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Pharmacokinetics of Dasatinib

Jana Hořínková, Martin Šíma, Ondřej Slanař
Institute of Pharmacology, First Faculty of Medicine, Charles University and General University Hospital in Prague, Prague, Czech Republic

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Abstract: Tyrosine kinase inhibitors have recently become an essential tool in management of chronic myeloid leukaemia (CML). Dasatinib, a representative of those drugs, acts by inhibiting key proteins included in CML development, predominantly Bcr-Abl and Src. Its advantage is that it shows activity in many cases where other agents bring no improvement due to resistance. Pharmacokinetics of dasatinib has specific characteristics that may play an important role in achieving sufficient exposure in patients. Therefore, the key pharmacokinetic properties are summarized in this report. For example, dasatinib absorption is significantly influenced by gastric pH and its modulation can be a source of serious interactions, as well as simultaneous administration of drugs affecting cytochrome P450.

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Mailing Address: Mgr. Jana Hořínková, Institute of Pharmacology, First Faculty of Medicine, Charles University and General University Hospital in Prague, Albertov 4, 128 00 Prague 2, Czech Republic; Phone: +420 224 968 035; Fax: +420 224 968 149; e-mail: jana.horinkova@lf1.cuni.cz

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Introduction

Possibilities of chronic myeloid leukaemia (CML) therapy have recently been broadening as there are new agents with antitumor activity that can be used to treat this hematologic malignancy. Dasatinib belongs among small molecules inhibiting tyrosine kinases (Cohen, 2002).

The first reports on dasatinib (formerly BMS-354825) in literature reach to 2004 (Lombardo et al., 2004). Two years later, in 2006, it was approved by FDA and EMA (brand name Sprycel®). Indications in adults include Philadelphia chromosome-positive chronic myeloid leukaemia (Ph+ CML) in chronic phase and Philadelphia chromosome-positive acute lymphoblastic leukaemia (Ph+ ALL), it is also approved for treatment of Ph+ CML in chronic phase in paediatric patients (Bristol-Myers Squibb, 2017). Dasatinib shows its benefits in cases where imatinib (Gleevec®, older tyrosine kinase inhibitor firstly approved by FDA in 2001) (Novartis, 2018) fails because of resistance and it has been reported that dasatinib has 325-fold greater activity in inhibiting Bcr-Abl than imatinib (O'Hare et al., 2005). Studies *in vitro* as well as *in vivo* have shown that dasatinib inhibits the kinase activity of 14 out of 15 imatinib-resistant Bcr-Abl isoforms with the only one not responding mutant, T315I (Shah et al., 2004).

The way dasatinib acts against cancer cells is explained by inhibition of several proteins that have their role in cancer pathogenesis as they are employed in cell differentiation, proliferation and survival, most importantly Bcr-Abl, Src, c-kit and PDGFRβ (platelet-derived growth factor receptor β) (Ikeda et al., 1991; Szczylik et al., 1991; Thomas and Brugge, 1997; Lombardo et al., 2004; Yang et al., 2010).

In conducted studies, dasatinib showed variable pharmacokinetic profiles with high intra subject variability (Chandani et al., 2017). This is the reason why the aspects of dasatinib pharmacokinetics are being studied in this review.

Physical/chemical properties

Dasatinib is a white to off-white powder with melting point of 280 to 286 °C (Bristol-Myers Squibb Pharmaceutical Research Institute, 2007). It is a lipophilic substance with partition coefficient (*logP*) between octanol and water 2.71, which means it is able to pass well through cell membranes (Minematsu and Giacomini, 2011).

As a monohydrate, it is insoluble in water (0.008 mg/ml at 24 ± 4 °C), slightly soluble in ethanol, methanol, polyethylene glycol 400 and propylene glycol and very slightly soluble in acetone and acetonitrile (USP definition). It is practically insoluble in corn oil (Bristol-Myers Squibb Pharmaceutical Research Institute, 2007).

Solubility in water is pH dependent. The anhydrous free drug has characteristics of a weak base which is a subject of dissociation when placed into water environment. Two basic ionization constants (pK_a) were determined (6.8 and 3.1) and one weekly acidic pK_a (10.9) (Bristol-Myers Squibb Pharmaceutical Institute, 2007). According to *in vitro* investigation, the solubility surpasses 0.690 mg/ml at pH values lower than

4.0, whereas in higher values it rapidly decreases (0.205 mg/ml at pH 4.28 and less than 0.001 mg/ml at pH 6.99) (Eley et al., 2009).

