Effect of esomeprazole on the oral absorption of dasatinib in a patient with Philadelphia-positive acute lymphoblastic leukemia

Elise Pape, Delphine Michel, Julien Scala-Bertola, Thomas Schiestel, Alexandre Harlé, Stéphane Bouchet, Audrey Contet, Cécile Pochon, Nicolas Gambier

Title: Effect of esomeprazole on the oral absorption of dasatinib in a patient with Philadelphia-positive acute lymphoblastic leukemia.

Authors:

- Elise Pape, PharmD, Department of Clinical Pharmacology and Toxicology, CHU Nancy, France
- Delphine Michel, MD, Department of Paediatric Haematology/Oncology, CHU Nancy, France
- Julien Scala-Bertola, PharmD PhD, Department of Clinical Pharmacology and Toxicology, CHU Nancy, France
- Thomas Schiestel, PharmD, Department of Clinical Pharmacology and Toxicology, CHU Nancy, France
- Alexandre Harlé, PharmD PhD, Université de Lorraine, Faculté de Pharmacie, Nancy, France ; CNRS UMR 7039 CRAN, Vandoeuvre-lès-Nancy, France ; Institut de Cancérologie de Lorraine, Service de Biopathologie, Vandoeuvre-lès-Nancy
- Stéphane Bouchet, PharmD PhD, Department of Clinical Pharmacology, CHU Bordeaux, France
- Audrey Contet, MD, Department of Paediatric Haematology/Oncology, CHU Nancy, France
- Cécile Pochon, MD, Department of Paediatric Haematology/Oncology, CHU Nancy, France
- Nicolas Gambier, Pharm D PhD, Department of Clinical Pharmacology and Toxicology, CHU Nancy, France

Corresponding/submitting author

Dr Julien Scala-Bertola

Department of Clinical Pharmacology and Toxicology, CHU Nancy, France

Phone number: +33(0) 3 83 85 25 40 Fax number: +33(0) 3 83 85 27 54

Email: j.scala-bertola@chu-nancy.fr

All authors have completed the Unified Competing Interest form and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

Keywords: Dasatinib, Esomeprazole, Drug-drug interaction, Pharmacokinetics, Leukemia

Word count: 1006

Figure: 1

Running head: Dasatinib-Esomeprazole drug-drug Interaction

Consent of the patient: Available for review

ABSTRACT

Dasatinib is of particular interest in chronic myelogenous leukemia or in philadelphia chromosome-positive acute lymphoblastic leukemia resistant to imatinib. However, its efficacy is reported to be decreased when used simultaneously with gastric acid pH modulators. We report herein the first case reporting a drug-drug interaction between dasatinib and esomeprazole in a patient with Philadelphia-positive acute lymphoblastic leukemia leading to a decrease in dasatinib oral absorption. An extensive review of drug-drug interactions between tyrosine kinase inhibitors used in leukemia and proton pump inhibitors was performed in order to provide some strategies to avoid or to limit this drug-drug interaction.

We describe herein the first reporting case of a drug-drug interaction between dasatinib and esomeprazole in a patient with Philadelphia-positive acute lymphoblastic leukemia leading to a decrease in dasatinib oral absorption.

The patient was a 16-year-old man (1.76 m, 61.5 kg) who benefited from allogeneic stem cell transplantation after a myeloablative conditioning regimen based on 12-Gy total body irradiation and etoposide (60 mg/kg). This case is presented in the context of progression of imatinib-resistant chronic myelogenous leukemia (CML) in acute lymphoblastic leukemia (ALL) with B-cell lineage. One month after stem cell transplantation, Bcr/Abl transcripts were undetectable and chimerism (on total leucocytes) was assessed at 98 % donor cells in blood. Two months later, the patient experienced a molecular relapse with 0.06 % and 0.03 % Bcr/Abl transcripts in blood and bone marrow, respectively. The degree of chimerism was assessed at 99 % donor cells in bone marrow. Immunosuppressive treatment was quickly diminished and dasatinib was introduced at a daily dose of 100 mg but was thereafter decreased to 70 mg per day because of a severe leukopenia (white blood cells at 690/mm^3). At this dose, plasma trough concentration of dasatinib was 5.1 $ng.mL^{-1}$ (Normal value <2.5

