Tissue Distribution of Radioactivity after Intravenous and Oral Administration of $[^{14}\text{C}]$Brincidofovir to Rats

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**Purpose**

To determine the tissue distribution of radioactivity after single intravenous (IV) or oral administration of $[^{14}\text{C}]$brincidofovir (BCV) to rats.

**Methods**

$[^{14}\text{C}]$BCV was administered to pigmented and non-pigmented rats by 2-hour IV infusion or by oral gavage at a dose of 15 mg/kg. Tissue distribution was determined by quantitative whole body autoradiography at time points up to 35 days post dose.

**Results**

Radioactivity was well distributed with similar qualitative distribution patterns of the radioactivity after IV and oral administration. Quantitatively, tissue radioactive concentrations in small intestinal tissue after IV administration were approximately 1/10 the concentrations in small intestinal tissue after oral administration. For most other tissues, tissue radioactive exposure was generally higher after IV administration than after oral gavage administration. Peak concentrations of radioactivity in most tissues occurred at 4 to 8 hours after oral administration, or at the end of the 2 hour IV infusion. Regardless of route of administration, tissues with highest concentrations of radioactivity were associated with organs of clearance or elimination (liver, kidney and small intestine). The tissue-to-plasma ratios (T/P) in these organs were high (>30) and for kidney cortex and liver were similar between the IV and oral routes of administration. Tissues with lowest concentrations of radioactivity were brain, spinal cord, skeletal muscle, white adipose tissue and bone. Association of radioactivity in the brain and spinal cord was higher after IV administration (~20% of plasma concentration compared to ~5% after oral administration). At 35 days post-dose, radioactivity was below the limit of quantification in all tissues except for bone marrow, lymph node, spleen and adrenal gland after IV administration, which was different from those tissues with residual concentrations after oral administration (kidney cortex, liver and small intestine). No evidence of specific association with melanin containing tissues (eye, uvea) was detected for either administration route.

**Conclusion**

Compared to the oral route, IV administration of $[^{14}\text{C}]$BCV results in lower small intestinal concentrations of BCV-related radioactivity, which is consistent with lower incidence and severity of GI findings in toxicology studies after repeat IV BCV administration to rats. These data support further clinical development of IV-administered BCV in order to mitigate the dose-limiting GI events observed with long-term orally administered BCV in patients with gastrointestinal susceptibility.