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The Disposition in Rats and Monkeys of 2-Bromo-5,6-dichloro-1-(ß-D-ribofuranosyl)-benzimidazole (BDCRB) and Its 2,5,6-Trichloro Congener (TCRB). S. S. Good, and B. S. Owens. Wellcome Research Laboratories, Research Triangle Park, NC 27709 USA; L. B. Townsend and J. C. Drach. University of Michigan, Ann Arbor, MI 48109 USA.

The pharmacokinetics and metabolism of BDCRB and TCRB, two benzimidazole ribonucleosides with potent and selective activity against human cytomegalovirus, were studied in CD® rats and Cynomolgus monkeys given single 10 mg/kg doses by bolus intravenous (i.v.) injection or by gastric intubation. After i.v. dosing of rats, both nucleosides were rapidly cleared from plasma, with average elimination-phase half-lives ($t_{1/2}$) of 0.6 hr and total body clearances (tbc) of 2.6 and 2.8 L/hr/kg. After oral administration, peak plasma concentrations (C_{max}) of both BDCRB and TCRB showed wide individual variations, but averaged 3.3 and 3.6 µM, respectively. Mean oral bioavailabilities were 53% and 60%, respectively. In monkeys, $t_{1/2}$'s were 0.7 and 0.5 hr and tbc's were 3.1 and 4.1 L/hr/kg for BDCRB and TCRB, respectively. After oral dosing, C_{max}'s ranged from 0.4-1.0 µM for BDCRB and 0.3-0.5 µM for TCRB. Oral bioavailabilities of the two ribosides were lower in monkeys, averaging 16% and 14%, respectively. Extensive metabolism of both BDCRB and TCRB to their aglycones (2-bromo-5,6-dichlorobenzimidazole and 2,5,6-trichloro-benzimidazole) were observed. In rats given i.v. doses, the areas under the plasma concentration vs. time curves (AUC) for the aglycones of BDCRB averaged 47% and 107% of the corresponding estimates for the parent ribosides. In monkeys, the mean AUC's for the aglycones were 7- and 12-fold higher than the AUC's for the respective parent compounds. In both species, aglycone formation was even greater after oral administration. The urinary recoveries of BDCRB and TCRB and their corresponding aglycones in both species after either dose route were less than 5% of the administered dose, suggesting that metabolism is the primary route of elimination for both parent compounds as well as their aglycones. Attempts to identify additional metabolites are in progress.

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New Micromethod for Titration of DNA Viruses Encoding Thymidine Kinase. M.Dragúň, J.Dragúňová, B.Rada and J.Pešlová, Institute of Virology, Slovak Academy of Sciences, 842 46 Bratislava, Slovakia.

New micromethod for titration of DNA viruses is based on the incorporation of labelled thymidine into DNA of viruses encoding proper thymidine kinase (HSV-1 and vaccinia viruses) in cells deficient in TK (L and Rat2 cells). In one-step growth experiments we found a linear correlation between the incorporation of thymidine into virus-infected cells and the multiplicity of infection (MOI). The range of linearity varied between 2-3 logs. This dependence was supported by two independent methods : virus titration and DNA-DNA hybridization which afforded the same linear dependence on MOI. Very advantageous utilization of this micromethod is a determination of virus titer at dose-response experiments in one-step growth arrangement. We tested the method on 8 substances with different mode of action and inhibiting the multiplication of HSV-1 virus in L(TK^-) cells and on 7 other substances blocking vaccinia virus multiplication in Rat2(TK^-)cells We determined the values of IC_{50} by the method of radioactive thymidine incorporation and by classical virus titration. The ratios of IC_{50} received by micromethod and by titration ranged between 0.87-2.85 for HSV-1 and between 0.61-1.12 for vaccinia virus, respectively. Both methods give very close or identical results, comparable with literature data. However, it is necesary to underline, that the micromethod enables a simple enumeration of virus titer from calibration curve for various concentrations of tested substance.