Effects of BST204 extract, a purified ginseng dry extract, on pharmacokinetics of imatinib in rats

Soon Uk Chae, Su Jeong, Chae Bin Lee, Doyun Kim, Jee Sun Min, Soo Kyung Bae

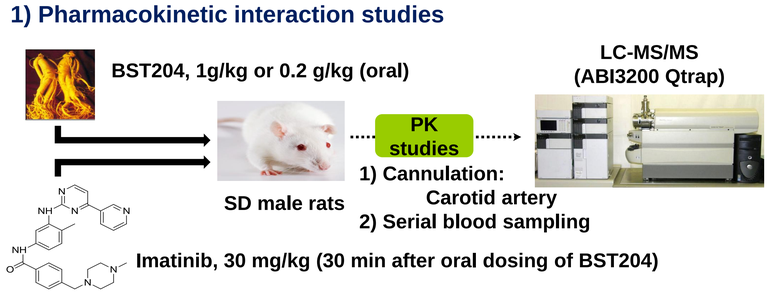
Department of Pharmacology, College of Pharmacy, The Catholic University of Korea, Bucheon, Gyeonggi-do, Republic of Korea

Abstract

BST204 is a purified ginseng dry extract that is a highly concentrated mixture of racemic (1:1) Rh2 (not less than 5.0%) and Rg3 (not less than 10.0%) developed by *Green Cross Health Science* (Republic of Korea). It is undergoing Phase IIa clinical trials for the treatment of cancer cachexia in Europe. We previously reported that oral dosing of BST204 extract had no effect on the pharmacokinetics of two anti-cancer drugs, 5-fluorouracil, and irinotecan, after intravenous dosing in rats. This study aimed to investigate the influences of BST204 extract on the oral absorption and disposition of imatinib, an oral cancer drug, in rats. Rats were orally administered imatinib (30 mg/kg) alone and in combination with BST204 extract (1 g/kg or 0.2 g/kg) concomitantly, respectively. Plasma concentrations of imatinib and N-desmethyl imatinib were determined using an LC-MS/MS. Pharmacokinetic parameters were calculated using a non-compartment model of WINNONLIN software. High oral dose of BST204 extract (1 g/kg) resulted in marked reductions (62.1% decrease) in the maximum concentration (C_{max}) and increases (6-fold) in the time to reach a C_{max} (T_{max}), respectively, as compared with imatinib alone, while the terminal half-life of imatinib was not different between two groups. Similar patterns of N-desmethyl imatinib, which are decreased C_{max} and delayed T_{max}, were observed by co-administration with high oral dose of BST204 extract. In contrast, the pharmacokinetics of imatinib and N-desmethyl imatinib were not altered by orally in combination with low dose of BST204 (0.2 g/kg). In conclusion, high dose of BST204 extract significantly decreased the oral bioavailability of imatinib, and the interaction should occur at the absorption phase, possibly through the inhibition of its intestinal absorption mediated by uptake transporters. We suggest that concurrent intake of BST204 extract with imatinib are better avoided in order to ensure the efficacy of imatinib.

Methods

1) Pharmacokinetic interaction studies



-BST204 (Lot No.203; *S*-Rh2: 6.8%, *R*-Rh2: 6.8%, *S*-Rg: 3.15%, *R*-Rg3: 3.15%)

-BST204 (1 g/kg or 0.2 kg/kg) and imatinib (30 mg/kg) were suspended with 5% tween 80 in 2% methylcellulose solution.

-Blood sampling time: 15, 30, 60, 120, 180, 240, 360, 480, 720, 1080, 1440, and 1800 min

-Blood volume per sampling points: 0.12 mL

2) Bioanalysis of imatinib and N-desmethyl imatinib

-Sample preparation:

A 100 μL aliquot of acetonitrile containing 1 μg/mL verapamil was added to a 50 μL aliquot of rat plasma sample and vortexed. The mixture was then centrifuged at 13,000 × *g* for 15 min to isolate the supernatant (100 μL). A 100 μL aliquot of 5 mM ammonium formate was added to a 100 μL of supernatant. The mixture was vortex-mixed and centrifuged at 13,000 × *g* for 10 min. A 5 μL of clear supernatant was injected into the LC-MS/MS system.

