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Determination of serum imatinib and its' metabolite in patients chronic myeloid leukemia

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ABSTRACT

Introduction: Imatinib has favorable pharmacokinetic properties, but primary and secondary resistance mechanisms may cause a decrease in clinical response over time. There is a positive correlation between serum imatinib concentrations and treatment response. Our aim was to develop a method for the measurement of imatinib and its' active metabolite *N*-desmethyl imatinib.

Methods: Serum imatinib and *N*-desmethyl imatinib levels were determined by liquid chromatography-tandem mass spectrometry (LC-MS/MS) and validation studies were carried out according to CLSI (The Clinical & Laboratory Standards Institute) protocols. Serum samples were collected from 40 patients with chronic myeloid leukemia (CML) and analyzed with LC-MS/MS and ultra high-performance liquid chromatography (UHPLC) methods.

Results: The linearity range and correlation coefficient were 12.2–12,500 ng/mL and 0.9987 for LC-MS/MS method, respectively. Limit of quantitation was determined as 24.4 ng/mL. The retention times of imatinib and *N*-desmethyl imatinib were 1.66 and 1.60 min, respectively. There was no statistically significant difference between the results of both methods.

Discussion: This LC-MS/MS method is cost-effective and has adavantages such as using low serum volumes, requiring simple pretreatment steps (only protein precipitation) and reduced turnaround times for analysis.

1. Introduction

Tyrosine kinases are key mediators for the cell signaling cascade and these enzymes play a critical role in regulation of various biological processes such as cell growth, proliferation, modulation of apoptosis [1]. Overexpression of tyrosine kinases lead to cell proliferation defects and this is usually associated with tumor invasion, metastasis, angiogenesis. Therefore, several tyrosine kinase enzymes are considered as target molecules for the anti-cancer drug discovery [2]. Imatinib was the first tyrosine kinase inhibitor that was approved for the cancer treatment [3]. Imatinib is a potent and selective inhibitor for tyrosine kinases such as PDGFR A and B (Platelet Derived Growth Factor Receptor A and B), c-KIT (Stem Cell Factor Receptor) and especially for BCR-ABL (Breakpoint cluster region-Abelson) [4]. Thus, imatinib has been successfully used in the treatment protocols of chronic myeloid leukemia (CML) and gastrointestinal stromal tumors [5]. Imatinib was approved by FDA (Food and Drug Administration) in 2001 and accepted as a milestone for the treatment of CML. According to comparison of BCR-ABL tyrosine kinase-targeted and conventional therapy, 5-year survival rates of patients increased from 20% to 80–90% [1,6].

Imatinib has pharmacokinetic properties such as high oral bioavailability (> 98%), linear dose-response curve, rapid absorption from gastrointestinal system [7]. Its' half-life is 20 h and can be used as a daily single dose [8]. Imatinib administration is usually well tolerated

Abbreviations: BCR-ABL, breakpoint cluster region-abelson; c-KIT, stem cell factor receptor; CLSI, The Clinical & Laboratory Standards Institute; CML, chronic myeloid leukemia; ELISA, enzyme-linked immunosorbent assay; FDA, Food and Drug Administration; HPLC-UV, high-performance liquid chromatography-ultraviolet; LC-MS, liquid chromatography-mass spectrometry; LC-MS/MS, liquid chromatography-tandem mass spectrometry; PDGFR A and B, platelet derived growth factor receptor A and B; UHPLC, ultra high-performance liquid chromatography.

