Pharmacokinetic, Mass Balance and Tissue Distribution of $[^{14}C]$-BC-3781 in Non-Pigmented Rats

W.W. Wicha, Z. Ivezic-Schoenfeld, R. Novak

Nabriva Therapeutics AG, Vienna, Austria

**Abstract**

Background: BC-3781 is a new antimicrobial agent of the pleuromutilin class. BC-3781 showed activity against a large variety of bacterial pathogens when evaluated in in vitro and in vivo assays. BC-3781 is a highly potent, broad-spectrum antibiotic, with a good safety profile with low toxicity and a high therapeutic index. 

**Methods:** Male and female rats were dosed at a nominal dose level of 10 mg/kg with $[^{14}C]$-BC-3781 and returned to separate metabolism cages where urine and faeces were collected via aluminium feeders placed into the cages. In addition, radioactivity in feed, faeces and in the cage contents was measured as well. Furthermore the radiolabel in the faecal and/or urinary excreta was measured by liquid scintillation counting techniques. The tissue distribution was investigated by quantitative whole-body autoradiography (QWBA). 

**Results**

Blood levels of $[^{14}C]$-BC-3781 in Sprague Dawley Rats 

$[^{14}C]$-labeled BC-3781 was administered as a single bolus application (10 mg/kg) to two groups of five male and female Sprague Dawley rats each. Radioactivity concentrations were measured in blood and plasma samples obtained pre-dose and 1, 5, 15 and 30 min and 1, 4, 8, 12, 24, and 48 h post-dose and were expressed as µg/g equivalents. The plasma-concentration time curve and respective pharmacokinetic parameters (Table 1) showed no statistically significant difference between female and male animals. After 12 h radioactivity levels dropped below the detection limit. Mean ratio of whole blood and plasma concentrations was comparable in both genders. 

Conclusions: BC-3781 showed a high tissue affinity and a rapid and homogeneous distribution of radioactivity. The plasma concentration-time curve of i.v. administered $[^{14}C]$-BC-3781 described a multi-phasic decline, with a rapid initial distributional phase followed by a terminal elimination phase. Drug concentrations measured in the majority of tissues including skin, soft tissues and lungs were substantially higher compared to plasma levels. Within the investigated time all intra-organ concentrations of BC-3781 approached the lower limit of quantification, being in line with a 96 % total recovery of radioactivity after 7 days. No differences in gender could be determined. 

**Table 1:** Pharmacokinetic parameters measured in plasma collected from male and female rats 48 h post-dose and are expressed as µg equivalent/g. The plasma-concentration time curve and respective pharmacokinetic parameters (Table 1) showed no statistically significant difference between female and male animals. After 12 h radioactivity levels dropped below the detection limit. Mean ratio of whole blood and plasma concentrations was comparable in both genders. 

Methods

**Radiochemical purity:** The radiochemical purity of $[^{14}C]$-BC-3781 was >95 % prior to dosing as determined by HPLC analysis. 

**Concentration measurements:** For the determination of radioactivity associated with dosing solutions, whole blood, plasma, expired air, urine, tissues, carcasses and cage washings were determined using liquid scintillation counting techniques. The tissue distribution was investigated by quantitative whole-body autoradiography (QWBA). 

Conclusions

- The concentration-time curve of intravenously administered $[^{14}C]$-BC-3781 showed a multi-phase decline, with a rapid distribution phase and a prolonged terminal phase. 
- QWBA showed a rapid distribution into tissues and organs demonstrating:
  - higher concentrations in tissue compared with blood 
  - good penetration into tissues of relevance for therapeutically indicated areas, i.e. SSIs and COP 
  - no radioactivity crossing the blood brain barrier 
  - a total elimination of the drug and/or its metabolites. 

**Table 2:** Concentrations of radioactivity in the tissues of male and female rats 48 h post-dose following a single i.v. administration of $[^{14}C]$-BC-3781 at a dose level of 10 mg/kg. 

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**Table 3:** Mass balance results in rats following a single i.v. injection of $[^{14}C]$-BC-3781. 

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