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The Phosphonate Ganciclovir Derivative SR 3745A Demonstrates Severe Toxicity In Cell Culture And In Guinea Pigs. E. S. Levine*, F. J. Bravo†, D. I. Bernstein†, L. R. Stanberry†, and W. Lewis*, *Department of Pathology and Laboratory Medicine, University of Cincinnati College of Medicine, and †Children's Hospital Research Foundation, Cincinnati, OH 45267.

New anti-cytomegalovirus (CMV) drugs are needed to improve efficacy and decrease the toxicity of existing therapies. We evaluated SR 3745A, a phosphonate derivative of ganciclovir for its *in vitro* toxicity using HepG2 cells and *in vivo* toxicity and activity against guinea pigs infected with CMV (gpCMV). Hartley guinea pigs were immunocompromised using cyclophosphamide (cyc: 100 mg/kg; 50 mg/kg follow-up). Animals were randomized to receive cyc + SR 3745A (50 mg/kg *b.i.d.*), cyc + SR 3745A + gpCMV or cyc + placebo + gpCMV. Animals that received SR 3745A lost weight by day 2 with mortality attributable to drug of >60% (by day 10) in both treated groups. Serum chemistries suggested target organs included liver, kidney and heart. Toxicity also was seen in immunocompetent, treated guinea pigs. Subcellular mechanisms of hepatic toxicity were examined *in vitro* by measuring lactate accumulation in the medium of HepG2 cells exposed to SR 3745A, acyclovir, or ribavarin (10-1000 μg/mL; 7 days). Each drug disturbed cellular oxidative metabolism of HepG2 cells with a dose-dependent increase of lactate in the medium. SR 3745A (10 μM) was more toxic than acyclovir (10 μM), showing a 156% increase above control lactate levels after 7 days compared to a 46% increase for acyclovir. The guanosine analog ribavarin (10 μM) caused a 91% increase in HepG2 cell lactate after 7 days. These results demonstrate that SR 3745A exhibits severe *in vivo* and *in vitro* toxicity. Subcellular mechanisms of toxicity may relate to disturbed energy metabolism.

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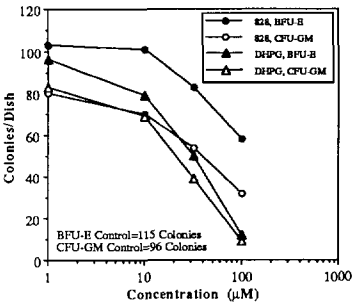
Human Bone Marrow Toxicity of a Non-nucleoside Pyrrolo[2,3-*d*]pyrimidine. M. R. Nassiri, R. S. Taichman, T. E. Renau, S. G. Emerson, L. B. Townsend, and J. C. Drach. University of Michigan, Ann Arbor, Michigan, 48109-1078, USA.

CMV infections are common in immunocompromised and HIV infected individuals. Unfortunately, most antivirals exhibit significant bone marrow suppression. The novel non-nucleosid, pyrrolo[2,3-*d*]pyrimidine, UMJD 828, selectively inhibits human CMV replication [T. E. Renau *et al.*, 7th I.C.A.R., March 1994]. To determine the potential for bone marrow toxicity, we evaluated the effects of compound 828 on hematopoietic progenitor cell survival *in vitro*. Non-adherent low density bone marrow cells were isolated from healthy adult volunteers and placed into methylcellulose containing cytokines (GM-CSF, IL-3, Epo) with various concentrations of test agents. As a control for marrow toxicity, ganciclovir (DHPG) was included in the evaluation. At 2 weeks colony formation was scored as either CFU-GM (colony forming unit granulocyte/macrophage) or BFU-E (burst forming units-erythroid). As shown in the figure, DHPG decreased colony formation by 85% for BFU-E and 72% for CFU-GM at 100 μM. In contrast, compound UMJD 828 was significantly less toxic with IC_{50}'s of >100 μM and 62 μM for BFU-E and CFU-GM respectively. These *in vitro* data suggest that compound 828 is significantly less toxic for human hematopoietic progenitor cells compared to DHPG. The relatively low hematotoxicity of compound 828 together with its selective antiviral activity make this novel compound a good candidate for further study.



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