124

Pharmcokinetics and Therapeutic Efficacy of Prodrugs of N7-Isomeric Acyclic Nucleoside Analogues in Animals.

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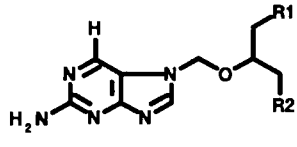
The N7-isomeric acyclic nucleoside analogue **I** (compound 2242), which is highly active against herpes viruses *in vitro* and *in vivo*, is significantly absorbed after oral administration. To further increase the enteral bioavailability, ether-, ester-, and mixed ether-ester-prodrugs of **I** were synthesized. These prodrugs of **I** were antivirally active against HSV-1 in infected mice. Pharmacokinetic experiments in several animal species revealed that the diacetate **III** of the parent compound **I** was best absorbed and metabolized to yield high serum concentrations of the active metabolite. This prodrug ester **III** (code number HOE 961) was selected for further development.



I:	R1 = R2 = OH
II:	R1 = R2 = OiPr
III:	R1 = R2 = $OC(O)CH_3$ (HOE 961)
IV:	R1 = R2 = $OC(O)CH_2CH_3$
V:	R1 = R2 = $OC(O)C(CH_3)_3$
VI:	R i = R2 = OC(O)Ph
VII:	R1 = OiPr, R2 = $OC(O)CH_3$

125

The Tolerability and Pharmacokinetics of 882C87, a Potent Anti-VZV Agent, after 400 mg or 800 mg Once-daily Dosing for 1 Week in Elderly Volunteers.

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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. Oral 882C87 50-200 mg bid for 1 week in elderly volunteers and patients with shingles, gives steady-state plasma concentrations that are proportional to dose. In the current study, three groups of eight healthy elderly volunteers received either 400 mg or 800 mg 882C87, or placebo in a randomized double-blind study. Plasma and urine samples were collected for 120 hours after the last dose and assayed for 882C87 and the pyrimidine base 5-(1-propynyl)uracil (5PU), which is formed by breakdown of 882C87 within the lumen of the large intestine. All volunteers completed the study and 882C87 was well tolerated. Preliminary mean (SD) pharmacokinetic parameters are given below.

	400 mg (n=6)		800 mg (n=7)	
	882C87	5PU	882C87	5PU
C_{min} (μM)	12.4 (5.8)	7.4 (4.5)	21.8 (8.1)	8.7 (7.3)
C_{max} (μM)	30.1 (10.6)	10.2 (4.4)	51.8 (17.5)	12.3 (7.9)
$AUC_{(0-24)}$ (μM.h)	475.0 (180.5)	190.8 (107.0)	801.5 (225.6)	239.9 (165.9)
$t_{½}$ (h)	17.5 (2.1)	17.4 (6.7)	17.2 (1.3)	17.2 (6.8)
CL/F (ml/min/kg)	0.82 (0.31)		0.97 (0.19)	
V/F (l/kg)	1.22 (0.54)		1.42 (0.27)	

Plasma concentrations of 882C87 after 400 mg once-daily dosing are similar to those predicted from data obtained at lower doses. In contrast to acyclovir, the rise in plasma concentrations with 800 mg 882C87 is approximately dose proportional suggesting no significant reduction in bioavailability at higher doses. The small increase in 5PU concentrations suggests that formation or absorption of 5PU may be limited. These data confirm that once-daily 400 mg and 800 mg doses of 882C87 are well tolerated and give trough plasma levels well above the IC_{50} for VZV.