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Studies on the *In Vivo* Synthesis and *In Vitro* Biochemical Properties of Penciclovir Triphosphate.

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We have shown previously that the nucleoside analogue penciclovir (PCV) and its pro-drug famciclovir have similar activities to acyclovir (ACV) against herpes simplex virus type 1 (HSV-1) both *in vitro* and in animal models. In contrast, we have also reported that the same studies show that PCV is not as active as ACV against HSV-2. In addition, *in vitro* studies show that ACV has superiority over PCV against human cytomegalovirus (CMV) and Epstein-Barr virus (EBV) (ICAR, Venice, 1993). We have examined a number of mammalian cell lines exposed to PCV for the presence of PCV triphosphate and have found significantly more PCV triphosphate than in similar studies with ACV. Given the relatively long half-life of PCV triphosphate we are examining these cells for the possibility of incorporation into DNA. Biochemical studies with a number of herpesvirus and cellular DNA polymerases have shown that PCV triphosphate is a much weaker inhibitor (100x) of the viral DNA polymerase than that of ACV triphosphate. This finding may have consequences in the effect of PCV against herpesvirus replication *in vivo*. Work is in progress to investigate the relative efficiencies of both ACV and PCV as substrates for the herpesvirus thymidine kinases. It has also recently been reported that PCV has an effect against hepatitis B virus (HBV) (Bacon, EADV, Copenhagen, 1993). Because HBV does not code for a thymidine kinase, the mode of action of PCV against HBV is unknown but must differ considerably from that of ACV (which has only a weak activity). We are examining the metabolism of PCV in uninfected and infected liver cells and the effect of PCV triphosphate on the HBV DNA polymerase. These studies should allow us to determine whether the reported activity of PCV against HBV is virus specific.

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Pharmacokinetics and Metabolism of systemic administration of 1-(2-Deoxy-2-Fluoro-ß-D-Arabinofuranosyl)-5-Iodo-2,4(1H,3H)-Pyrimidinedione (FIAU) In Hartley Guinea Pigs.

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FIAU is a highly effective drug for the treatment of various viral diseases. The present study evaluated the pharmacokinetic and metabolic disposition of FIAU in adult female Hartley guinea pigs following administration of 1 mg/kg [2-^{14}C]-FIAU intravenously or orally. After intravenous and oral administration, urinary recovery of total administered radioactivity was essentially complete within 24 and 48 h respectively. In addition to FIAU, its major metabolite, FAU, was detected in plasma and urine following intravenous and oral administration. The mean (SD) FAU/FIAU AUC ratio after intravenous and oral administration was 0.26(0.13) and 0.83(0.23) respectively. A second metabolite was identified by LC-MS/MS as FMAU. This metabolite represented approximately 2% of the total FIAU dose recovered in urine and was detected both in plasma and urine only 12 hr after drug administration. The plasma elimination $T_{1/2}$ of FIAU was variable with mean (SD) values of 1.01(0.44) and 0.86(0.43) hr after intravenous and oral administration respectively. The absolute bioavailability of FIAU after oral administration based on AUC values or urinary excretion was good with mean (SD) values of 71.0 (0.3)% and 74.0 (0.6)% respectively. The significance of FMAU formation on the pharmacodynamic properties of the parent drug following oral FIAU administration remains to be elucidated.