DEVELOPMENT AND VALIDATION OF A UPLC-MS/MS METHOD FOR QUANTIFICATION OF IMATINIB IN ORAL FLUID

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INTRODUCTION: Imatinib (IM) is a first-line tyrosine kinase inhibitor for the treatment of chronic myeloid leukemia (CML). Therapeutic drug monitoring is recommended due to interindividual variations in pharmacokinetics and challenges in evaluating adherence. Oral fluid is a noninvasive alternative matrix with a detection window similar to that of blood and is being explored for therapeutic drug monitoring. **OBJECTIVE**: This study aims to develop an UPLC-MS/MS method for the quantification of IM in oral fluid as an alternative matrix for drug monitoring. **MATERIALS AND METHODS**: Calibrators and quality controls were prepared in blank oral fluid and further diluted (1:3 v/v) with the extraction buffer from the Quantisal® kit. IM was extracted using liquid-liquid extraction. An aliquot of 1 mL of diluted oral fluid was mixed with 50 µL of 1M NaOH, 2 mL of ethyl acetate, and 100 µL of the internal standard (IM D-8, 0,5 µg/mL). The organic layer was dried and resuspended in 100 µL of methanol. Analysis was performed on a UPLC-MS/MS Xevo® TQD-micro system using a C18 column (10 × 2.1 mm, 1.7 µm) at 40°C, with gradient elution using water with 0.1% formic acid (A) and acetonitrile with 0.1% formic acid (B) from 40% to 90% (B). The method was validated according to FDA guidelines. Paired IM trough concentrations in oral fluid and plasma from 11 CML patients were compared. **RESULTS AND CONCLUSION**: The chromatographic run time was 6 minutes, with a retention time of 1.7 minutes for both IM and the internal standard, showing no interfering peaks. The calibration curve was linear between 10 and 800 ng/mL (r = 0.999). The method exhibited precision (CV% 4.3% to 8.9%) and accuracy (92% to 112%). The extraction yielded an average recovery of 80%, with no significant matrix effect. IM concentrations in oral fluid ranged from 15 to 1,500 ng/mL and were significantly correlated (r = 0.72, p < 0.05) with plasma levels ranging from 10 to 2,210 ng/mL. Two patients were identified as nonadherent, with undetectable concentrations in both matrices. This methodology shows promise for saliva-based analysis due to its non-invasive collection and favorable preliminary results.

Key-words: Imatinib; Therapeutic drug monitoring; oral fluid.