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Sequential Ascending Multiple-dose Safety and Pharmacokinetic Study of Oral Lobucavir (BMS-180194) in Asymptomatic Volunteers Seropositive for HIV and CMV. BG Petty, M Wachsman, MC Jordan, H Burgee, D DeHertogh, D Collins, RS Summerill, DA Jabs, JP Dunn, N Hellmann, B Kringstad, C Fletcher, L Smaldone, PS Lietman, MB Stewart. Division of Clinical Pharmacology, The Johns Hopkins University School of Medicine, Baltimore, MD; University of Minnesota, Minneapolis, MN; and Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ and Wallingford, CT, USA.

Lobucavir is a promising new drug with activity against cytomegalovirus in vitro and good bioavailability in animals. A single-dose study in humans showed that it was as safe as placebo, and oral bioavailability was about 40%, with saturable absorption at high doses. The current study was conducted to determine the safety and kinetics of twice-daily doses of lobucavir in clinically stable subjects seropositive for HIV and CMV. Thirty-two such subjects completed this double-blind, placebo-controlled study. Groups of 8 subjects received lobucavir (n=6) or placebo (n=2) at dose levels of 20, 70, 200, or 400 mg orally twice daily. Plasma and urine samples were collected before and for 24 hours after the first dose and after receiving the dose twice daily for 14 days. The subjects then continued twice-daily dosing for another 14 days (for a total of 28 days of treatment), and were followed for 14 more days to assess safety. The areas under the concentration-time curves were linear relative to dose at 20-200 mg, but did not remain linear to the 400 mg dose. There was no evidence of significant change in AUC at Day 15 compared to Day 1. Adverse experiences were noted in equal proportions at the four doses. Only 2 subjects had an adverse event requiring discontinuation of study drug; both were receiving placebo. These data confirm the saturable absorption of this compound, and show that twice-daily dosing for 28 days at these doses is acceptably safe.

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Inhibitors of Varicella Zoster Virus Thymidine Kinase. George E. Wright,[1] Federico Focher,[2] Hongyan Xu,[1] Annalisa Verri,[2] Thida Sou[1] and Silvio Spadari,[2] [1] Department of Pharmacology, University of Massachusetts Medical School, Worcester, MA 01655, and [2] Istituto di Genetica Biochimica ed Evoluzionistica, Consiglio Nazionale Delle Ricerche, Pavia 27100, Italy.

Herpesvirus thymidine kinases (TK) phosphorylate a wide range of nucleoside analogs resulting in activation of certain antiherpes drugs. The TKs are also of growing interest as targets for preventing recurrent herpetic infections. TKs from Herpes simplex virus types 1 and 2 (HSV1,2) are potently inhibited by N^2-phenylguanines substituted in the phenyl ring and/or the 9 position of the purine ring. We postulated that a Phe residue in a conserved sequence in the enzymes, FDRH, is responsible, in part, for inhibitor binding and potency among these inhibitors. Given a single amino acid replacement in the analogous region of Varicella zoster virus (VZV) TK, yielding SDRH, we predicted that guanines with different N^2 substituents would selectively inhibit the VZV enzyme. Recombinant VZV TK (a gift of Burroughs Wellcome Co.) was assayed with ATP and [^{3}H]thymidine in the presence of numerous guanine derivatives. N^2-alkylguanines and related 9-(2-deoxyribofuranosyl) derivatives were found to be moderately potent, competitive inhibitors of VZV TK, but N^2-phenylguanines were generally inactive or weakly active. Structure-activity relationships, substrate assays, and comparison with activity against the HSV TKs will be presented for the VZV TK inhibitors, and discussed with respect to a model for the inhibitor binding site of the enzymes. The authors are grateful to NATO for a collaborative research grant.