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Metabolism in vitro and pharmacokinetics in vivo of 2'-fluoro-2'-3'-dideoxyarabinosyladenine (FddA), an inhibitor of HIV with improved stability over 2',3'-dideoxyadenosine. M.J.M. Hitchcock, H-T. Ho, K. Woods, H. De Boeck, J.W. Russell, V.J. Whiterock and L.J. Klunk, Bristol-Myers Squibb Company, Wallingford, Connecticut, USA.

FddA and its deamination product, FddI, display anti-HIV activity in a number of cell lines, but in many cases are significantly (an order of magnitude) less potent than their non-fluorinated congeners, ddA and ddI. Thus, the interaction of FddA and FddI with cells and isolated enzymes was studied to assist in identifying their potential in vivo utility as anti-HIV agents. FddA is deaminated by adenosine deaminase but the Km is 4-fold higher and the Vmax 12-fold lower than for ddA. Unlike ddI, FddI is resistant to hydrolysis by purine nucleoside phosphorylase. Like ddI, FddI can be phosphorylated by 5'-nucleotidase using IMP as the phosphate donor. In cells, both FddA and FddI are phosphorylated to the triphosphate of FddA (FddATP). However, the concentration of FddATP produced from FddA is about 2 to 5-fold higher than with FddI. On removal of extracellular compound from the medium, the FddATP persisted with a half life of 20 h. FddATP inhibited HIV reverse transcriptase and was competitive with respect to dATP. However with both an RNA and a DNA template, the Ki for FddATP was 20 to 40-fold higher than that for ddATP. In mice, FddA and FddI have oral bioavailabilities of 87% and 35%, respectively, compared with only 38% for ddA and 13% for ddI. The inherently lower potency of the fluorinated derivatives may be offset by an increased stability both to metabolism and to low pH, the latter leading to increased bioavailability.

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Pharmacokinetics and safety of anti-HIV-1 TIBO-derivatives in rats, dogs and man.

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Derivatives of tetrahydro-imidazo [4,5,1-jk](1,4)-benzodiazepin-2(1H)-one and thione (TIBO) are potent and selective inhibitors of HIV-1 replication in vitro (R.Pauwels et al., Nature, 343:470-474, 1990). The pharmacokinetics of two TIBO-derivatives, R 82150 and its 9-chloro derivative R 82913, have been studied. In rats, tissue distribution studies with R 82913 showed brain concentrations twice higher than corresponding plasma levels. Also in dogs, R 82150 exhibited an extensive tissue distribution (Vd_{area} = 10.2 l/kg). Elimination was by metabolism and the terminal half-life was 3.2 h. No adverse cardiovascular or behavioural effects were seen at plasma concentrations exceeding the antiviral IC-50 by 1000-fold. Plasma levels of R 82150 in healthy subjects showed a narrow interindividual variability for intravenous (25 mg) as well as for oral administration (100 and 200 mg). The elimination half-life averaged 13 hours, whereas Vd_{area} was similar to that in dogs. For the 200-mg dose the absolute bioavailability amounted to 31 % and plasma levels exceeding the IC_{50} could be maintained for 24 hours. Both compounds were well tolerated. The extensive tissue distribution, the relatively long half-life and the acceptable oral bioavailability are features of a favourable pharmacokinetic profile of the TIBO-derivatives.