-Equipment: Shimadzu HPLC, ABI 3200 Qtrap

-Detector: Tandem mass spectrometer (triple quadrouple type)
Ion source: Electrospray ionization (positive ion mode)
Desolvation temperature: 600℃
Nebulizing gas: Nitrogen, Collision gas: Nitrogen
Quantitation: SRM (selected reaction monitoring) mode

-Column: Luna C18(2) column (2.0 × 50 mm, 3 μm, Phenomenex)

-Mobile phase: 5 mM ammonium formate: methanol (in 0.1% 5 mM ammonium formate)=5:95(v/v)

-Flow rate: 0.4 mL/min

-Mass parameters

Analytes	Transition (*m/z*)	Polarity	DP (eV)	EP (eV)	CE (eV)	CXP (eV)
Imatinib	494.2→394.2	+	70	20	30	15
N-desmethyl imatinib	480.1→394.2	+	81	20	35	15
Verapamil (IS)	455.3→165.1	+	60	10	40	15

DP: Declustering potential;
EP: Entrance potential;
CE: Collision energy;
CXP: Collision cell exit potential

3) Pharmacokinetic analysis and statistical comparison

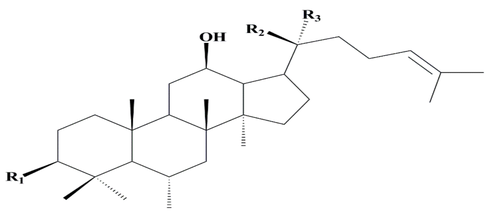
-Pharmacokinetic analysis: Winnonlin Professional (Pharsight, Mountain View, CA, USA)

-Statistical comparison: Independent *t*-test (A *p* value < 0.05 was considered statistically significant.)

Introductions

BST204 is a purified ginseng dry extract that is a highly concentrated mixture of racemic (1:1) Rh2 (not less than 5.0%) and Rg3 (not less than 10.0%) developed by Green Cross Health Science (South Korea). It is derived from crude ginseng by treatment with ginsenoside-β-glucosidase and acid hydrolysis to enrich both 20(*S*)- and 20(*R*)-ginsenoside Rh2 and 20(*S*)- and 20(*R*)-ginsenoside Rg3 (*S*-Rh2, *R*-Rh2, *S*-Rg3, and *R*-Rg3), which have diverse biological effects. These four ginsenosides Rg3 (*S*-Rh2, *R*-Rh2, *S*-Rg3, and *R*-Rg3) probably account for the spectrum of medicinal properties of ginseng, and they are viewed as bioactive markers of its extracts. BST204 is undergoing Phase IIa clinical trials for the treatment of cancer cachexia in Europe. We previously reported that oral dosing of BST204 extract had no effect on the pharmacokinetics of two anti-cancer drugs, 5-fluorouracil, and irinotecan, after intravenous dosing in rats. The objective of the present work was to evaluate the pharmacokinetic profiles of imatinib after oral administration of BST204, a purified ginseng dry extract, at high (1 g/kg) or low (0.2 g/kg) dose in rats.

Identification	R_1	R_2	R_3
R-Rg3	-Oglc(2-1)glc	$-CH_3$	-OH
S-Rg3	-Oglc(2-1)glc	-OH	$-CH_3$
R-Rh2	-Oglc	$-CH_3$	-OH
S-Rh2	-Oglc	-OH	$-CH_3$



We previously reported that oral dosing of BST204 extract had no effect on the pharmacokinetics of two anti-cancer drugs, 5-fluorouracil, and irinotecan, after intravenous dosing in rats. The objective of the present work was to evaluate the pharmacokinetic profiles of imatinib after oral administration of BST204, a purified ginseng dry extract, at high (1 g/kg) or low (0.2 g/kg) dose in rats.

Results

1) Pharmacokinetic properties of imatinib after oral administration (High oral dose of BST204)

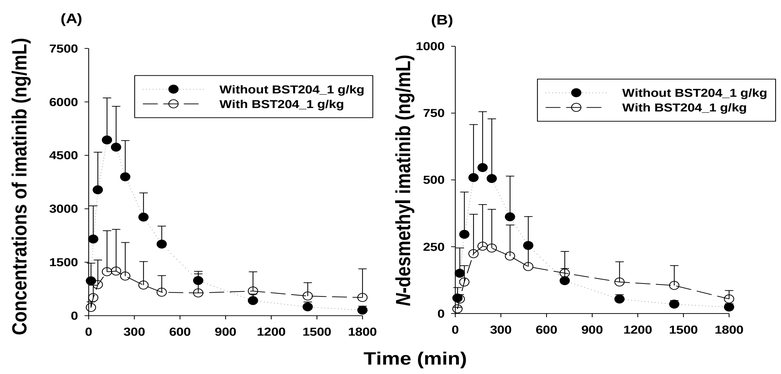


Figure 1. Mean plasma concentrations of imatinib (A) and N-desmethyl imatinib (B) after oral administration of imatinib (30 mg/kg) without (●, *n* = 10) or with (○, *n* = 10) high dose of BST204 extracts (1 g/kg) to rats. Vertical bars mean standard deviation.