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by patients and minimal adverse effects are observed [9]. Nevertheless, various adverse effects such as anemia, thrombocytopenia, neutropenia can be observed following the treatment; [10]. The efficiacy of imatinib treatment may eventually decrease due to BCR-ABL kinase mutations, lack of patient adherence to treatment, inter-individual differences in enzyme activities and drug transporters that play central roles in drug metabolism [7,11]. Imatinib is mainly metabolized by CYP3A4, CYP3A5 and CYP2C8 [12]. N–desmethyl imatinib is primary metabolite of imatinib and has similar pharmacological properties [13]. There are wide inter-patient variations of imatinib metabolism [14]. In addition to the variations in enzyme and transporter activities, plasma imatinib concentrations may differ due to factors such as age, gender, body size, liver and kidney functions, drug interactions and adherence to the treatment. Blood imatinib concentrations were ranged between 109 and 4980 ng/mL after 24 h following the standard dose of 400 mg/day [15]. There is a positive correlation between plasma imatinib concentration and clinical response [16]. In order to achieve optimal treatment response and avoid serious adverse effects such as neutropenia and thrombocytopenia, plasma imatinib concentrations should be maintained in the range of 1000–3000 ng/mL. Therapeutic drug monitoring provides a new strategy for faster evaluation of clinical response compared to cytogenetic and molecular tests [15]. Serum and plasma imatinib levels were measured with methods such as capillary electrophoresis, ELISA (Enzyme-Linked ImmunoSorbent Assay), HPLC-UV (High-Performance Liquid Chromatography-Ultraviolet), LC-MS (Liquid Chromatography-Mass Spectrometry), LC-MS/MS (Liquid Chromatography-Tandem Mass Spectrometry) [17].

In this study, our aim was to develop a method for the measurement of serum imatinib and its'active metabolite *N*-desmethyl imatinib levels.

2. Materials and methods

2.1. Study design

2.1.1. Patients

Serum samples were collected from patients who admitted to Department of Haematology, Selcuk University Faculty of Medicine, Konya, Turkey. The study was carried out with 40 CML patients using imatinib for at least 3 months at 400 mg/day doses. 3 mL blood samples were obtained to serum separator gel tubes after 24 h of drug usage, and centrifuged at 3500 rpm for 10 min. Serum samples were aliquoted and stored at −80 °C until LC-MS/MS and UHPLC (Ultra High-Performance Liquid Chromatography) analyses. This study was approved by local ethics committee (Selcuk University ethics committee Number: 050.01.04, Date:18/01/2018).

2.1.2. Chemicals

Imatinib mesylate (≥98% (HPLC); cat no: CDS022105), acetonitrile (CAS Number: 75-05-8), HPLC grade water (CAS Number: 7732-18-5), formic acid (CAS Number: 64-18-6), ammonium formate (CAS Number: 540-69-2) were obtained from Sigma Aldrich (St. Louis, MO, USA).

Imatinib mesylate was dissolved in HPLC grade water at a concentration of 50 mg/mL. Working solutions were prepared at concentration range of 12.2 ng/mL to 12,500 ng/mL using serial dilution. The internal standard, nilotinib was prepared in dimethyl sulfoxide at a concentration of 5000 ng/mL. Solutions of imatinib and nilotinib were stored at 4 °C and −20 °C until analysis, respectively.

2.1.3. LC-MS/MS analysis

Sample preparation was performed using the procedure described by Caterino et al. with a slight modification [18]. Briefly; 100 µL of the internal standard (5000 ng/mL of nilotinib) was added to 200 µL standard solution or serum sample and vortexed for 30 s. Protein precipitation was achieved by adding 500 µL of acetonitrile. The mixture was centrifuged at 12000 rpm for 10 min. The supernatants were taken into glass tubes and evaporated with nitrogen gas. The residue was dissolved in 200 µL acetonitrile:water (10:90; v:v%) and 25 µL was enjected into LC-MS/MS system.

Chromatographic separation was performed with Shimadzu Prominence HPLC system and Phenomenex Luna C18 (50 × 4.6 mm,5 µm; part no: 00B-4041-E0). The mobile phase A and B were HPLC grade water containing 0.05% formic acid, 4 millimolar ammonium formate and 100% acetonitrile, respectively. Total run time was 5 min.