Another study confirming those findings was performed at the temperature of 37 °C. The results show that the solubility of dasatinib was surprisingly high at pH approximately 1 (49.6 mg/ml), due to full protonation of both basic nitrogen atoms. As expected, the solubility drops down to 3.62 mg/ml at pH 3.64 and it reaches only 1.40 mg/ml at pH 3.81. At higher values dasatinib becomes practically insoluble (Lubach et al., 2013). This fact of pH-dependent solubility plays an important role in absorption from gastrointestinal tract, as the pH values can range variously, and they can be influenced by other concomitantly using drugs.

Pharmacokinetics of dasatinib

Pharmacokinetic parameters of dasatinib are summarized in Table 1.

Absorption

After oral administration, dasatinib is quickly absorbed from gastrointestinal tract. Preclinical testing in various species (mice, rats, dogs and monkeys) showed that maximum plasma concentrations were most frequently reached within 0.6 to 2 h

Table 1 – Pharmacokinetic parameters of dasatinib in preclinical and clinical trials

Parameter	Preclinical data			Clinical data		
T_{max} (h)	0.6–2.0 (Kamath et al., 2008)	1 (Luo et al., 2006)	2 (Lagas et al., 2009)	1.0 (Aplenc et al., 2011)	0.5 (Christopher et al., 2008b)	1.0 (Takahashi et al., 2011)
F (%)	14–34 (Kamath et al., 2008)	45–51 (Luo et al., 2006)	–	–	–	–
Plasma protein binding (%)	92–97 (Kamath et al., 2008)	–	–	94 (Kamath et al., 2008)	–	–
V_{ss} (l/kg)	3.5–6.3 (Kamath et al., 2008)	–	–	–	–	–
V_z/F (l)	–	–	–	606–9113 (Takahashi et al., 2011)	600–9464 (Demetri et al., 2009)	–
$t_{1/2}$ (h)	0.9–4.2 (Kamath et al., 2008)	–	–	1.9–3.6 (Aplenc et al., 2011)	3.6 (Christopher et al., 2008b)	2.2–4.9 (Demetri et al., 2009)

T_{max} – time to reach maximum plasma concentration; F – bioavailability; V_{ss} – apparent volume of distribution at steady state; V_z/F – apparent volume of distribution during terminal phase after non-iv administration; $t_{1/2}$ – half-life

(T_{max} – time to reach maximum plasma concentration) (Luo et al., 2006; Kamath et al., 2008; Lagas et al., 2009). Clinical studies achieved similar results with T_{max} 0.5 to 1.0 h. Among subjects, substantial variability was observed with T_{max} values ranging from 0.28 up to 6.3 h (Christopher et al., 2008b; Aplenc et al., 2011; Takahashi et al., 2011; Bristol-Myers Squibb, 2017).

Bioavailability is known to be variable between subjects, too. First preclinical studies in mice showed bioavailability from 45 to 51% (Luo et al., 2006), whereas other experiments performed in various species led to values between 14 and 34% (14% and 17% mice, 27% rats, 34% dogs, 15.2% monkeys) (Kamath et al., 2008). Bioavailability in humans was not determined because intravenous administration would be risky, but we know that interindividual variability in AUC (area under the curve) can range from 32 to 118% (Dai et al., 2008) and intraindividual variability from 40 to 50% (Chandani et al., 2017).

Experiments, where dasatinib was administered intraportally in rats suggest that first-pass metabolism does not have a significant effect on bioavailability, and it is therefore limited mostly by absorption (Kamath et al., 2008).

Absorption of dasatinib can be influenced by meal, which is taken with the medicine, although the change is not significant. After a single dose of 100 mg, the mean AUC was increased by 14% in subjects with high-fat meal (Bristol-Myers Squibb, 2017).

Another factor impacting dasatinib absorption is gastric pH likely due to alteration of the drug solubility as described above. Dasatinib dissolves better in low pH values, leading to higher amount of drug being absorbed into blood. Gastric pH can be modulated by many substances including medications such as H_2-receptor antagonists (e.g. famotidine, ranitidine), antacids or proton pump inhibitors (e.g. omeprazole, lansoprazole, rabeprazole) which cause increased gastric pH (Pali-Scholl et al., 2010; Mylan Pharmaceuticals, 2011; AstraZeneca Pharmaceuticals, 2012). On the other hand, there are agents that are able to induce gastric acid secretion or by other mechanism decrease gastric pH such as pentagastrin or betaine HCl (Chu et al., 1999; Yago et al., 2013; Šíma et al., 2019).