$ng.mL^{-1}$ [1]) suggesting a suspected role of dasatinib in the occurrence of leukopenia. Despite the decrease in dasatinib dosing, a severe pancytopenia in a context of staphylococcus bacteraemia was observed and dasatinib was stopped. One week later, dasatinib was restarted at a daily dose of 50 mg then increased to 60 mg. Four months after transplantation, as the immunosuppressive drugs were withdrawn, the degree of chimerism reached 100 % donor cells in blood, and Bcr/Abl transcripts were still detectable but not quantifiable. Despite a prolonged mild pancytopenia, the patient was treated with 50 mg per day of dasatinib to limit molecular relapse. In this context, a study of plasma concentrations of dasatinib was performed as previously described by Bouchet *et al.* using liquid chromatography-tandem mass spectrometry (limit of quantification of 0.1 $ng.mL^{-1}$) [2]. This revealed a maximal concentration (C_{max}) of 23.1 $ng.mL^{-1}$ (Normal value >50.0 $ng.mL^{-1}$ [1]) 4 hours after the administration of dasatinib (Figure 1). The estimated area under the curve between 0 and 6.5 hours ($AUC_{0\text{-}6.5h}$) using the trapezoidal rule was 89.6 $ng.h.mL^{-1}$. The terminal elimination half-life ($t_{1/2}$) was estimated to be 4.9 h. From these results, we concluded that there was a decrease in dasatinib absorption, probably related to a drug-drug interaction influencing dasatinib pharmacokinetics. Drugs concomitantly taken with dasatinib by the patient included prednisolone (15 mg q.d.), valaciclovir (500 mg b.i.d.), cefuroxime (250 mg b.i.d.), ursodeoxycholic acid (200 mg b.i.d.), itraconazole (200 mg b.i.d.), human immunoglobulins (25 g monthly), pentamidine (300 mg monthly) and esomeprazole (40 mg q.d.). As itraconazole was simultaneously used with dasatinib, an increase could have been expected due to an inhibition of CYP3A4 by itraconazole but it was not observed. This result could be explained by a limited absorption of itraconazole due to the effect of esomeprazole on gastric acidity [4]. Thus, esomeprazole was considered as the main suspected drug in the decrease of dasatinib absorption and its dosing was first decreased from 40 mg to 20 mg once daily but finally stopped. A second drug concentration-time profile of dasatinib was established four

days after esomeprazole discontinuation (Figure 1). This revealed an increase of C_{max} and the estimated $AUC_{0\text{-}6.5h}$ from 23.1 to 52.0 ng.mL^{-1} and from 89.6 to 130.6 ng.h.mL^{-1}, respectively. The increase of these two pharmacokinetics parameters with an unmodified estimated $t_{1/2}$ (4.7 versus 4.9 hours) and a 1 hour-earlier T_{max} (3 versus 4 hours) after esomeprazole discontinuation confirmed the influence of esomeprazole on the oral absorption of dasatinib. The influence of esomeprazole on the pharmacokinetics of dasatinib resulting in a 56 % decrease of C_{max} and a 32 % decrease of $AUC_{0\text{-}6.5h}$ was in the same order of magnitude as the study led by Bristol-Myers Squibb. This study found a decrease in C_{max} and $AUC_{0\rightarrow\infty}$ of 41 % and 42 %, respectively when dasatinib was concomitantly used with omeprazole [5]. Besides omeprazole, the efficacy of dasatinib was also described to be encumbered by a decrease of its absorption when used and administered simultaneously with gastric acid pH modulators such as lansoprazole [6], famotidine or aluminium-magnesium hydroxides [7]. In the case of CML or ALL with no resistance to imatinib, imatinib remains an excellent first choice and presents the advantage of being relatively spared by the influence of PPI (pKa value of 7.7). In alternative first-line therapies such as dasatinib or nilotinib with an absorption encumbered by a concomitant use of PPI, PPI could be replaced by aluminium-magnesium hydroxides or H2-receptor antagonists administered 2 hours before or 2 hours after the administration of TKI, respectively [7]. In case of a concomitant use of PPI with TKI, the current available pharmacokinetics and pharmacodynamics studies seem to describe dexlansoprazole, esomeprazole and rabeprazole as the three most potent PPIs to modify the pH of the gastric medium (intragastric pH value above 4 for significantly longer periods of time (>12-16h)) [8,9]. Furthermore, considering the study of Röhss *et al.*, the administration of PPI in a once-daily regimen during a 24h-period revealed for all the tested PPIs (esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole) the two lowest values of intragastric pH measured around 16 hours and 24 hours after PPI intake, respectively [10]. In consequence, the

administration of PPI in a once-daily dose regimen 2 or 3 hours after the TKI intake (as advised for H2 receptor agonist [7]) could probably constitute an alternative option to explore limiting the decrease in TKI absorption due to a concomitant use of PPI therapy.

Finally, dasatinib was stopped 3 weeks after esomeprazole discontinuation because of a pancytopenia and severe acute hepatitis suspected to be attributable to the treatment toxicity, but was attributed to hepatic grade 3 chronic graft *versus* host disease (GVHD) after liver biopsy. Nine months after transplantation, our patient is still alive and he has not received any TKI since, with no relapse of his leukemia at this time. Immunosuppressive treatment for hepatic GVHD is still on-going.