API 3200 triple quadrupole mass spectrometer (Applied Biosystems/MDS Sciex, Toronto, Canada) coupled with electrospray ionization source was performed at the positive mode for the study. Imatinib, nilotinib and *N*-desmethyl imatinib ions were identified in MRM mode with Q1/Q3 transitions such as 494.3/394.2, 531.0/290.0, 480.0/394.0, respectively. Declustering, entrance, collision cell exit potential, collision energy, ionspray voltage, source temperature, curtain and CAD gas values were adjusted to 30, 10, 5, 25 V, 5000 V, 400 °C, 20 and 6, respectively.

2.1.4. UHPLC analysis

Sample preparation was performed using modified procedure described by Ivanovic et al. [19]. Briefly, 200 µL of nilotinib internal standard was added to 500 µL serum samples or standards. Proteins were precipitated by adding 750 µL of acetonitrile/methanol (50:50, *v*/v%). After 30 s vortexing, the mixture was centrifuged at 13000 rpm for 5 min. and supernatants were injected into the UHPLC system.

The chromatographic analysis was performed on Thermo Ultimate 3000 UHPLC system (Thermo Scientific, Germering, Germany). The chromatographic seperation was carried out with Phenomenex Luna C18 (50 × 4.6 mm, 5 µm; part no:00B-4041-E0) column and isocratic 40% solvent A (water:methanol:triethylamine/72.5:25:2.5, pH 9.3), 20% methanol, 40% acetonitrile mixture was used as mobile phase. The column oven temperature and flow rate were 35 °C and 0.5 mL/min. Column output was monitored 267 nm wavelength. Total analysis time was 5 min.

2.1.5. Validation

The validation study was designed according to CLSI (The Clinical & Laboratory Standards Institute) protocols [20]. Thus, accuracy, linearity, precision, recovery, selectivity parameters were evaluated.

2.1.6. Statistical analysis

Statistical analysis was carried out by MedCalc version 9.2.0.1 statistics program, EP Evaluator Release 8 version and Excel (2011). Bland-Altman, Passing-Bablok, Deming regression analyses were performed in the method comparison study, $p < .05$ was accepted as statistically significance level.

Table 1
Precision study results of imatinib mesylate.

Concentration	Intra-assay			Inter-assay		
	Mean	SD	%CV	Mean	SD	%CV
3125 ng/mL	3164	99.6	3.1	3172	100.7	5
781 ng/mL	777.1	24.8	3.2	761.5	37.9	3.2

Table 2
Imatinib mesylate % recovery and matrix effect results.

	Recovery			Matrixeffect		
Concentration(ng/mL)	2500	625	781	3125	1563	781
% Results	98.80	99.04	100.50	−7.91	−13.1	−15.03

Table 3
Imatinib mesylate stability study %bias results.

Concentrations(ng/mL)	Frozen (−20° C) for 45 day			Freeze-thaw stability		
	15.Day (%)	30.Day (%)	45.Day (%)	2. (%)	3. (%)	4. (%)
781	1.52	5.33	5.96	−5.1	−12.6	−27.5
3125	2.4	5.6	7.2	−5.0	−11.9	−21.9

Table 4
Imatinib interference study %bias results.

	Lipemic			Hemolysed			Icteric		
	D1	D2	D3	D1	D2	D3	D1	D2	D3
781 ng/ml %bias	−0.88	−1.13	−3.25	−2.34	−5.62	−7.22	3.12	6.23	11.12
3125 ng/ml %bias	−1.92	−1.86	−1.38	−0.9	−4.93	−6.91	2.31	5.24	11.36

% Bias values of lipemic, icteric and hemolysed samples; D1: 25%, D2: 50%, D3: 100% interfering level.

