Phenotype standardization for drug-induced kidney disease

Ravindra L. Mehta[1,10], Linda Awdishu[2,10], Andrew Davenport[3], Patrick T. Murray[4], Etienne Macedo[5], Jorge Cerda[6], Raj Chakaravarthi[7], Arthur L. Holden[8] and Stuart L. Goldstein[9]

[1]University of California San Diego School of Medicine, La Jolla, California, USA; [2]University of California San Diego Skaggs School of Pharmacy, La Jolla, California, USA; [3]Royal Free Hospital and University College Medical School, UCL Centre for Nephrology, London, UK; [4]University College Dublin School of Medicine and Medical Science, Health Sciences Centre, Belfield, Dublin, Ireland; [5]University of São Paolo, São Paolo, Brazil; [6]Albany Medical College, Albany, New York, USA; [7]Care Hospitals, Hyderabad, Telangana, India; [8]International Serious Adverse Event Consortium, Chicago, Illinois, USA and [9]Division of Nephrology and Hypertension at Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, Ohio, USA

Drug-induced kidney disease is a frequent cause of renal dysfunction; however, there are no standards to identify and characterize the spectrum of these disorders. We convened a panel of international, adult and pediatric, nephrologists and pharmacists to develop standardized phenotypes for drug-induced kidney disease as part of the phenotype standardization project initiated by the International Serious Adverse Events Consortium. We propose four phenotypes of drug-induced kidney disease based on clinical presentation: acute kidney injury, glomerular, tubular, and nephrolithiasis, along with the primary and secondary clinical criteria to support the phenotype definition, and a time course based on the KDIGO/AKIN definitions of acute kidney injury, acute kidney disease, and chronic kidney disease. Establishing causality in drug-induced kidney disease is challenging and requires knowledge of the biological plausibility for the specific drug, mechanism of injury, time course, and assessment of competing risk factors. These phenotypes provide a consistent framework for clinicians, investigators, industry, and regulatory agencies to evaluate drug nephrotoxicity across various settings. We believe that this is the first step to recognizing drug-induced kidney disease and developing strategies to prevent and manage this condition.

Kidney International advance online publication, 8 April 2015; doi:10.1038/ki.2015.115

KEYWORDS: acute kidney injury; adverse reaction; drugs; glomerulonephritis; hypersensitivity; nephrotoxicity

Correspondence: *Ravindra L. Mehta, University of California San Diego School of Medicine, 200 Arbor Drive 8342, San Diego, California 92103, USA. E-mail: rmehta@ucsd.edu*

[10]Co-first authors.

Received 7 May 2014; revised 16 February 2015; accepted 4 March 2015

Drug-induced kidney disease (DIKD) accounts for ~19–26% of cases of acute kidney injury (AKI) in hospitalized patients.[1] There are no standards to identify drug-induced nephrotoxicity and as a result DIKD is often unrecognized. In recent years, the International Serious Adverse Event Consortium has initiated a phenotype standardization project for drug-induced adverse events.[2] In conjunction with the International Serious Adverse Event Consortium, we have developed consensus definitions for DIKD, taking into account its wide spectrum and the need for balancing practicality with reliability of the classifications across different settings.

CONSENSUS PROCESS

With the support of the International Serious Adverse Event Consortium, we organized a series of eight teleconferences followed by two face-to-face meetings of international, adult and pediatric, nephrologists and pharmacists. The panel developed the phenotypic criteria using a modified Delphi process to allow identification of patients across four categories representing the spectrum of DIKD, for subject recruitment into a genetic study of DIKD (DIRECT). The panel was divided into subgroups and researched specific phenotypes. The criteria were summarized and presented to the larger group for consensus. They were considered in the context of using electronic medical records to screen for patients with DIKD in both hospitalized and ambulatory settings. Panelists were asked to consider the known mechanisms of nephrotoxicity, time course of drug exposure, and the setting as discussed in more detail below. For the AKI phenotype, established definitions were considered as the starting point and adapted for DIKD (e.g. Acute Kidney Injury Network/Kidney Disease: Improving Global Outcomes (AKIN/KDIGO) criteria for AKI).[3]