Parameters	Without BST204 (*n* = 10)	With BST204 (*n* = 10)	*p*
Imatinib			
AUC_t (μg min/mL)	2400±498	1320±532	0.0001
$t_{1/2}$ (min)	521±424	424±98.1	0.63
C_{max} (μg/mL)	5.02±1.09	1.86±1.07	0.000083
T_{max} (min)[a]	120 (120~180)	720 (120~1800)	0.020
N-desmethyl imatinib			
AUC_t (μg min/mL)	287±104	244±75.0	0.38
$t_{1/2}$ (min)	391±110	409±89.0	0.78
C_{max} (μg/mL)	0.564±0.214	0.305±0.117	0.014
T_{max} (min)[a]	180 (120~180)	720 (180~1440)	0.017

Table 1. Mean (± standard deviations) pharmacokinetic parameters of imatinib and N-desmethyl imatinib after oral administration of imatinib (30 mg/kg) without or with high dose of BST204 extracts (1 g/kg) to rats.

- High oral dose of BST204 extract (1 g/kg) resulted in marked reductions (62.1%) in the C_{max} (5.02 ± 1.09 μg/mL *versus* 1.86 ± 1.07 μg/mL) and increases (6-fold) in the time to reach a C_{max} ($T_{max;}$ 120 min *versus* 720 min), respectively, as compared with imatinib alone, while the terminal half-life of imatinib was not different between two groups. These results suggest that the combination of imatinib with high dose of BST204 reduces the absorption of imatinib in the gastrointestinal tract after oral administration but continues to be absorbed.
- Similar patterns of N-desmethyl imatinib, which are decreased C_{max} and delayed T_{max}, were observed by co-administration with high oral dose of BST204 extract. The oral absorption of BST204 high-dose oral administration reduced imatinib oral absorption, and the C_{max} of N-desmethyl imatinib was also reduced.

2) Pharmacokinetic properties of imatinib after oral administration (Low dose of BST204)

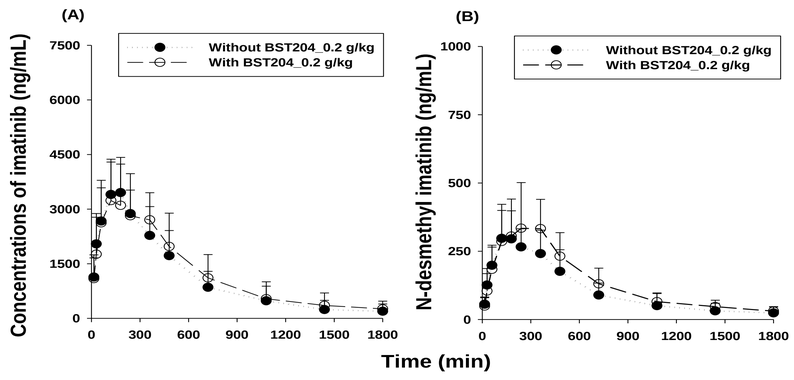


Figure 2. Mean plasma concentrations of imatinib (A) and N-desmethyl imatinib (B) after oral administration of imatinib (30 mg/kg) without (●, *n* = 8) or with (○, *n* = 8) low dose of BST204 extracts (0.2 g/kg) to rats. Vertical bars mean standard deviation.

Parameters	Without BST204 (*n* = 8)	With BST204 (*n* = 8)	*p*
Imatinib			
AUC_t (μg min/mL)	2310±727	2180±575	0.66
$t_{1/2}$ (min)	454±192	426±48.5	0.53
C_{max} (μg/mL)	3.56±0.307	3.65±0.791	0.84
T_{max} (min)[a]	120 (120~240)	120 (60~180)	0.12
N-desmethyl imatinib			
AUC_t (μg min/mL)	192±71.3	236±86.9	0.32
$t_{1/2}$ (min)	455±162	466±109	0.89
C_{max} (μg/mL)	0.328±0.103	0.345±0.143	0.81
T_{max} (min)[a]	180 (120~360)	180 (180~360)	0.86

Table 2. Mean (± standard deviations) pharmacokinetic parameters of imatinib and N-desmethyl imatinib after oral administration of imatinib (30 mg/kg) without or low dose of BST204 extracts (0.2 g/kg) to rats.

- The plasma levels of imatinib and N-desmethyl imatinib were similar in both two groups (Figure 2). The pharmacokinetics of imatinib and N-desmethyl imatinib were not altered by combination with low dose of BST204 (0.2 g/kg).
- Thus, the molar AUC ratio of N-desmethyl imatinib to imatinib, was also similar both in the presence and absence of low dose of BST204 extracts.
- Concomitant administration of high dose (1 g/kg) or low dose (0.2 g/kg) of BST204 resulted in BST204 dose-dependent decrease in oral absorption of imatinib by BST204 co-administration.
- These results might be caused by the inhibition of the organic anion transporting polypeptide (OATP) 1A2, 1B3, and 1B1, which are known as uptake transporters involved in the gastrointestinal absorption of imatinib by the BST204 extract.

Conclusions

In conclusion, high dose of BST204 extract significantly decreased the oral bioavailability of imatinib, and the interaction should occur at the absorption phase, possibly through the inhibition of its intestinal absorption mediated by uptake transporters, OATP1A2, 1B3, and 1B1. We suggest that concurrent intake of BST204 extract with imatinib are better avoided in order to ensure the efficacy of imatinib.