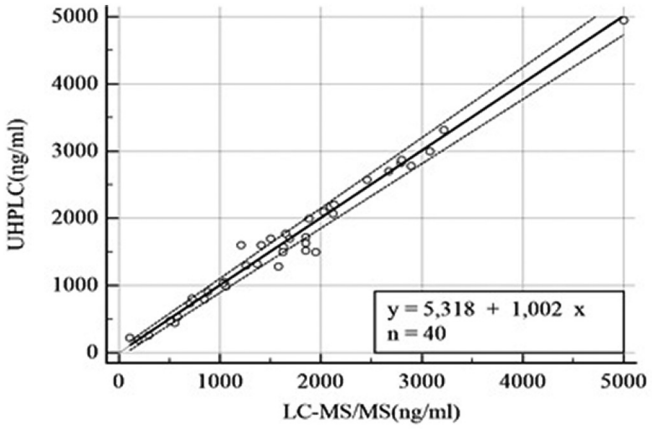

Fig. 1. Comparison of LC-MS/MS and UHPLC results with Bland-Altman plot.

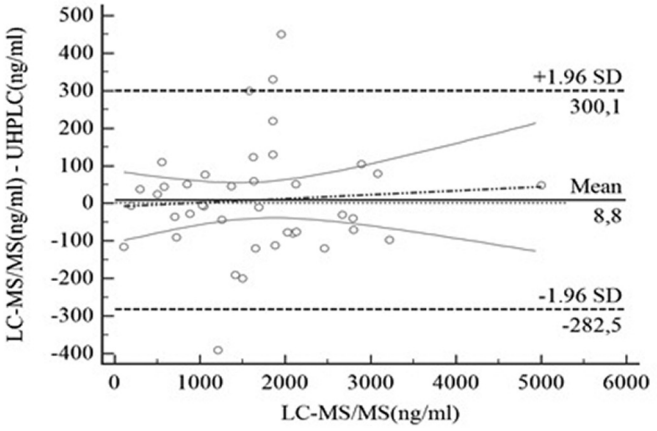

Fig. 2. Comparison of UHPLC and LC-MS/MS results.

3. Results

3.1. Method validation of imatinib

Linearity study was performed according to the CLSI EP6-A protocol and the results were calculated using Ep Evaluator Release 8 program. Correlation coefficient, slope and intercept parameters were calculated as 0.9987, 0.00275 and 0, respectively. Correlation coefficient was > 0.99. The method was linear at the 12.2–12,500 ng/mL concentration range.

Limit of detection and quantitation levels were determined as 12.2 ng/mL and 24.4 ng/mL by using signal to noise ratio (> 3 and 10, respectively) according to the CLSI EP17-A protocol.

Precision study was performed according to CLSI EP5-A protocol. For intra-day and inter-day precision studies, two concentration levels were selected properly with the medical decision points. Results were expressed in Table 1.

Recovery and the matrix effect studies were performed according to CLSI EP6-A protocol and procedure used by Chambers et al. (20), respectively. Results were expressed in Table 2.

Stability studies were performed for samples that were freezed and thawed for 4 cycles and kept frozen at −20 °C. Results were expressed in Table 3.

Carry-over study was performed according to CLSI EP10-A. Low and high level standards were analyzed sequentially then mean and standard deviations of groups were calculated with EP Evaluator Release 8 program. The carry-over value was calculated as 88.4 ng/mL.

Interference study was performed with icteric, hemolysis and lipemic samples according to CLSI EP7-A. Interference values from lipemia, icterus and hemolysis were in the range of −4.22% to 11.3%. No significant interference was observed at 40 mg/dL bilirubin, samples at 600 mg/dL triglyceride and at 1000 mg/dL haemoglobin. Results were expressed in Table 4.

Method comparison study was carried out in accordance with the CLSI EP 9 protocol. LC-MS/MS and UHPLC results ranged between 107 and 5000 ng/mL with a mean value of 1561.5 ng/mL and 196 to 4951 ng/mL with a mean value of 1642.7 ng/mL, respectively. Correlation coefficients and standard error were calculated as 0.977 and 154.6, respectively. The intercept and slope values were found as 5.32 (95% confidence interval: -62.45–56.55) and 1 (95% confidence interval: 0.96–1.049), respectively. Method comparison study results were expressed in Figs. 1, 2 and Table 5.