DESCRIPTION OF PHENOTYPE

We propose that DIKD presents in one of four phenotypes: AKI, glomerular disorder, tubular disorder, or nephrolithiasis/crystalluria. The clinical presentation of each phenotype is

Table 1 | Primary and secondary criteria for individual phenotypes

Phenotype	Acute kidney injury	Glomerular disorder	Nephrolithiasis	Tubular dysfunction
Characteristics	• ATN[a] • AIN • Osmotic nephrosis	• Hematuria • Proteinuria	• Crystalluria • Nephrolithiasis • Ultrasound findings of stone with or without obstruction	• Renal tubular acidosis • Fanconi syndrome • SIADH[b] • Diabetes insipidus • Phosphate wasting
Primary criteria	• Rise in Scr that presents as or progresses to stage 2 (KDIGO) 2–2.9 × reference Scr or higher • If child has baseline Scr <0.5 mg/dl, must double Scr to get to at least 0.5 mg/dl or above OR • Decline by at least 50% from peak Scr over 7 days in relationship to change in drug dosing adjustment or discontinuation within 2 weeks	• Biopsy-proven drug-induced glomerular disease (within 4 weeks of stopping drug) AND *Proteinuria as defined by:* • 24 h collection >1 g protein • UPC or UACR >0.8 • Urinalysis 2+ protein100–300 mg/dl albumin • Children: 100 mg/m^2 per day or 4 mg/m^2 per h hematuria • >50 RBC per HPF	• Must be new onset following drug exposure with no prior history of nephrolithiasis • No evidence of congenital etiology for nephrolithiasis • If obstructive, rise in Scr that presents as or progresses to stage 2 (KDIGO) or higher • If non-obstructive, then: • Urinalysis with crystals • Ultrasound with stone	Tubular: *Hypophosphatemia* OR *Glucosuria* • Urinalysis with 3+ glucose without diabetes OR Hyperchloremic metabolic acidosis AND Hypokalemia or hyperkalemia • *Diabetes insipidus:* • Hypernatremia >155 mEq/l on multiple occasions • Polyuria >3 l per day
Secondary criteria	• Oliguric <500 ml per day or <0.5 ml/kg per h for 12 h (KDIGO stage 2) • Non-oliguric >500 ml per day, >1 ml/kg per h for 24 h (pediatrics) • Urinalysis findings: granular and muddy casts consistent with ATN, urinary eosinophils, proteinuria • FeNa >1% • Negative ultrasound findings • Positive gallium scan for AIN • Clinical symptoms for AIN: fever, rash, and joint pains	• Culture negative leukocyturia • >50 WBC per HPF • Casts • RBC; granular • Absence of secondary disorder that can cause GN: DM, lupus, after infectious, hepatitis, and so on. • Microangiopathic changes in blood • Smear, LDH; haptoglobin • Nephritic, nephrotic, mixed	• Urine electrolytes • Stone workup	*Phosphaturia* • $FePO_4$ >5% • Urinary PO_4 excretion >100 mg per day *Hypomagnesemia* • Serum magnesium <1.2 mg/dl *Hypouricemia* • Serum uric acid <2 mg/dl *Tubular proteinuria* • 24 h collection <1 g protein • UPC <0.8 • Urinalysis <2+ protein *Diabetes insipidus* • Serum osmolality >300 mOsm/kg • Urine osmolality <100 mOsm/kg • Urine sodium <10 mEq/l

Abbreviations: AIN, acute interstitial nephritis; AKI, acute kidney injury; ATN, acute tubular necrosis; DM, diabetes mellitus; FeNa, fractional excretion of sodium; $FePO_4$, fractional excretion of phosphorus; GN, glomerulonephritis; HPF, high powered field; KDIGO, Kidney Disease: Improving Global Outcomes; LDH, lactate dehydrogenase; RBC, red blood cell; SIADH, syndrome of inappropriate antidiuretic hormone; UPC, urine protein-to-creatinine ratio; UACR, urine albumin-to-creatinine ratio; WBC, white blood cell.

[a]Hemodynamic changes may contribute to ATN; however, in the absence of any specific features are not considered individual criteria for the AKI phenotype.

[b]SIADH does not reflect direct tubular damage but rather the impact of a drug on ADH secretion and subsequent impaired water handling.