P908

ECCMID 2010

Pharmacokinetic, Mass Balance and Tissue Distribution of [^{14}C]-BC-3205 in Non-pigmented Rats

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Abstract

Background: BC-3205, a pleuromutilin antibiotic, is a new oral development compound for human use. It has finished four Phase I studies demonstrating good oral bioavailability in combination with a favorable safety and tolerability profile. Current clinical development targets the indications skin and skin structure infections (SSSI) and community-acquired pneumonia (CAP). BC-3205 has demonstrated both *in vitro* activity and *in vivo* efficacy in animal models against a broad range of bacteria often encountered in SSSI and CAP. Target pathogens include among others methicillin-resistant *Staphylococcus aureus* (MRSA), multi-drug resistant *Streptococcus pneumoniae,* atypicals and *Haemophilus influenzae*.

Methods: [^{14}C]-labeled BC-3205 was administered to non-pigmented male and female rats as single oral dose of 30 mg/kg via gavage. The substance-associated radioactivity of whole blood, plasma, expired air, urine, feces, and carcasses was detected using liquid scintillation counting techniques. The tissue distribution was investigated by quantitative whole-body autoradiography (QWBA).

Results: Following a single oral administration of [^{14}C]-BC-3205 to male and female rats C_{max} was reached within 3 h after administration. QWBA showed rapid and uniform tissue distribution with peak tissue concentrations around C_{max}. Within the investigated time all intra-organ radioactivites approached the lower limit of quantification, indicating a total elimination of the BC-3205 associated radioactivity. This was in line with the results of the excretion balance, showing 96 % total recovery of radioactivity after 7 days in males and females. No differences in gender could be observed.

Conclusions: BC-3205 showed a rapid and homogeneous tissue distribution of radioactivity from blood to tissues. The excretion of BC-3205 related radioactivity was rapid with 92.5 % of material being excreted within 48 h. Following an oral dose of [^{14}C]-BC-3205, the majority of the radioactivity was excreted via the fecal route (93.1 %).

Introduction

The absorption, distribution, metabolism and excretion of BC-3205 was investigated in the rat, using a [^{14}C]-labelled test substance. BC-3205 is in clinical development for the oral treatment of skin and skin structure infections (SSSI) and community-acquired pneumonia (CAP). The objectives of the study were as follows:

- To determine the rates and routes of excretion of [^{14}C]-BC-3205, and its metabolite(s) after single dose administration to male and female rats
- To determine the tissue distribution of radioactivity after a single dose administration to male and female rats

Methods

Radiochemical purity: The radiochemical purity of [^{14}C]-BC-3205 was >95 % prior to dosing as determined by HPLC analysis. The specific activity of the radiosynthesized BC-3871 was 42.6 µCi/mg.

Animals: Sprague Dawley rats Crl:CD(SD) within a weight range of 173–344 g and were 6-12 weeks old at the time of dose administration.

Experimental procedures: All animals were dosed orally via gavage with 30 mg/kg [^{14}C]-BC-3205. From the first group of animals (five female and five male) blood samples were collected to investigate the PK of BC-3205 in whole blood and plasma. A second group of rats was dosed and returned to separate metabolism cages where urine and faeces were collected over a period of 168 h. At the end of the collection period the residuals in the carcasses and the cages were measured as well. The radioactivity in the expired air was measured within the first 72 h. The third group of animals was dosed and the tissue distribution of [^{14}C]-BC-3205 was investigated at 3 h, 8 h, 24 h, 72 h and 120 h.

Analytical methods: The radioactivity associated with dosing solutions, whole blood, plasma, expired air traps, urine, faeces, carcasses and cage washings was determined using liquid scintillation counting techniques. The tissue distribution was investigated by quantitative whole-body autoradiography (QWBA).

Results

Blood levels of [^{14}C]-BC-3205 in Sprague Dawley Rats

Following a single oral administration of 30 mg/kg of [^{14}C]-BC-3205 to male and female rats, maximum concentrations of radioactivity in plasma were calculated to occur at 2.7 hours post dose for both male and female animals. The maximum concentration of radioactivity in the whole blood of male rats was also determined to occur at 2.7 hours, and at 2.8 hours for female rats.