3.2. Therapeutic drug monitoring

Imatinib and *N*-desmethyl imatinib levels of 40 serum samples were analyzed by LC-MS/MS. Imatinib serum levels ranged between 107 ng/mL to 5000 ng/mL, mean value was 1561.5 ng/mL. *N*-desmethyl imatinib serum levels ranged between 16 ng/mL to 850 ng/mL and mean value was 202.9 ng/mL. An example chromatogram of imatinib and *N*-desmethyl imatinib in a sample of a CML patient were presented in Fig. 3.

4. Discussion

Tyrosine kinase inhibitors have become one of the most investigated

Table 5
Passing and Bablok regression analysis results.

Variable X	LC_MS_MS_ng_mL_ LC-MS/MS(ng/mL)
Variable Y	UHPLC_ng_mL_ UHPLC(ng/mL)
Sample size	40

	Variable X	Variable Y
Lowest value	107,0000	196,0000
Highest value	5000,0000	4951,0000
Arithmetic mean	1651,5250	1642,7400
Median	1625,0000	1585,0000
Standard deviation	977,7462	978,7108
Standard error of the mean	154,5952	154,7478

Regression equation	
y = 5,318,400 + 1,001,917 x	
Systematic differences	
Intercept A	53,184
95% CI	−62,4498 to 56,5456
Proportional differences	
Slope B	10,019
95% CI	0,9593 to 10,485
Random differences	
Residual Standard Deviation (RSD)	107,2058
± 1.96 RSD Interval	−210,1234 to 210,1234
Linear model validity	
Cusum test for linearity	No significant deviation from linearity (P = 0,53)
Steady-state concentrations (ng/mL)	UPLC: 1585 (196–4951); LC-MS/MS:1625 (107–5000)