Effect of pentagastrin (0.25 mg/kg, sc) and famotidine (10 mg/kg, iv) on dasatinib absorption was investigated in a preclinical study in rats. Both substances were administered 2 h prior to dasatinib administration. Unexpectedly, pentagastrin led to a slight decrease in AUC (from 0.421 μg×h/ml in control group to 0.297 μg×h/ml). That could have been caused by rapid onset of pentagastrin action and too early dosing 2 h before dasatinib since the measured gastric pH after pentagastrin administration was the same as in control group and thus it probably stayed without effect on dasatinib absorption. Famotidine had a significant impact with dasatinib AUC decrease to 0.094 μg×h/ml (Lubach et al., 2013).

There was another interaction study in dogs with famotidine (40 mg, orally, 3 h prior to dasatinib), pentagastrin (6 μg/kg, im, 30 min prior to dasatinib) and betaine HCl (750 mg, orally, either 5 min, or 5 and 20 min prior to dasatinib), in which

probably due to administration only 30 min before dasatinib, pentagastrin led to a doubling of dasatinib AUC (measured gastric pH was also lower than in control group). Two tablets of betaine HCl (1,500 mg in total) had the same effect on absorption as pentagastrin while when dasatinib was given with famotidine and petagastrin the negative effect of famotidine was mitigated (Pang et al., 2013).

In humans, the influence of famotidine and antacids (Maalox® – aluminium/magnesium hydroxides) was examined in a study where dasatinib (50 mg) was administered twice a day, famotidine (40 mg) was given 2 h after dasatinib (and therefore 10 h before another dose of dasatinib) and the antacid (30 ml) was given firstly 2 h before and then at the same time as dasatinib. Although famotidine didn't change first dasatinib dose absorption, the next dasatinib dose 10 h after famotidine was absorbed significantly worse (mean AUC decreased from 136 to 40.2 ng×h/ml). Concomitant use of antacid similarly decreased dasatinib exposure (mean AUC of 46.3 ng×h/ml), however, when separated by 2 h, absorption remained unaltered (Eley et al., 2009).

Decrease of dasatinib exposure was also confirmed in a study in which pharmacokinetic profiles of Japanese patients treated with or without H_2-receptor antagonists (famotidine 20-40 mg/day, nizatidine 300 mg/day) or proton pump inhibitors (lansoprazole 30 mg/day) were analysed. Results were variable but acid suppressants caused decrease in the extent of dasatinib absorption (mean AUC decreased from 3.51 to 1.47 ng×h/ml/mg) (Takahashi et al., 2012).

The effect of famotidine on dasatinib absorption has been also indicated in a case report suggesting more than 3fold decrease in dasatinib exposure when given concomitantly (Matsuoka et al., 2012).

Another study conducted in humans receiving dasatinib (100 mg) alone, with rabeprazole (20 mg twice a day) or altogether with betaine HCl (1,500 mg) confirmed that proton pump inhibitors have negative effect on dasatinib absorption. However, betaine HCl mitigated this interaction (Yago et al., 2014).

Table 2 – The effect of gastric pH modulators on dasatinib AUC

Comedication	AUC (% of dasatinib monotherapy AUC)
Pentagastrin	↓ (71%) (Lubach et al., 2013); ↑ (223%) (Pang et al., 2013)
Famotidine	↓ (22%) (Lubach et al., 2013); ↓ (39%) (Eley et al., 2009)
Rabeprazole	↓ (14.7%) (Yago et al., 2014)
Any H2RA or PPI	↓ (42%) (Takahashi et al., 2012)
750 mg betaine HCl	≈ (119%) (Pang et al., 2013)
1,500 mg betaine HCl	↑ (229%) (Pang et al., 2013)
Famotidine + 750 mg betaine HCl	≈ (113%) (Pang et al., 2013)
Famotidine + 1,500 mg betaine HCl	↑ (149%) (Pang et al., 2013)
Rabeprazole + 1,500 mg betaine HCl	≈ (96%) (Yago et al., 2014)
Antacid (2 h prior to dasatinib)	≈ (104%) (Eley et al., 2009)
Antacid (concomitantly with dasatinib)	↓ (45%) (Eley et al., 2009)

AUC – area under the curve

The effect of gastric pH modulators on bioavailability of dasatinib is summarized in Table 2.

