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Benzimidazoles For The Treatment Of Human Cytomegalovirus. G. W. Koszalka, S. D. Chamberlain, R. J. Harvey, L. W. Frick, S. S. Good, M. L. Davis, A. Smith, J. C. Drach*, L. B. Townsend*, and K. K. Biron, Glaxo Wellcome Inc., Research Triangle Park, NC, 27709, USA, *University of Michigan, Ann Arbor, MI 48109 USA.

A novel, potent, selective, orally bioavailable benzimidazole has been selected for clinical development. BW1263W94 is one of the most potent members of a new class of compounds that inhibits human cytomegalovirus (HCMV) replication. In side-by-side assays it is 3- to 20-fold more potent than ganciclovir, and based on literature IC_{50} values it is 3- to 20-fold more potent than either cidofovir or lobucavir, and at least 100-fold more potent than foscarnet. BW1263W94 inhibits viral replication by interfering with CMV DNA synthesis. It blocks a virus-specific process which is a novel anti-viral target. BW1263W94 is not appreciably phosphorylated to a triphosphate form and does not significantly inhibit HCMV polymerase. Furthermore, BW1263W94 is a weak inhibitor of DNA processing, the mechanism common to trihalobenzimidazole ribosides. Mechanism of action studies are continuing. The ganciclovir-resistant strains tested to date are not cross-resistant to BW1263W94. The average bioavailability of BW1263W94 is >90% in rats and monkeys. Despite a high degree of protein binding, the high volume of distribution in both species suggests significant tissue penetration. Clearance in rats and monkeys is mediated primarily by biliary secretion, with metabolic and renal mechanisms playing minor roles. This compound is mildly inhibitory to human bone marrow progenitor cells and various human leukemic cell lines. In preclinical toxicology assays, the no-effect dose (p.o.) was 200 mg/kg/day in the rat and 60 mg/kg/day in the monkey. Average maximal plasma levels in these studies are greater than 100-fold the mean IC_{50} value for ten HCMV clinical isolates. Initial clinical studies to evaluate tolerance and pharmacokinetics are scheduled to begin in early 1996.

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A New Class of Herpesvirus Inhibitors Differentially Affects Herpes Simplex Virus and Human Cytomegalovirus DNA Replication. J. Morin, B. O'Hara, S. Johann, T. Jones, B. Feld, J. LaRocque, J. Bloom, K. Curran, M. DiGrandi, R. Dushin, E. Norton, A. Ross, and Y. Gluzman. Wyeth-Ayerst Research, Pearl River, NY 10965, USA.

A synthetic chemical, HI-1, was discovered as an inhibitor of HSV1 and 2, but had little activity against CMV. Mechanism-of-action studies revealed the compound prevented processing of HSV1 DNA from the concatameric to the monomeric form. A HI-1-resistant HSV1 was selected by growth in the presence of compound. Using marker rescue, the locus responsible for resistance was identified as UL6. This is consistent with previous work showing that ts mutants for UL6 fail to process viral DNA at nonpermissive temperatures. The sequence of the gene contained a single change, converting alanine 618 to valine. The efficacy of HI-1 against HSV2 was tested in the mouse vaginal infection model. Applied topically, HI-1 protected mice from death following infection with HSV2. Over 90 analogs of the lead compound have been synthesized. Some are more potent against HSV1 and HSV2 than the lead and also show potent *in vitro* activity against CMV. This broad-spectrum anti-herpetic activity presumably reflects the high conservation of the UL6 protein among herpesviruses. These compounds interfere with CMV DNA replication, as expected of compounds interfering with UL104, the CMV homolog of UL6. However, in this case, the steady-state level of the concatameric form of viral DNA is decreased. It is thus possible that interference with the function of UL6/UL104 can manifest either as failure to process viral DNA (HSV) or as failure to synthesize viral DNA (CMV).