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The Single-dose Pharmacokinetics and Metabolism of 882C87, a Potent Anti-VZV Agent with a Long Half-life.
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882C87 (1-(β-D)-arabinofuranosyl-5-(1-propynyl)uracil) is a thymidine analogue with an IC_{50} of 1.97 μM against varicella zoster virus (VZV), seven times as potent as acyclovir. Plasma concentrations rapidly exceed the IC_{50} after oral doses as low as 50 mg and remain above it for at least 24 hours. They are proportional to dose up to 400 mg and continue to rise substantially although less than dose-proportionally at higher doses. After 200 mg and 1600 mg C_{max} is 9.0 μM and 34.7 μM, respectively, and AUC is 166.7 μM.h and 822.9 μM.h. The oral bioavailability of 882C87 is 20-25% after a 200 mg dose and mean V, CL and $t_{½}$ are 0.77 l/kg, 0.17 ml/min and 11.8 hours, respectively. After intravenous dosing 70-80% of the drug is recovered unchanged in the urine and CL_R is 0.14 ml/min/kg. Plasma concentrations of 882C87 are significantly higher in elderly volunteers than in young adults and are associated with a slightly lower $t_{½}$ (14 hours) and a lower CL_R (0.11 ml/min/kg). Administration with a fatty meal produces a 10-15% decrease in C_{max} and AUC. After oral dosing substantial concentrations of the pyrimidine base 5-(1-propynyl) uracil (5PU) are detected in plasma, with a lag time of 5-24 hours. Urinary recovery of 5PU and 882C87 accounts for 35-40% and 15-20% of the dose, respectively. After oral dosing with ^{14}C-882C87, 85% of the radioactivity is recovered in urine, mostly as 882C87 or 5PU. Absorbed 882C87 is eliminated unchanged in urine and it is likely that much unabsorbed drug is broken down to 5PU in the large intestine. In summary, oral dosing with 882C87 gives plasma concentrations substantially above the IC_{50} for VZV with a half-life suggesting once- or twice-daily dosing for treatment of VZV infections.

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Increased Bioavailability of Acyclovir from Oral Valaciclovir in Healthy Volunteers.
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Valaciclovir (VACV) is the L-valyl ester of acyclovir (ACV). Previous studies in healthy volunteers have estimated that the bioavailability of ACV following oral VACV is 3-5 times that following high dose oral ACV.[1] This may extend the range of viral infections amenable to oral suppression or therapy. However, in previous studies a formal measurement of bioavailability was not carried out. The aim of this study was, therefore, to determine the absolute bioavailability of ACV following oral administration of 1000 mg of VACV. Twelve fasted healthy volunteers (age range 23-50 years) received 2 x 500 mg VACV tablets or 350 mg ACV as a 70 ml infusion over 1 hour according to an open, randomized, balanced two period crossover study. Plasma samples were taken at intervals up to 24 hours following each dose and all urine was collected for 24 hours. Plasma and urine ACV were assayed by RIA. Following oral VACV the mean (± SD) C_{max}, T_{max} and AUC of ACV were 6.6 ± 2.8 μg/ml, 1.7 ± 0.7 h and 20.1 ± 4.4 μg/ml.h, respectively. Following intravenous ACV the mean (± SD) C_{max}, T_{max} and AUC were 9.2 ± 1.9 μg/ml, 1.0 ± 0.1 h, and 18.9 ± 3.2 μg/ml.h. Mean (95% CI) absolute bioavailability of ACV from oral VACV, calculated from the ratio of AUCs after adjusting for molar dose, was 54.2% (49.4% to 59.5%). The estimated bioavailability from the ratio of urinary recovery of ACV was 52.8%. The mean (± SD) $t_{½}$ of ACV following VACV was 2.6 ± 0.4 h and following ACV was 2.4 ± 0.3 h. The 95% CI of the difference in $t_{½}$ for VACV and ACV was 0.03 h to 0.45 h. This slight increase in ACV $t_{½}$ following VACV is not clinically significant and is probably due to a small component of continuing absorption of VACV. The absolute bioavailability of ACV from oral VACV of 54.2% supports the conclusions of previous studies that the bioavailability of ACV from oral VACV is 3-5 times greater than that following high dose oral ACV.

[1] Weller *et al.* Pharmacokinetics of the acyclovir pro-drug valaciclovir after escalating single- and multiple-dose administration to normal volunteers. Clin Pharm Ther. In Press.