To conclude, combination of dasatinib with acid suppressants is problematic due to decreased dasatinib bioavailability. If necessary, it is advisable to use antacids separated from dasatinib at least by 2 h. A wish to increase dasatinib bioavailability lead to an attempt to synthesize a compound that could act like a dasatinib prodrug. Thus, a compound called JLTN was synthesized with oral bioavailability increase to 150% of the original value. However, no additional development of the compound has followed so far (Liu et al., 2013).

Distribution

When absorbed into blood, most of dasatinib molecules bind to serum proteins (>90%). The volume of distribution is very high, suggesting that dasatinib distributes well from vascular system to other tissues. A preclinical study performed in various species came with mean Vd values ranging from 3.5 to 6.3 l/kg and human volume of distribution was predicted to be around 4.2 l/kg (using scaling by body weight) (Kamath et al., 2008). Later experiments in men confirmed high volume of distribution with mean values from 600 to 9,464 l and with large variability. After repeated administration, dasatinib does not show any signs of accumulation in the body (Demetri et al., 2009; Takahashi et al., 2011).

In breast-feeding females, dasatinib, as a basic molecule, reaches high concentrations in milk. First estimations considering only passive diffusion predicted lacteal distribution to be rather mild. However, dasatinib is a substrate of BCRP (breast cancer resistance protein) and since this protein is also expressed in mammary gland, we can suppose that BCRP is employed in active transport to the milk (He et al., 2008).

Although dasatinib crosses placental barrier, foetal plasma concentrations reach lower values than those in maternal blood. Concentrations measured in foetal plasma, brain, kidneys and liver were similar, suggesting that distribution in foetus occurs mostly by passive diffusion without specific transporters, which may not be fully evolved yet (He et al., 2008).

Elimination (metabolism and excretion)

Dasatinib half-life was determined in four different species – mice, rats, dogs and monkeys. Mice exhibited the lowest value (0.9 h), the longest half-life was observed in dogs (4.2 h) (Kamath et al., 2008). Human half-life values based on three clinical studies range from 2.2 to 4.9 h (Christopher et al., 2008b; Demetri et al., 2009; Aplenc et al., 2011).

Dasatinib undergoes several routes of metabolism, particularly oxidative and conjugative. Hydroxylation, N-dealkylation, N-oxidation, alcohol oxidation and direct glucuronide or sulphate conjugation seem to be the most employed reactions, leading to formation of many metabolites of which nineteen have been identified.

Dasatinib represents the major circulating moiety in a mass balance study, whereas metabolites are accountant for 40 to 60% of total radioactivity (Christopher et al., 2008a; Kamath et al., 2008).

Although the most abundant metabolite observed in rats is piperazine-N-oxide (M5), its concentrations in human plasma are low. On the other hand, the most frequent metabolites in monkeys and humans are M20 and M24, the products of hydroxylation. In spite of the fact that all of these compounds hold certain activity, they don't significantly contribute to total dasatinib efficacy, due to their low potency (Christopher et al., 2008a, b).

The bile of duct cannulated rats contains mainly N-oxides and conjugates, while dasatinib and oxidative metabolites other than N-oxides are found in faeces of intact rats. That can be caused by a hydrolysis of conjugates and a reduction of N-oxides by microorganisms in the course of passage through gastrointestinal tract before being excreted (Christopher et al., 2008a).

When various metabolism of dasatinib via CYP enzymes or flavin-containing monooxygenase 3 (FMO3) were tested *in vitro*, it turned out that all of them are able to metabolize dasatinib with CYP3A4 showing to be the most potent enzyme (Kamath et al., 2008).

Dasatinib exposure was increased when coadministred with ketoconazole in man (Johnson et al., 2010). Conversely, rifampicin, a CYP3A4 inducer, led to a decrease in dasatinib exposure, confirming that dasatinib is a CYP3A4 substrate (Bristol-Myers Squibb, 2017). Therefore, it is recommended to avoid simultaneous administration with strong CYP3A4 inhibitors or inducers such as grapefruit juice because of possible drug interactions. If necessary, dasatinib doses can be modified in order to maintain adequate plasma concentrations. Concomitant administration with other CYP3A4 substrates should be employed with caution as dasatinib itself acts as a CYP3A4 inhibitor (Bristol-Myers Squibb, 2006).