The concentration versus time profiles were generally similar, indicating no significant gender differences. Whole blood:plasma ratios were calculated with mean values of 0.901 and 0.848 in male and female rats respectively, indicating similar distribution of the test compound between blood cells and plasma.

A summary of the mean pharmacokinetic parameters of total radioactivity in plasma and whole blood observed following oral administration of [^{14}C]-BC-3205 to male and female rats is given in Table 1.

Quantitative Whole-body Autoradiography of [^{14}C]-BC-3205 in Sprague Dawley Rats Following an oral Administration

The mean radioactive tissue concentration-time data of tissues of therapeutic interest and excretion organs are provided in Table 2. Tissue:blood ratios were greater than 1 in most tissues at the first and second sampling time (3 and 8 hours) indicating rapid distribution from the blood into tissues. Concentrations in the brain and spinal cord were lower than those in blood at early sampling times indicating that drug-related material had not crossed the blood/brain barrier.

In the terminal elimination phase of the BC-3205 PK profile all investigated organs and tissues showed a rapid decrease in radioactivity, indicating that no intra organ accumulation of BC-3205 and/or its metabolites occurs.

Highest concentrations of radioactivity were mainly observed in the gastrointestinal tract content between 3 and 24 h, indicating a major excretion *via* the bile and/or the mucosa.

An overview of the qualitative distribution pattern for female male animals around C_{max} is shown in Figure 1. Figure 2 shows the distribution during the elimination phase of BC-3205 in a female rat 8 h and 24 h after application.

Table 1: Pharmacokinetic parameters measured in plasma collected from male and female Spraque Dawley rats following a single oral dose of [^{14}C]-BC-3205 at a dose level of 30 mg/kg

PK-Parameter	30 mg/kg	30 mg/kg
Sex	male	female
Route of Administration	p.o.	p.o.
Number of animals per group	5	5
Vehicle	water	water
C_{max} ± SD [µg equivalents/g]	1.76 ± 0.56	1.60 ± 0.56
$AUC_{0\text{-}inf}$ [µg equivalents·h/g]	17.2	23.6
Terminal $t_{1/2}$ [h]	9.90	11.0
Mean whole blood/plasma ratio	0.90	0.85

Figure 1: Whole-body autoradiography of female (upper image) and male (lower image) rats 3 h after a single oral dose of 30 mg/kg [^{14}C]-BC-3205

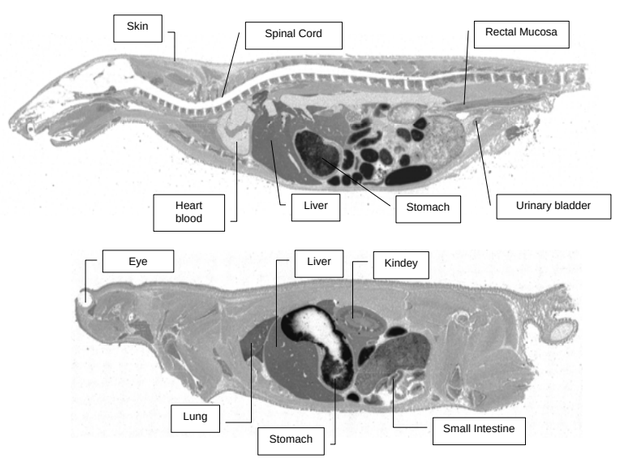

Figure 2: Whole-body autoradiography of a female rat 8 h and 24 h after single oral dose of 30 mg/kg [^{14}C]-BC-3205

