Potential of LC-MS/MS in Pharmacology and Toxicology: From Classical Applications to Personalized Medicine

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During the last few decades, important advances in chromatography and mass spectrometry have positioned liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) as a powerful analytical tool that enables the identification and quantitation of endogenous (e.g. neurotransmitters) and exogenous (e.g. drugs/xenobiotics) small molecules with a wide range of physicochemical properties (e.g. from ionic metabolites to non-polar lipids) in biological samples. As a result, LC-MS/MS allows for the measurement of specific compounds with high accuracy and sensitivity, and it has become a gold-standard analytical approach commonly applied in both in vitro (e.g. cell cultures) and in vivo studies (both animal and human studies). In the specific fields of pharmacology and toxicology, some of the classical practical applications in which LC-MS/MS has proven useful are listed as follows:

1. Pharmacokinetics and toxicokinetics, to study the processes of absorption, distribution, metabolism and excretion of drugs, including the identification of new metabolites and the direct detection of phase II metabolites [1].
2. Monitoring a disease progression or a response to a therapeutic intervention, by measuring changes in biomarkers of the disease [2].
3. Studying the mechanism of action of drugs through the direct measurement of the intermediates involved in specific pathways [3].
4. Disease diagnosis, generally in those pathologies characterized by a lack (or an important alteration) of enzymatic activity [4].
5. Therapeutic drug monitoring, to adjust the dose of those drugs that have a narrow therapeutic range, and modify (or not) the prescribed dose [5].
6. Forensic applications like the identification of illegal drugs, new psychoactive substances and toxic compounds in various biological matrices [6].

Consequently, LC-MS/MS is currently the technique of choice in targeted metabolomics and its applications are two-fold: the targeted detection of specific compounds (for diagnosis, drug monitoring or forensic applications) and the development of targeted metabolomics approaches (e.g. to study mechanisms of action or to identify biomarkers). Thus, LC-MS/MS offers an analytical tool that, in combination with the information obtained from other techniques and other omics sciences (i.e. (epi)genomics, transcriptomics, proteomics), can be employed to face some of the current challenges in pharmacology and toxicology. These include the elucidation of some pitfalls when translating in vitro to in vivo results, the prediction of new psychoactive substances’ toxicity, the role of gut microbiome on pharmacological and toxicological responses, the identification of the mechanisms of action of a new drug or toxin, the study of the sources of therapeutic failure, and the causes of inter-individual variability towards a specific treatment, amongst others. The answers to these challenging topics will provide the knowledge needed to overcome current therapeutic limitations and help shed light on the field of personalized medicine with the final goal of improving the patient’s quality of life.
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Bibliography