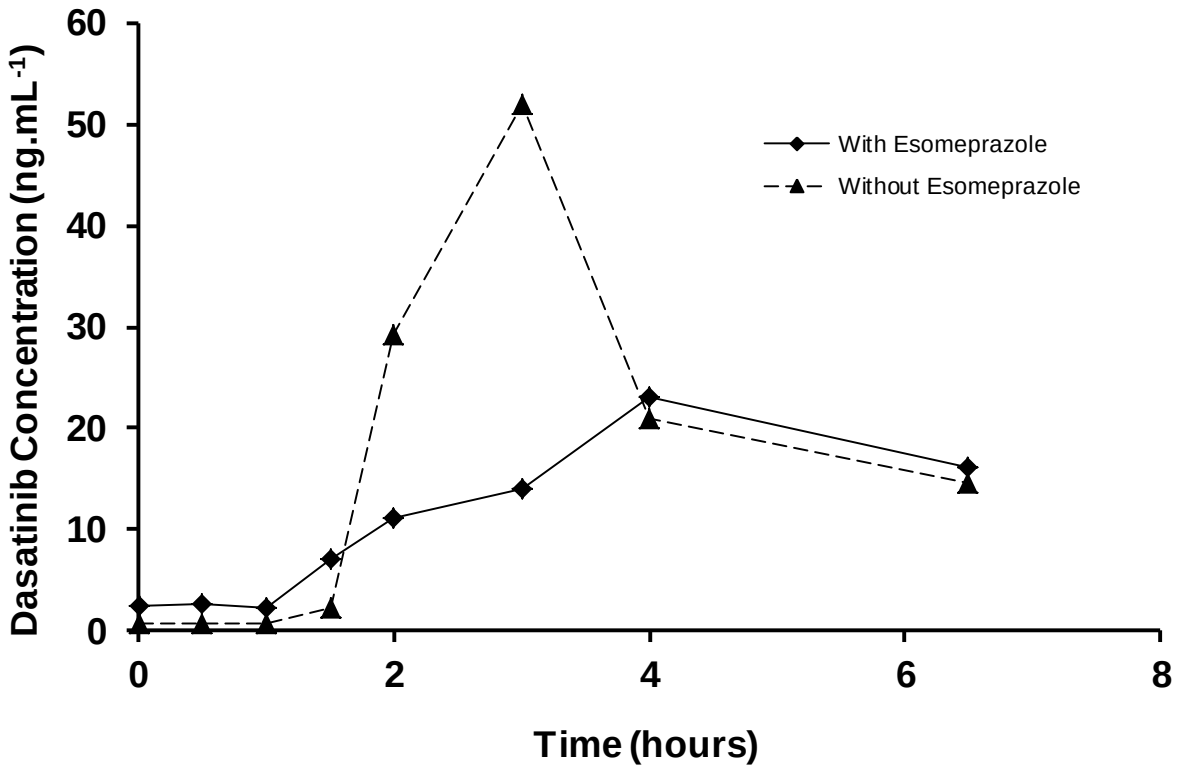

Figure 1: Dasatinib blood concentrations in the presence and the absence of Esomeprazole after an administration of a 50 mg daily dose.

References

1. Miura M. Therapeutic drug monitoring of imatinib, nilotinib, and dasatinib for patients with chronic myeloid leukemia. Biol Pharm Bull 2015; 38:645-54.

2. Bouchet S, Chauzit E, Ducint D, Castaing N, Canal-Raffin M, Moore N, Titier K, Molimard M. Simultaneous determination of nine tyrosine kinase inhibitors by 96-well solid-phase extraction and ultra performance LC/MS-MS. Clin Chim Acta 2011; 412:1060-7.
3. Christopher LJ, Cui D, Wu C, Luo R, Manning JA, Bonacorsi SJ, Lago M, Allentoff A, Lee FY, McCann B, Galbraith S, Reitberg DP, He K, Barros A Jr, Blackwood-Chirchir A, Humphreys WG, Iyer RA. Metabolism and disposition of dasatinib after oral administration to humans. Drug Metab Dispos 2008; 36:1357-64.
4. Li W1, Zeng S, Yu LS, Zhou Q. Pharmacokinetic drug interaction profile of omeprazole with adverse consequences and clinical risk management. Ther Clin Risk Manag 2013; 9:259-71.
5. Bristol-Myers Squibb. The Effect of Omeprazole on the Pharmacokinetics of Dasatinib (BMS-354825) in Healthy Subjects. http://www.clinicaltrials.gov. Accessed in 25 Aug 2015.
6. Takahashi N, Miura M, Niioka T, Sawada K. Influence of H2-receptor antagonists and proton pump inhibitors on dasatinib pharmacokinetics in Japanese leukemia patients. Cancer Chemother Pharmacol 2012; 69:999-1004.
7. Eley T, Luo FR, Agrawal S, Sanil A, Manning J, Li T, Blackwood-Chirchir A, Bertz R. Phase I study of the effect of gastric acid pH modulators on the bioavailability of oral dasatinib in healthy subjects. J Clin Pharmacol 2009; 49:700-9.
8. Shin JM, Kim N. Pharmacokinetics and pharmacodynamics of the proton pump inhibitors. J Neurogastroenterol Motil 2013; 19:25-35.
9. Kirchheiner J, Glatt S, Fuhr U, Klotz U, Meineke I, Seufferlein T, Brockmöller J. Relative potency of proton-pump inhibitors-comparison of effects on intragastric pH. Eur J Clin Pharmacol 2009; 65:19-31.
10. Röhss K, Lind T, Wilder-Smith C. Esomeprazole 40 mg provides more effective intragastric acid control than lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg and rabeprazole 20 mg in patients with gastro-oesophageal reflux symptoms. Eur J Clin Pharmacol. 2004;60:531-9.