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EXPERT OPINION

Can Pharmacometabolomics and LC-HRMS develop a new Concept for Therapeutic Drug Monitoring?

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TDM today

Therapeutic drug monitoring (TDM) is a concept for individualized drug dosing that was developed into clinical routine as a consequence of research findings on variable drug effects and analytical technology developments made in the 1950th and onwards, and founded the clinical pharmacology discipline (1,2). TDM in practice is about measuring a specific drug concentration in blood, serum or plasma, but may also include pharmacogenetic and pharmacodynamic investigations (3). For some time big hopes were put on pharmacogenetics to help explain inter-individual variability in drug response. It is now realized that variability may occur over time and relate to influences from both inborn as well as environmental factors, and that a more multifactorial approach is needed for complex biological systems (4). Examples of important use of TDM comprise treatment of epilepsy, infection, psychiatric disease and immunosuppression after transplantation (1,5,6).

Analytical methods for TDM were using immunochemical, HPLC and GC techniques for long time, but this has recently, but slowly, been challenged by LC-MS techniques (7). One good example of this is methods for the immunosuppressive drugs tacrolimus, ciclosporin, sirolimus and everolimus (8,9). LC-MS methods have offered significant improvements in the quality of analytical method performance. It has been demonstrated that LC-MS offer improvement in accuracy, precision and cost-effectiveness, and also can be made robust. With the use of LC-MS in LC-tandem MS SRM mode multi-component methods can be constructed with unique combination of selectivity and sensitivity. Analytical method demands in TDM are set by the requirements of accuracy, cost-effectiveness, rapid reporting and robustness in a routine laboratory environment.

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Pharmacometabolomics

Pharmacometabolomics is a new "omics" field that has developed following the advancements of genomics, proteomics and metabolomics (10). While therapeutic drug monitoring gives 107786 hits in a PubMed search pharmacometabolomics gives only 62 (February 2015). A related term is metabonomics, which gives 12 hits in PubMed. The starting point of pharmacometabolomics can be traced to a report of Clayton and coworkers, who in a Nature paper from 2006 pointed out the importance of phenotype and that the hopes on pharmacogenetics partly have been disappointing (11). The pharmacometabolomic approach comprises using both NMR and mass spectrometry methods to collect non-targeted analytical data sets and apply statistical methods to make discoveries. Pharmacometabolomics has been used by the pharmaceutical industry in drug development, since it can make the process of discovery and documentation of pharmacological and toxicological profile more effective (12). Other examples from research investigations are discovery of drug response biomarkers. In trying to explain observed inter-individual variability in aspirin treatment for prevention of cardiovascular disease metabolomics was used to discover serum serotonin levels as having a strong correlation to lack of treatment effect (13). Me-

tabolomics was used to identify S-adenosylmethionine as a key parameter for TPMT activity (along with genotype) in subjects being TPMT heterozygous (14). In studying treatment resistance to SSRI treatment of major depressive disorder, a negative association to plasma glycine concentrations was discovered using metabolomics approach (15). The reason for this was later found to be a SNP alteration. Likewise, resistance to ketamine treatment of bipolar depression was found to be associated with mitochondrial oxidation of fatty acids (16). Also examples of early detection of adverse effects are available. For example, after a single dose of ciclosporin a urine sample can reveal a future risk for kidney toxicity (17). Taken together there are now numerous examples where pharmacometabolomics has contributed to better understanding of drug treatment and risk for adverse effect. It is now time to use pharmacometabolomics not only in drug development and research, but also to explore its potential for further developing the TDM service.

Mass spectrometry

It is recent developments in LC-MS technology that has laid the ground for the successful use of mass spectrometry methods in clinical laboratories (18,19). The development of chromatography using sub 2 μm particles has given increased resolution power and shortened analysis times (20). The resolution power in the chromatography dimension can make application of very simple sample preparation procedure possible, e.g. protein precipitation using solvent. The developments in high resolution mass spectrometry have provided a new platform for retrieving a large amount of information in a single analytical investigation. In order to design a method suitable for TDM based on pharmacometabolomics, a non-discriminative sample preparation procedure is preferable in order to obtain data from as broad polarity spectrum of compounds as possible. Also in order to get optimal analytical information the mass spectrometry should be done with highest resolution power and enable precise quantification with wide linear range. For analytes in range of 100-1000 mass units the orbitrap technology seems to provide best performance at present (21-23). The value of high resolution power for providing optimal multi-component information for metabolome information has been pointed out (24). Not only is the technique capable of quantifying a large number of target analytes, as is routine in clinical chemistry, but it may also provide new information by metabolic profiling in untargeted investigations (24). The pharmaceutical industry quickly adapted LC-HRMS at the expense of low resolution triple quadrupole technology for drug metabolism investigations, and its potential for providing both qualitative and quantitative data in full scan mode was demonstrated (23,25).

Future development of TDM

The discoveries and insights made using pharmacometabolomics and high resolution mass spectrometry, and the tradition of TDM to precisely quantify the target drug and/or metabolites can form a fundament for developing TDM further. The scientific knowledge that genetics and environmental factors play a role must be taken into account and be explored. There may be several ways to do this (26) but one way could be to further develop the concept of TDM in order to better meet the trend towards a more specific and personalized drug therapy.

The following menu of features is proposed to be included in such a concept:

- Concentration determination of parent drug and/or active metabolites
- Metabolite pattern
- Markers of metabolic phenotype
- Control of compliance by monitoring all other relevant therapeutic drugs and their metabolites
- Control of substances that could cause drug/drug interactions
- Control of dietary supplement and illicit drugs when relevant
- Biomarkers for adverse effects
- Disease and health status biomarkers

Analytical method and other requirements

Rather different demands must be set on a method that is to be used in TDM service as compared with a research project method. Optimal design remains to be determined. However, reliable results and robustness over time, short reporting times and a low cost are important requisites that such a method must have in order to be successful. It is also important in the near future to more precisely determine the clinical need for the possible additional information that can be retrieved from a new TDM concept, and to develop methods designed to exactly meet those needs. It will be important to make clear already when the analytical investigation is requested what kind of information is wanted. This will require a tight collaboration with clinicians when further exploring this possibility to an expanded laboratory service.

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