Dasatinib is mainly excreted in the form of metabolites, as only 15 to 19% remains unchanged. The excretion occurs into faeces (particularly bile), the amount of drug being excreted in urine is very low (Christopher et al., 2008a, b; Kamath et al., 2008).

Impact of drug transporters

The role of dasatinib transport through cell membranes has been investigated in order to map possible influence of some efflux proteins and transporters on dasatinib distribution. Unlike imatinib, dasatinib cell uptake isn't dependent on the activity of human organic cation transporter 1 (hOCT1) (Giannoudis et al., 2008; Hiwase et al., 2008). This transporter was found to be important for imatinib active transport into cells and its lower expression can contribute to treatment resistance (Thomas et al., 2004).

ATP-binding cassette transporters (ABC transporters) have major importance on dasatinib influx/efflux. For example, ABCC4 participates in its gastric absorption

(Furmanski et al., 2013). There are other important transporters belonging to this family, like ABCB1 (P-glycoprotein – P-gp) and ABCG2 (breast cancer resistance protein – BCRP). Those proteins are expressed at various barriers, such as intestinal epithelium and blood-brain barrier or blood-testis barrier, where they are able to transport endogenous substances as well as xenobiotics through membranes. Sometimes, their efflux function can cause drug resistance as they prevent the drug to reach its intracellular target (Borst and Elferink, 2002).

Dasatinib may be transported by both of these proteins (Giannoudis et al., 2008; Hiwase et al., 2008; Chen et al., 2009; Hegedus et al., 2009). First findings comparing wild-type and P-gp knockout mice suggested that although dasatinib is a P-gp substrate, it doesn't contribute to low bioavailability (Kamath et al., 2008). Nevertheless, later investigations brought results saying that P-gp can limit dasatinib absorption after oral administration (Lagas et al., 2009). The importance of both transporters (P-gp and BCRP) is supported by results of a study with double knocked-out rats for P-gp and BCRP, which had two-fold higher dasatinib AUC compared with wild-type rats (Tang et al., 2013). Dasatinib can also act as an inhibitor of both of these proteins in higher concentrations and thus it could influence transport of another substances (Hegedus et al., 2009). Nevertheless, the practical impact of those findings on a clinical use in patients with CML has not yet been reliably elucidated.

P-gp also plays a major role in restricting dasatinib accumulation in central nervous system. Although absence of BCRP didn't affect dasatinib brain concentration, inhibition of both these transporters together resulted in considerably higher brain concentration compared to inhibition of only P-gp (Chen et al., 2009; Lagas et al., 2009; Tang et al., 2013). Possible explanations are that P-gp might be able to compensate BCRP loss, or that BCRP can partly take over P-gp's function in its absence.

Pharmacokinetics in special populations

Pharmacokinetic properties of dasatinib were also studied in paediatric settings. Overally, the pharmacokinetics is very similar to that observed in adults and there were no substantial differences. The doses should be reduced and adjusted by body weight or by occurred adverse reactions (Aplenc et al., 2011; Bristol-Myers Squibb, 2017).

Although dasatinib is metabolised through liver, it is not recommended to reduce the dose in patients with mild to moderate hepatic dysfunction (Bristol-Myers Squibb, 2006; Sasaki et al., 2016).

Relationship of pharmacokinetics and pharmacodynamics

Dasatinib exhibits time-dependent effect where plasma concentrations above inhibitory concentration ($IC50_{CD34+cells}$) for more than 12.8 h led to a better clinical response (Ishida et al., 2016). Dasatinib shows many adverse effects like

thrombocytopenia, neutropenia, leucopenia, anaemia, asthenia, pleural effusion, fatigue, nausea or diarrhoea (Visani et al., 2010). The toxicity increases with higher plasma concentrations and so it can be useful to monitor plasma levels of dasatinib in patients in order to prevent serious side effects, particularly in patients with decreased clearance (Demetri et al., 2009).

Conclusion

Dasatinib is a drug with an important role in the management of CML. Its absorption is strongly dependent on gastric pH as it only dissolves at low pH values. For that reason, it is important to pay attention to concomitant use of medications that could modulate gastric pH (e.g. antacids, H_2-receptor antagonists, proton pump inhibitors). After being absorbed into circulatory system, dasatinib binds to plasma proteins to a high degree and it is well distributed to the organs as well as to the breast milk of lactating females. Before being excreted mostly by faeces, dasatinib undergoes predominantly oxidative metabolism mediated by cytochrome P450 and inhibitors or inducers of this enzymatic system can alter dasatinib pharmacokinetics.

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