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Analytical Chemistry 2018: Challenges and considerations for quantitative analysis of cholesterol precursors and metabolites in human plasma by lc-ms/ms methodology-Yong-Xi Li-Medpace Bioanalytical Laboratories

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Concentrations of Cholesterol Precursors and Metabolites in human body are very closely related to human cognitive performance and human heart health as well. Many new drugs are developed to improve the rations of among the precursors or metabolites in human body for human health needs. Because they are so important biomarkers that sensitive and accurate determinations of all concentrations of the precursors and metabolites are critical during the drug developments and studies. For such purpose, Bio-analytical methods were developed and fully validated following US FDA and European EMA guidance for Cholesterol three precursors: Lathosterol, Lanosterol and Desmosterol, and 4 Cholesterol metabolites: 4β-Hydroxycholesterol, 24S-Hdroxycholesterol, 25-Hdroxycholesterol and 27-Hdroxycholesterol by LC-MS/MS methods at our laboratories. Since such marker molecule structures and polarities are very similar or the same with only a double bond position different, the bio-analytical methodology faced extremely challenge during our method development stage, which include all extraction procedures, HPLC conditions and spectrometer parameters. Especially in human plasma samples, Cholesterol is dominate marker that had significant interference with the analysis. During the method validations, we have considered that the methods need to be conducted from regulatory point of view, that is, "method validation for biomarker assays should address the same questions as method validation for PK assays……" so that the method accuracy, precision and all stabilities were completed for all assessments to meet acceptance criteria from the regulatory agencies, instead, not reference methods "fit-for-purpose" for diagnostic. In this presentation, all above scientific challenges and regulatory considerations are introduced and discussed. All methods were successfully applied to our several clinical studies, and with later on the methods for phytosterol have provided very useful insights for the drug developments. Oxysterols are oxygenated forms of cholesterol or its precursors. They are formed enzymatically and via reactive oxygen species. Oxysterols are intermediates in steroid and steroid biosynthetic pathways and also are bioactive molecules in their title , being ligands to nuclear receptors and also regulators of the processing of steroid regulatory element-binding proteins (SREBPs) to their active forms as transcription factors regulating cholesterol and carboxylic acid biosynthesis. Oxysterols are implicated within the pathogenesis of multiple disease states starting from atherosclerosis and cancer to MS and other neurodegenerative diseases including Alzheimer's and Parkinson's disease. Analysis of oxysterols is challenging on account of their low abundance in biological systems as compared to cholesterol, and thanks to the propensity of cholesterol to undergo oxidation in air to get oxysterols with an equivalent structures as those present endogenously. In this article we review the mass spectrometry-based methods for oxysterol analysis paying particular attention to analysis by liquid chromatography–mass spectrometry24(S)-hydroxycholesterol [24(S)-HC] is a cholesterol metabolite that is formed Liquid chromatography (LC) based techniques together with mass spectrometry (MS) detection have had an outsized impact on the event of latest pharmaceuticals within the past decades. Continuous improvements in mass spectrometry and interface technologies, combined with advanced liquid chromatographic techniques for high-throughput qualitative and quantitative chemical analysis , have resulted during a wider scope of applications in the pharmaceutical field. LC-MS tools are increasingly wont to analyze pharmaceuticals across a spread of stages in their discovery and development. These stages include drug discovery, product characterization, metabolism studies (in vitro and in vivo) and therefore the identification of impurities and degradation products. The increase in LC-MS applications has been enormous, with retention times and molecular weights (and related fragmentation patterns) emerging as crucial analytical features within the drug development process. The goal of this review is to offer

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an summary of the most developments in LC-MS based techniques for the analysis of small pharmaceutical molecules within the last decade and give a perspective on future trends in LC-MS in the pharmaceutical field.almost exclusively in the brain. The concentrations of 24(S)-HC in spinal fluid (CSF) and/or plasma could be a sensitive marker of altered cholesterol metabolism within the CNS. A sensitive 2D-LC-MS/MS assay was developed for the quantification of 24(S)-HC in human plasma and CSF. In the development of an assay for 24(S)-HC in CSF, significant nonspecific binding of two 4(S)-HC was observed and resolved with the addition of 2.5% 2-hydroxypropyl-β-cyclodextrin (HP-β-CD) into CSF samples. The sample preparation consists of liquid-liquid extraction with methyl-tert-butyl ether and derivatization with niacin . Good linearity was observed during a range from 1 to 200 ng/ml and from 0.025 to five ng/ml, for plasma and CSF, respectively. Acceptable precision and accuracy were obtained for concentrations over the calibration curve ranges. Stability of 24(S)-HC was reported under a spread of storage conditions. This method has been successfully applied to support a National Institutes of Health-sponsored clinical test of HP-β-CD in Niemann-Pick type C1 patients, in which 24(S)-HC is used as a pharmacodynamic biomarker.

Biography:

Yong-Xi Li has completed his PhD in Beijing Institute of Petroleum Research in China and Postdoctoral training at Cornell University, USA. Currently he is Executive Director at MedpaceBioanalytical Laboratories focusing on bioanalytical analysis, including TK, PK, ADA and Nab method developments, validations and sample analysis for small molecule, polypeptides, protein and antibody therapies. He has published more than 100 papers and one book in reputed journals and publishing house and serving as one of organizers in a biotech conference.

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