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Pharmacokinetics and distribution of penciclovir to the brain and muscle in the rat studied by microdialysis.

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Famciclovir, the oral form of penciclovir, is a potent, highly selective antiherpesvirus agent and it is licenced for the treatment of herpes zoster (shingles). Herpesvirus have the potential to reach the central nervous system. To obtain guidance for the possible treatment of herpes encephalitis it is important to study the extent of penciclovir transport into the brain. We have used microdialysis to sample the unbound extracellular concentration of the drug in the gastrocnemic muscle (which corresponds directly to plasma free concentrations) and in the brain of Sprague Dawley rats under halothane anaesthesia. Penciclovir 50 mg/kg was given iv and samples were taken for 5 hours after administration. In vivo recovery of each microdialysis probe was measured by perfusion with a 5 μM solution prior to administration of penciclovir. The recovery of penciclovir was smaller in the brain than in muscle. The AUC(0-5 hours) of penciclovir in the brain was 9.6 ± 0.9% of the AUC in muscle while the mean ratio of brain to muscle concentration 5 hours post injection was 17.9%. The results demonstrate that penciclovir enters the rat brain to a significant extent and that the total exposure of brain cells of the uninfected rat is around 10% of the exposure of peripheral cells. Studies comparing famciclovir and penciclovir are ongoing.

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High Bioavailability and Rapid Distribution of Penciclovir Following an Oral Dose of Famciclovir
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Famciclovir (FCV) is the oral dose form of penciclovir (PCV), a new antiviral agent with activity against herpes simplex and varicella zoster viruses. The single dose pharmacokinetics and bioavailability of PCV were determined following oral administration of FCV. In a randomised crossover design study, 12 healthy male volunteers received a single oral dose of FCV (500 mg) and a single intravenous (iv) infusion (1 h) of PCV (400 mg). PCV plasma concentrations from each phase of the study were submitted to model-independent analysis. Following oral FCV, maximum plasma concentrations of PCV [mean (SD) 2.73 (0.69) μg/mL] were achieved rapidly (median Tmax 1.00 h). The mean (SD) T1/2 was 2.19 (0.47) h. The mean (SD) AUC(0-inf) was 7.92 (1.16) ug.h/mL. Mean absorption T1/2 from compartmental analysis of the PCV data following oral FCV was 0.22 h (n=10). Thereafter, PCV was rapidly distributed with an initial disposition T1/2 in the range 0.14-0.39 h. The mean (SD) Vdss for PCV, estimated from the iv phase (non-compartmental analysis), was 1.09 (0.11) L/kg. Comparison of AUC(0-inf) values from oral FCV and iv PCV indicated that the absolute bioavailability of PCV following oral FCV was 0.77 (95% confidence interval 0.72, 0.83). The within-subject coefficient of variation for AUC(0-inf) was 7.5%. Thus, variability in the availability of PCV from oral FCV is low. In conclusion, following oral FCV the absolute bioavailability of PCV is high (77%) with low variability and attainment of maximum plasma concentrations of PCV and subsequent distribution of the active entity are rapid.