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Some Biological Properties of BRL 42810, a Well Absorbed Oral Prodrug of the Antiherpesvirus Agent BRL 39123. M.R. Boyd, R. Boon, S.E. Fowles, K. Pagano, D. Sutton, R.A. Vere Hodge and B.D. Zussman. Beecham Pharmaceuticals, Research Division, Great Burgh, Epsom, Surrey, United Kingdom.

BRL 42810, the diacetate ester of the 6-deoxy derivative of BRL 39123, showed good antiviral activity when administered orally to mice infected intraperitoneally or cutaneously with herpes simplex virus type 1. When administered to mice and rats, BRL 42810 gave peak plasma concentrations of BRL 39123 over 10-fold higher than those seen after an equivalent oral dose of BRL 39123. The major metabolites of BRL 42810 in the three species were BRL 39123 and its 6-deoxy precursor whereas little BRL 42810 was found. After an oral dose of BRL 42810 (equivalent to 5mg/kg BRL 39123) to healthy subjects, more than half the dose was absorbed and rapidly converted to BRL 39123. Peak plasma concentrations of BRL 39123 (mean,4.5µg/ml) were observed within one hour, and were over 10-fold higher than those following a similar oral dose of BRL 39123. In repeat dose studies in which BRL 42810 was administered 8-hourly for 5 days, plasma profiles of BRL 39123 were almost superimposable following the first and last doses. There was no noticeable accumulation of any metabolic precursor of BRL 39123. BRL 42810 was well tolerated in these human subjects. The terminal half-life of BRL 39123 in man was about 2-3 hours after oral administration of BRL 42810, comparable to that after intravenous administration of BRL 39123. Clearance of BRL 39123 was predominantly renal.

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Selection of an Oral Prodrug (BRL 42810) for the Anti-Herpesvirus Agent BRL 39123. R.A. Vere Hodge, D. Sutton, M.R. Boyd and M. Cole. Beecham Pharmaceuticals Research Division, Great Burgh, Epsom, Surrey, United Kingdom.

The 6-deoxy derivative of BRL 39123 (BRL 42359) and the corresponding diacetyl and dipropionyl 6-deoxy derivatives (BRL 42810 and BRL 43599) were tested as oral prodrugs. The *in vivo* assessment of absorption (dose 0.2 mmol/kg) and the conversion to the active compound, BRL 39123, was determined in rats. Compared with the sodium salt of BRL 39123 given iv, the bioavailability of BRL 39123 from orally administered BRL 39123, BRL 42359, BRL 42810 and BRL 43599 was 1.5%, 9%, 41% and 27% respectively. These prodrugs, and 6-deoxyacyclovir, were tested in rat duodenal contents, intestinal wall homogenate, liver homogenate and blood, and in the corresponding human fluids/tissues. BRL 42810 was much more stable than BRL 43599 in human duodenal contents (half-lives >2 hr and 7 min respectively) yet efficiently converted by the tissue homogenates. The major metabolic pathway was by deacetylation followed by oxidation at the 6-position. The rate of oxidation was comparable to that of 6-deoxyacyclovir which is known to be converted efficiently in man. BRL 42810 was selected for further evaluation and progression to volunteer studies.