar to the results in rat studies, the increase in $AUC_{(0\text{-inf})}$ were approximately linear with increasing dose in dogs. Clearance was lower in males relative to females. Sex differences in the metabolic profile have not been observed in preliminary studies with subcellular fractions derived from human livers. These data provided the basis for selection of initial starting doses in human clinical studies.

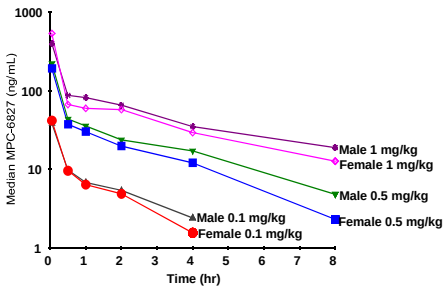
STUDY DESIGN

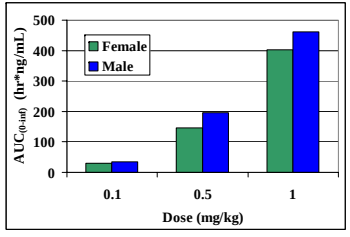
Nu/+ Mice: Animals were dosed with 2.5 mg/kg MPC-6827 as a single IV injection via the tail vein. Blood samples and whole brains were collected from five mice at each of the nine collection time points of 0.05, 0.25, 0.5, 1, 2, 4, 8, 12 and 24 hours post-dose. Plasma was collected from blood samples, and whole brain samples were homogenized in three volumes of water. Both tissues were analyzed for concentrations of MPC-6827 by LC-MS/MS.

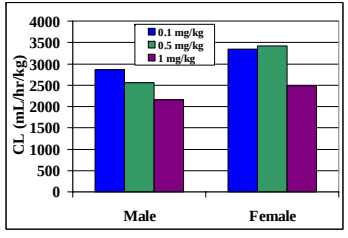
Sprague Dawley Rats: Animals were dosed weekly (study days 1, 8 and 15) with 0.1, 0.5 or 1 mg/kg of MPC-6827 by IV infusion over 2 minutes via the tail vein. Blood was collected just prior to infusion and 0.05, 0.5, 1, 2, 4, 8, 18 and 24 hours after administration of the last dose on Day 15. Plasma was analyzed for concentrations of MPC-6827 by LC-MS/MS.

Beagle Dogs: Animals were dosed with 0.1, 0.3 mg/kg or 0.6 mg/kg of MPC-6827 by slow IV infusion over 20 minutes via the cephalic vein. Blood samples were taken prior to dosing, at the end of the infusion period, and approximately 0.50, 1, 2, 4, 8, 18 and 24 hours after completion of the infusion.

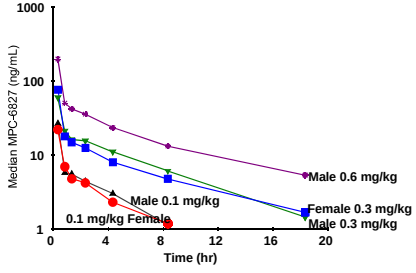
MPC-6827 PK Following a Third IV Infusion in Rats

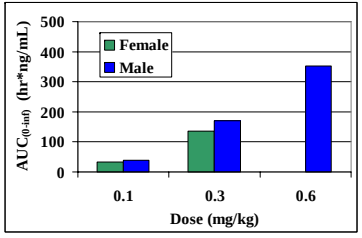


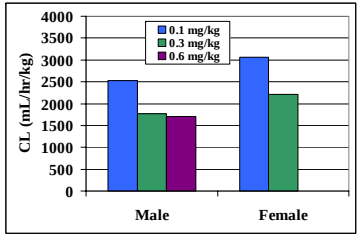




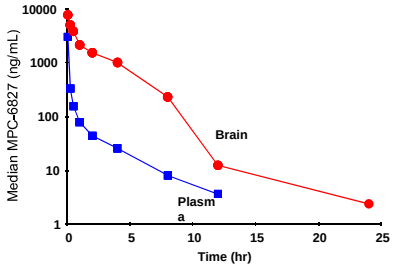
MPC-6827 PK Following a Single IV Infusion in Dogs







MPC-6827 PK Following a 2.5 mg/kg IV Bolus Dose in Male Nu/+ Mice



PHARMACOKINETIC ANALYSIS

Nu/+ Mice: Pharmacokinetic parameters were estimated on median plasma and brain concentrations using non-compartmental analysis in WinNonlin (Pharsight Corp., Mountain View, CA). The areas under the concentration-time curve ($AUC_{(0\text{-inf})}$) were calculated using a linear/log trapezoidal method.

Sprague Dawley Rats: Pharmacokinetic parameters were estimated on median plasma concentrations using a two compartment model for IV infusion with no lag time and first-order elimination in WinNonlin.

Beagle Dogs: PK parameters were estimated on individual plasma concentrations using a two compartment model for IV infusion with no lag time and first-order elimination in WinNonlin.

	Sex	Dose	t 1/2 (hr)	C_{max} (ng/mL)	$AUC_{(0\text{-inf})}$ (hr*ng/mL)	CL (mL/hr/kg)
Mouse Plasma	Male	2.5 mg/kg	2.75	3040	794	3150
Mouse Brain	Male	N/A	2.08	7810	11095	N/A
Rat	Male	0.1 mg/kg	2.13	42.4	35.0	2856
Rat	Male	0.5 mg/kg	2.58	256	196	2553
Rat	Male	1 mg/kg	3.01	600	463	2162
Rat	Female	0.1 mg/kg	1.69	46.6	29.9	3341
Rat	Female	0.5 mg/kg	2.08	225	146	3420
Rat	Female	1 mg/kg	3.26	795	403	2479
Dog	Male	0.1 mg/kg	3.43	26.4	39.5	2531
Dog	Female	0.1 mg/kg	2.30	21.8	32.6	3065
Dog	Male	0.3 mg/kg	4.00	59.2	170	1769
Dog	Female	0.3 mg/kg	4.44	75.5	135	2216
Dog	Male	0.6 mg/kg	3.90	197	353	1701

CONCLUSIONS

- MPC-6827 crosses the BBB and distributes rapidly into the CNS with exposure in the brain approximately 14 times higher than in plasma.
- In mice, the average concentrations in plasma and brain were approximately 55 and 825 times the concentrations shown to activate caspase and induce apoptosis *in vitro*.
- These data suggest that it is possible to reach therapeutic drug concentrations in the CNS with minimal systemic exposure.
- This property suggests a unique opportunity to study antitumor activity in patients with primary brain tumors.