Universität Basel

Publication

Development and Validation of a LC-MS/MS Method to Measure Phenytoin in Human Brain Dialysate, Blood, and Saliva and the Analytical Comparison with a GC-MS Method and a Recently Published LC-MS/MS Method

Book Item (Buchkapitel, Lexikonartikel, jur. Kommentierung, Beiträge in Sammelbänden)

ID 4699558
Author(s) Hösli, Raphael; Tobler, Andrea; Mühlebach, Stefan
Author(s) at UniBasel Mühlebach, Stefan ;
Year 2023
Title Development and Validation of a LC-MS/MS Method to Measure Phenytoin in Human Brain Dialysate, Blood, and Saliva and the Analytical Comparison with a GC-MS Method and a Recently Published LC-MS/MS Method
Editor(s) Scicchitano, Pietro
Book title Research Developments in Medicine and Medical Science
Volume 4
Publisher B P International
Place of publication London
Pages 47-67
ISSN/ISBN ISBN 978-81-19102-33-4 (Print); ISBN 978-81-19102-34-1 (eBook)
Series title Research Developments in Medicine and Medical Science
Number 4

Introduction and aim:ăTherapeutic drug monitoring (TDM) is crucial for critical dose drugs like antiepileptics for efficacious and safe therapeutic management of patients. Phenytoin (PHT) is a difficult to dose drug and an excellent example to show the development and the methodological progress realized for TDM in the last decade. The frequently prescribed PHT has a narrow therapeutic range with non-linear pharmacokinetics, a high interaction potential with other drugs, shows genetic polymorphisms in metabolism, and there is a correlation of plasma concentration with therapeutic/toxic response. Together with the often-long-term therapy, PHT fulfills the requirements for a rational TDM. Bioanalytical validation data from a state-of-the-art GC-MS and a highly sensitive selected LC-MS/MS methods for PHT were compared in this investigation and analyzed with a recently published LC- tandem MS method for PHT-TDM.

Methods:ăSensitivity, specificity, performance, sample preparation, stability, and cost of the TDM analytics were compared with reference to the FDA Guidance for Industry on bioanalytical methods. Both methods are suitable for specific scientific pharmacological investigations, for clinical TDM needs, and in forensic applications. Validation data of the two methods were analyzed and statistically compared. Data evidence was demonstrated by a literature review.

Results:ăThe GC-MS and the LC-tandem MS assay allow to specifically detect (LOD <15 ng/mL and <1 ng/mL for GC-MS and LC-MS/MS, respectively) and quantify (LOQ <50 ng/mL and <10 ng/mL for GC-MS and LC-MS/MS, respectively) very low PHT concentrations in different body fluids like blood, saliva, and brain microdialysis samples. Only small sample volumes (25-50ăýL) were needed for the analyses. The methods are compliant with the FDA guidance for bioanalytical testing. The LC-MS/MS was almost two to five times more sensitive (LOD, LOQ). It offers other significant advantages over the GC-MS assay like reduced sample volume, less laborious sample processing, larger linearity range for

different PHT concentrations, shorter analysis time with higher sample run capacity, and important cost savings.

Discussion and Conclusions:ăThe presented method evaluation makes LC-MS/MS a gold standard for large-scale specific and accurate measurements in pharmacokinetic / pharmacodynamic studies as well as for bedside and clinical routine analyses (PHT-TDM). Where needed or useful, e.g., in forensic or scientific investigations, and in compliance with the FDA guidance for bioanalytical methods, other than plasma samples can be analyzed like whole blood, urine, saliva, CSF, tissue biopsies or dried blood spots. For PHT-TDM with LC-MS/MS, PHT-D_{10}ăis an optimal internal standard. LC-MS/MS allow a less laborious sample processing compared to GC-MS. MS-MS detection enables high specificity, can detect metabolites, has no interference with chemical derivative reactions upon use of an external standard (GC) or with non-specific immune reactions (EMIT). To assess the free (unbound) PHT fraction, the Sheiner-Tozer algorithm in hypoalbuminemic patients was useful and correlated with the measured free PHT values. Very recent LC-MS/MS method publications are in-line with and confirm the results of this in-depth GC-MS and LC-MS/MS evaluation.

Keywords:ă

– Phenytoin-TDM in plasma ă
– blood ă
– saliva ă
– cerebrospinal fluid ă
– LC-MS/MS vs. GC-MS method ă
– Sheiner-Tozer equation for unbound PHT fraction ă
– bioanalytical validatio

Full Text on edoc ;
Digital Object Identifier DOI DOI: 10.9734/bpi/rdmms/v4