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Rapid, Convenient, Synthesis of γ-Emitting, No-Carrier-Added (NCA) 1-(ß-D-Arabinofuranosyl)-5(*E*)-(2-radiohalogenovinyl)uracil Probes for the Detection of Herpes Simplex Virus (HSV)-Specified Thymidine Kinase *In Vitro* and *In Vivo*. H. Dougan, B.A Rennie, R.J. Wanklin, D.M. Lyster, C. Vo and S.L. Sacks. TRIUMF and University of British Columbia, Vancouver, BC Canada.

An HSV-specific imaging agent would hold several advantages as an approach to noninvasive diagnosis of HSV. Favorable metabolic stability considerations have prompted investigations of 1-ß-D-arabinofuranosyl-*E*-5-(2-[*I]iodovinyl)uracil ([*I]IVaraU) for this purpose. Accordingly, NCA (absent ^{127}I) [*I]IVaraU having high specific radioactivity and high yield would be desirable. Existing methods for synthesis of iodovinyl nucleosides are problematic and have failed to produce NCA [*I]IVaraU. A novel successful method is described. 1-ß-D-arabinofuranosyl-*E*-5-(2-bromovinyl)uracil (BVaraU) was suspended in H_2SO_4 (0.01 M) and heated for 60 min (90°C) under nitrogen in the presence of up to 40 mCi [^{123,125}I]NaI and cuprous ions (generated *in situ* from $CuSO_4$), ascorbic acid and $SnSO_4$. NCA [*I]IVaraU was then purified by HPLC [RPC18 acetonitrile/water (15/85)] giving a pure product free of detectable BVaraU or impurities. Radiochemical yield was 95% with both ^{125}I and ^{123}I. To determine if [*I]IVaraU could be used as an HSV-specific probe for encephalitis (HSE), lip-inoculated A/J mice were studied at day 7 post infection, following tail vein injections of 1.0 µCi NCA [^{125}I]IVaraU or [^{125}I]NaI. Ratios of NCA [^{125}I]IVaraU uptake in HSV-infected compared with uninfected mouse brains were 6.5 (4 h), 15.8 (24 h), and 36.2 (48 h). NCA [^{125}I]IVaraU was found to be highly localized in HSE mouse brains, while free [^{125}I]NaI was not localized. This novel method for high yield synthesis of NCA [*I]IVaraU is rapid and convenient for both research and clinical applications as a tool for investigative noninvasive diagnosis of HSE. Ongoing developmental work shows progress with three additional labelling reactions for NCA [*I]IVaraU which are more rapid than the cuprous ion reaction. These additional advances may be applicable to urgent clinical use.

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BRL 44385: Selective anti-herpesvirus activity and mode of action.
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The novel anti-herpesvirus compound, BRL 44385 [9-(3-hydroxypropoxy)guanine] has highly potent and selective activity against clinical isolates of HSV-1, HSV-2 and VZV. In plaque reduction assays in MRC-5 cells the mean IC_{50} values were 0.15, 0.32 and 5.8 µM respectively. In the same tests, acyclovir was 10-fold, 5-fold and 4-fold less active, although the antiviral selectivities of the two compounds were similar. As an inhibitor of EBV DNA synthesis in P_3HR-1 cells, BRL 44385 was about 7-fold more active than acyclovir. In contrast, BRL 44385 showed no activity at all against cytomegalovirus (CMV). In vivo, BRL 44385 possesses high efficacy and is well tolerated. In a cream applied topically to guinea pigs, BRL 44385 was shown to be more active against HSV-1 than acyclovir ($p<0.05$) even though the activities of the two compounds against HSV-1 in guinea pig cells are comparable. BRL 44385 is phosphorylated in HSV-1, HSV-2 and VZV infected cells to give high levels of the triphosphate ester (after incubation for 8 h, 1130, 1480 and 23 pmol/10^6 cells respectively) whereas the corresponding values for acyclovir-triphosphate were low (6, 18 and <7 pmol/10^6 cells). In the virus infected cells, the half-life of BRL 44385-triphosphate was 3 h and this triphosphate inhibited the viral DNA polymerases competitively with dGTP (K_i 4.1, 1.5 and 15 µM respectively). The triphosphate esters of both BRL 44385 and acyclovir had little activity against the human DNA polymerase α but they did inhibit polymerases β and γ. In uninfected cells, phosphate esters of BRL 44385 were not detected. Therefore the major selectivity step is at the phosphorylation of BRL 44385 to the monophosphate by the herpesvirus encoded thymidine kinases. The key block to virus replication is by inhibition of the viral DNA polymerases.