Beloranib, an analog of the natural chemical compound fumagillin, is an experimental drug candidate for the treatment of obesity. Sprague Dawley rats, both intact and bile duct-cannulated (BDC), were administered a single IV dose of 4 mg/kg (200 µCi/kg) of [14C]beloranib. Blood, plasma, urine, feces, and bile were collected for mass balance, metabolite profiling, and identification. Within 24 hours, approximately 82% and 87% of the dose radioactivity was recovered in intact male and female rats, respectively. Total recoveries (0-120 hr) were 92.2% and 95.6%, respectively. From intact male and female rats, 67% and 60% of the dose radioactivity was excreted in the feces, with less found in urine (19% and 30%), respectively. In BDC rats, ca. 60% of the dose radioactivity was found in bile within 72 hrs. Metabolite profiles were determined by HPLC and LC/FT-MS, and the identifications were performed using the data presented in the text.

Conjugation

Glutathione conjugation and subsequent degradation products accounted for 92.2% and 95.6%, respectively. The major metabolites were found in the urine and feces, with 7% of the dose in males and females, respectively. A small amount of the N-oxide of beloranib was also observed in bile. Very little radioactivity derived from the GSH pathway was recovered in urine (3-4% of the dose). The major metabolites in urine were fumagillol-related metabolites, accounting for 7% of the dose in males and 13% of the dose in females, respectively. Beloranib was a prominent circulating radioactive component in rat plasma, accounting for ca.10% of the total radioactivity in 0-48-hr rat plasma samples. The highest proportion of radioactivity in plasma of rats (ca. 30%) was fumagillol-related metabolites. The metabolic fate of dimethylaminoethanoloxyl cinnamic acid, the non-radiolabeled portion of the hydrolys products of beloranib, was evaluated and the results indicated that it and each of its metabolites account for <10% of the dose in bile or urine. Overall, beloranib cleared mainly by metabolism and biliary excretion of metabolites in the rats. The major metabolic pathways include glutathione conjugation-derived metabolites and fumagillol-derived metabolites. No single major metabolite was detected at less than 10% of the dose except for one (10%) detected in feces. Some non-extractable radioactivity was observed in later time-point (48-hr post-dose) liver, however, it accounted for less than 0.15% of the administered dose.

Materials and Methods

Beloranib is a novel therapeutic candidate for the treatment of obesity1 and was previously evaluated for oncology2.3. Studies were done to evaluate the metabolic fate of the molecule from in vitro and in vivo metabolism4. The objectives of this study were 1) to determine the route and extent of radioactivity in both intact and bile duct-cannulated (BDC) rats after a single intravenous (IV) administration of [14C]beloranib; 2) determine the biotransformation profiles of [14C]beloranib in plasma, bile, urine, and feces; 3) to identify the major metabolites of beloranib.

Results and Discussion

Figure 1. Radioprofiles of Plasma, Urine and Feces (Intact rats) and Bile (BDC Male Rats)

Figure 2. Proposed Metabolic Pathways of Beloranib in Rats

Table 1. Recovery of Radioactivity in Urine and Feces (Intact Male Rats) and in Bile (BDC Male Rats)

Table 2. Relative Distribution of Beloranib and its Major Metabolites

References