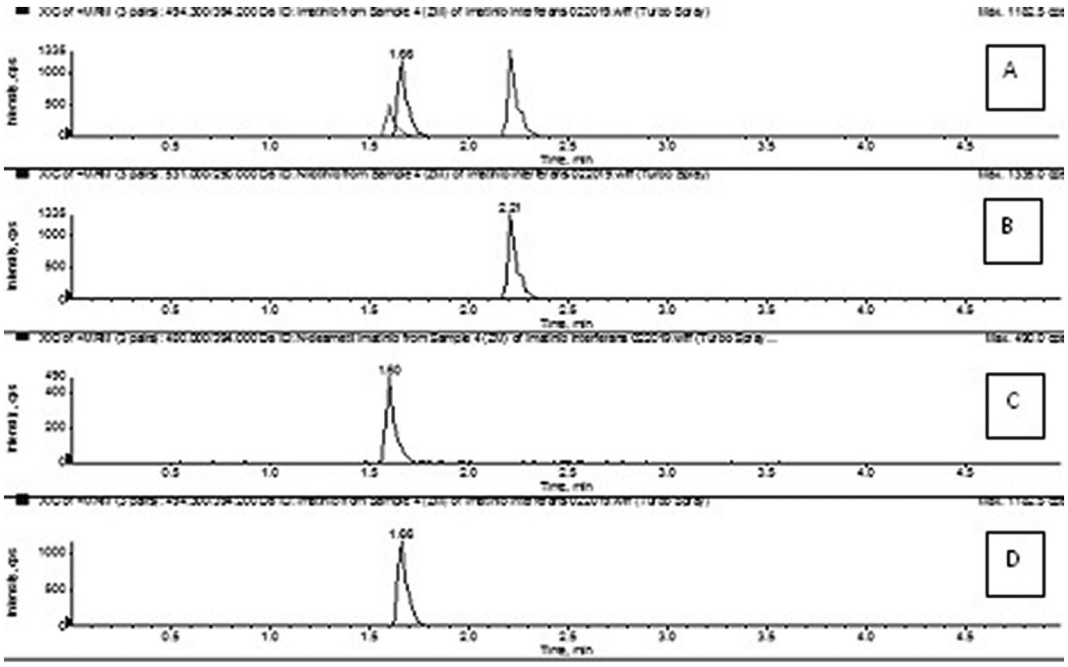

Fig. 3. Chromatogram from patient sample for the quantification of imatinib and *N*-desmethyl imatinib. A: Chromatogram of imatinib, *N*-desmethyl imatinib and nilotinib (internal standart), B: Chromatogram of nilotinib, C: Chromatogram of N- desmethyl imatinib, D: Chromatogram of imatinib.

drug groups for cancer treatment in recent years. With the implementation of imatinib mesylate in the treatment of CML in 2001, there has been a revolution in the therapy of this disease. Imatinib is usually well tolerated by patients, but primary and secondary resistance mechanisms may cause a reduction in treatment response over time. There is a correlation between blood imatinib concentration and treatment response. Therefore, monitorization of blood imatinib concentration is important.

Serum and plasma imatinib levels were measured with methods such as HPLC-UV, ELISA, capillary electrophoresis, LC-MS, LC-MS/MS up to date. Though, LC-MS/MS is superior compared to other methods in terms of high sensitivity, specificity and selectivity, thus it is considered as a reference method for therapeutic drug monitoring.

Several LC-MS/MS methods were reported for measurement of imatinib levels. However, our method has some advantages rather than other methods. Rezende et al. reported an LC-MS/MS method for imatinib measurement and its' total run time was 13 min [21]. Our method was very fast (5 min) and cost effective. Zhang et al. developed

a method that requires 400 µL sample volume [22]. Our method can perform imatinib measurement with a small amount of sample (200µL). Some methods use extraction procedures for the measurement of imatinib and these methods require long turnaround time and pretreatment steps, or lack of *N*-desmethyl imatinib detection in the same chromatogram. Goswami et al. [23] and Roth et al. [24] performed the solid phase extraction and liquid-liquid extraction procedure, respectively. These methods could solely measure imatinib levels. Our method is simple,practical and requires just a protein precipitation step and no other extraction, *N*-desmethyl imatinib levels can be concurrently measured by imatinib.

The method fulfilled the optimal validation properties compared to other methods. Awidi et al. developed LC-MS/MS method using liquid-liquid extraction for imatinib measurements [25]. This method was linear between 10 and 4000 ng/mL and correlation coefficient was > 0.99. Our method was linear between 12.2 and 12,500 ng/mL and correlation coefficient > 0.99.

The quantification limit was reported as 78.1 ng/mL and 10 ng/mL by Francia et al. [26] and Titier et al. [27], respectively. Our limit of quantitation was 24 ng/mL and suitable for clinical evaluation,

Adriamanana et al. [28] reported intra-day precision CVs as 6.5%, 5.8%, 5.4% for 150, 750 and 1500 ng/mL, respectively. Inter-day CVs were 5.3%, 6.4%,5.9% for 150, 750 and 1500 ng/mL, respectively. Our precision results were also comparable.

Zeng et al. [29] reported recovery values between 53.2% to 67.9% and our recovery were between %98.8 to %99.4.

UHPLC and LC-MS/MS imatinib results were compared in this study and there was no statistically significant difference between these results.

5. Conclusion

A spesific, sensitive, rapid, simple and robust LC-MS/MS method was developed and validated for analysis of imatinib and *N*-desmethyl imatinib. This method was proper and suitable for routine imatinib analysis. Plasma imatinib and its metabolite concentration can be measured to determine whether patients continue the treatment with optimal drug doses. By mass spectrometric determination, levels of this drug might be evaluated for treatment prognosis.

Declaration of Competing Interest

The authors declare that they have no conflict of interest relevant to the content of this manuscript.

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