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Brain Delivery of 2'-F-ara-ddI By Utilizing Xanthine Oxidase Biotransformation System. C.K. Chu*[1], T. Koudriakova[1], K. Shanmuganathan[1], L. Ni[2], F.D. Boudinot[2],J.M. Gallo[2], and R.F. Schinazi[3]. [1]Department of Medicinal Chemistry and [2]Department of Pharmaceutics, College of Pharmacy, University of Georgia, Athens, GA 30602, and [3]Emory University School of Medicine/VA Medical Center, Atlanta, GA 30033.

For *in vitro* study, 2'-F-ara-ddP was incubated in pH 2, mouse liver homogenate and mouse serum at 37°C. No degradation was observed at pH 2 and serum while in liver homogenate, 2'-F-ara-ddP was almost completely converted to 2'-F-ara-ddI within 20 min (t l/2 = 3.54 min). In order to determine the role of xanthine oxidase in the conversion of 2'-F-ara-ddP to 2'-F-ara-ddI, *in vitro* studies were conducted in phosphate buffer (pH 7.4) in the presence or absence of allopurinol, in which the half-lives of 2'-F-ara-ddP in the absence and presence of the allopurinol was 3.4 and 7.4 h, respectively, indicating the conversions were catalyzed by the xanthine oxidase. A similar experiment with aldehyde oxidase isolated from the human liver did not effect the biotransformation. The biotransformation was also detected in the brain homogenate, although the rate of conversion was low and incomplete. In order to access the bioconversion in *in vivo*, pharmacokinetic studies of 2'-F-ara-ddP and 2'-F-ara-ddI were conducted in mice. The maximum serum concentrations of 2'-F-ara-ddI administered itself and as 2'-F-ara-ddP reached 48.1 ± 10.00 and 89.3 ± 26.0 μM and were observed in 1 and 0.25 h, respectively. The data indicate that 2'-F-ara-ddI is absorbed at a slower rate than that of 2'-F-ara-ddP. The bioavailability of the prodrug after oral administration was 60.7 %. The concentration of 2'-F-ara-ddI following oral administration of 2'-ara-ddP was close to the detection limits, while 2'-F-ara-ddI was detected at significantly higher concentrations in the brain after oral administration of 2'-F-ara-ddP. The pharmacokinetic study in monkeys also suggested that 2'-F-ara-ddP is converted to 2'-F-ara-ddI, which can be also detected in CSF. From this study we have demonstrated the enhanced brain delivery of anti-HIV nucleoside, 2'-F-ara-ddI, by utilizing *in vivo* biotransformation system. (Supported by NIH Grant AI 25899 and AI 32351)