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 PK Following a Third IV Infusion in Rats

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 repeat 24-hour intravenous infusion of 0.1, 0.3 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 achieved over a 24 hour period extending the in vivo concentration ranges 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-inf) was approximately linear with increasing dose. Exposure was higher and clearance was lower in males than in females of the same sex. In dogs, clearance was lower in males relative to females. Sex differences in the metabolic profile have not been observed in preliminary studies with subcutaneous doses derived from human tissues. 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 postdose. Plasma was analyzed for concentrations of MPC-6827 by LC-MS/MS.

Sprague Dawley Rats: Animals were dosed weekly (total days 1, 8 and 15) with 0.1, 0.3 or 1.0 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, 12 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 1.0, 2.5 or 5.0 mg/kg of MPC-6827 by slow IV infusions over 20 minutes via the cephalic vein. Blood samples were taken prior to dosing, at the end of the infusion period, and approximately 0.5, 1, 2, 4, 8, 16 and 24 hours after completion of the infusion.

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.