Urinary biomarkers and nephrotoxicity

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Introduction

There are a number of definitions of the term “biomarker”. In general, they have in common three components: [1] that they are objectively measured indicators of specific anatomic, physiologic, biochemical, or molecular events; [2] that they are associated with normal biological processes or accompany the onset, progression and/or severity of specific pathological or toxic conditions and [3] are that they are useful for measuring the progress of injury, disease or the effects of therapeutic intervention. For example, according to the National Institutes of Health (NIH) working group, a biomarker is a characteristic that is objectively measured as an indicator of normal biological processes, pathogenic processes, or a pharmacological response to a therapeutic intervention [1].

The types of biomarkers and the purposes served vary to some extent depending on the population being observed. For public health purposes, the requirements of useful biomarkers to protect from injurious xenobiotic exposure are three-fold: firstly, to achieve the earliest identification of the potential for health impairment; secondly, to gain insight into the mechanism(s) responsible for any adverse impact on the health of individuals or specific populations at risk; and thirdly, to help assess the effects of interventions designed to minimize the short and long-term consequences of the initial injury. Important requirements for biomarker development are a detailed understanding of biochemical pathways involved in nephrotoxicity, minimal invasiveness and capacity to screen large at-risk populations.

Those involved in individual health assessment are concerned with the early detection of specific organ kidney injury. With regard to acute kidney injury (AKI), biomarkers may serve several additional purposes. That is, they may determine AKI subtypes (prerenal, intrinsic renal, or postrenal), identify the etiology of AKI (ischemia, toxins, sepsis, or a combination), differentiate AKI from other forms of acute kidney disease (urinary tract infections, glomerulonephritis, interstitial nephritis), predict the AKI severity (risk stratification for prognostication as well as guide to therapy), monitor the course of AKI, and monitor the response to AKI interventions. For chronic kidney disease (CKD), they provide both evidence and severity of exposure and may be used to assess response to removal of offending toxin.

The pharmaceutical industry has specific interest in the development and utilization of biomarkers for evaluating and predicting the safety of drug candidates during the process of their development. In drug trials, biomarkers have been proposed for use in efficacy determination and patient population stratification, in deducing pharmacokinetic-pharmacodynamic relationships and in safety monitoring [2]. These different phases of drug development involve different functional categories of biomarkers and often involve the patterns of several biomarkers - rather than a change in a single biomarker. The effort to identify reliable biomarkers often involves the interaction of several disciplines such as genetics and epigenetics, genomics, proteomics, metabonomics and assay development [3].

Categories of biomarkers

There have been a number of attempts to formally categorize biologic markers of renal injury in order to achieve a uniform and consistent approach. This have included biomarkers related to a specific physiologic parameter, such as markers of renal blood flow, glomerular filtration rate, or tubular function; and the chemical nature of the biomarker, such as growth factors, enzymes, adhesion molecules, inflammatory cytokines, etc. One additional classification attempts to define sequential changes in the appearance of one or more biomarkers as renal injury, either acute or chronic, progresses from the initial insult to clinical disease and includes four overlapping stages during that process [4]. These stages consider the nature and magnitude of the initial insult, its relationship to a biologically injurious stimulus, the presence of early biologic effects and eventually on alterations in the structure and/or function of the kidney. At each point along this line, individual susceptibility - which is also subject to various external factors - determines whether or not the process progresses to the development of clinical renal impairment (Figure 1).

In this schema, biomarkers are considered to fall in the three general designations. These include biomarkers of exposures, biomarkers of effect, and biomarkers of susceptibility. Each of these types of biomarkers has specific and relevant applications to the understanding of renal injury and disease. Specific and sensitive bi-