A Comparison of the CNS Pharmacokinetics of Letrozole following Intravenous and Oral Administration
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Purpose
The exposure of anti-cancer drugs to the brain and brain tumors, relative to systemic exposure, has significant pharmacological and toxicological implications. In ongoing studies, we are evaluating the brain and brain tumoral disposition of anti-cancer drugs including aromatase inhibitors such as letrozole. In this study, we compared the brain extracellular fluid (ECF) pharmacokinetics following intravenous and oral letrozole administration in Sprague Dawley rats.

Methods
Female Sprague-Dawley rats (225-250 g; N=6) were implanted with stainless steel guide cannulae in the striatum region using the coordinates according to the stereotactic atlas of Paxinos and Watson. On the day of the microdialysis experiment, concentric style dialysis probes connected to an infusion pump set to deliver modified Dulbecco’s phosphate buffered saline at a constant rate of 2.0 μL/min were inserted through the guide cannulae. After equilibration for 30 minutes, the animals were dosed 4 mg/kg of letrozole by oral gavage and dialysate samples were collected every 30 min for 8 hours. The samples were analyzed by a validated HPLC method using fluorescence detection & corrected for in vivo recovery. PK analysis was then performed using non-compartmental analysis using WinNonlin 6.2 (Pharsight Inc., Corporation, Mountain View, CA).

Results
The concentration-time profile of dialysate samples upon oral administration of letrozole estimated Tmax of 5.75±1.82 hours as compared to the Tmax of 1.4±0.6 hours reported earlier upon IV administration. The brain ECF Cmax and AUC with oral route were 175±23 ng/ml and 975.69±162.32 ng*hr/ml respectively which are consistent with the pharmacokinetic parameters reported earlier with IV route of administration.

Conclusion
Oral and intravenous administration of letrozole at the same dose level resulted in the similar systemic exposure as apparent from non-significant differences in the overall AUC and Cmax, although the Tmax is much longer. Thus, it appears that the exposure to letrozole in brain, and by extension to brain tumors, is equivalent following oral and i.v. administration.