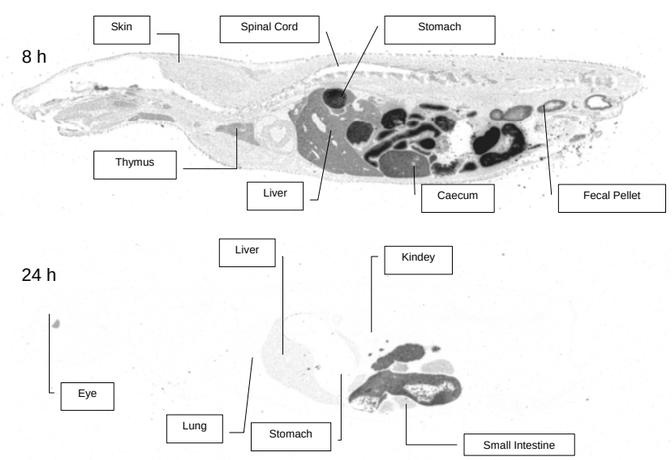

Table 2: Concentrations of radioactivity in the tissues of male and female Sprague Dawley rats following a single oral dose of [^{14}C]-BC-3205 at a nominal dose level of 30 mg/kg

Matrix	Sex	Concentrations Expressed as µg equivalents/g				
		3 h	8 h	24 h	72 h	120 h
Blood (heart)	Male	1.25	0.21	BLQ	BLQ	BLQ
	Female	1.79	0.68	0.19	BLQ	BLQ
	Combined	**1.52**	**0.45**	**0.19**	**BLQ**	**BLQ**
Muscle	Male	3.53	0.20	BLQ	BLQ	BLQ
	Female	4.93	0.98	BLQ	BLQ	BLQ
	Combined	**4.23**	**0.59**	**BLQ**	**BLQ**	**BLQ**
Skin	Male	3.77	0.67	0.19	BLQ	BLQ
	Female	3.42	1.23	0.19	BLQ	BLQ
	Combined	**3.60**	**0.95**	**0.19**	**BLQ**	**BLQ**
Lung	Male	32.9	2.92	0.14	BLQ	BLQ
	Female	30.5	12.0	0.21	BLQ	BLQ
	Combined	**31.7**	**7.46**	**0.18**	**BLQ**	**BLQ**
Kidney	Male	12.6	1.17	0.20	BLQ	BLQ
	Female	19.9	4.96	0.25	BLQ	BLQ
	Combined	**16.3**	**3.07**	**0.23**	**BLQ**	**BLQ**
Liver	Male	24.2	4.40	1.00	0.32	0.20
	Female	37.1	13.9	0.96	0.28	0.24
	Combined	**30.7**	**9.15**	**0.98**	**0.30**	**0.22**

Mass Balance

A mass balance study in female and male Sprague Dawley rats was conducted to obtain information on excretion rates and routes of radioactivity representing the drug and/or its metabolites after a single oral administration of 30 mg/kg [^{14}C]-BC-3205. As already observed in the QWBA, the majority of radioactivity was excreted via the fecal route identifying it as the primary route of elimination.

Elimination of the test compound was rapid, with means of approximately 96 and 89 % of the dose recovered from male and female rats, respectively, during the first 48 hours after administration. A small proportion of the dose (0.07 % in males and 0.14 % in females) was recovered in expired air up to 48 hours after dose administration. Mean total recoveries of 99.7 and 92.7 % were obtained from male and female animals respectively after 7 days.

Table 3: Mass balance results in rats following a single oral dose of [^{14}C]-BC-3205

Sex	Dose [mg/kg]	Matrix	Sampling Time [h]	Recovery [%]	Total Recovery ± SD [%]
Male	10	Urine	0-168 h	1.85	99.7 ± 8.98
		Feces		97.1	
Female	10	Urine	0-168 h	2.73	92.7 ± 6.20
		Feces		89.1	
Combined	**10**	**Urine**	**0-168 h**	**2.29**	**96.22 ± 7.74**
		Feces		**93.1**	

Conclusions

- Maximum concentration of radioactivity was reached after 2.7 h for both male and female animals
- QWBA showed a good distribution into tissues and organs demonstrating
  - higher concentrations in most tissues than in blood
  - good penetration into tissues of relevance for therapeutic indications of interest, SSSI and CAP
  - no radioactivity crossing the blood brain barrier
- A total elimination of the drug and/or its metabolites indicated
  - all intra-organ radioactivities approached the lower limit of quantification within 72 h (QWBA)
  - a total recovery of 96 %, mainly via feces (93 %), as determined by mass balance
  - fecal excretion being the most important route of elimination for BC-3205