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Review Article

Adverse effects of drugs on the kidney

Ettore Bartoli

Internal Medicine, Università del Piemonte Orientale "Amedeo Avogadro", Via Solaroli 17, Novara, Italy

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ABSTRACT

The number of drugs presently marketed is countless, their prescription is relentlessly growing, such that the likelihood of adverse effects is strikingly increasing. As many drugs are cleared by the body through kidney excretion, renal adverse events are likely. In this review we shall concisely describe the pathophysiologic mechanisms of renal damage by drugs, the different clinical presentations outlining renal toxicity in the course of pharmacologic treatment, and the main offending agents.

1. Introduction

The entire population is presently exposed to a number of different pharmacologic agents, most of which are noxious and taken with no scientific justification. An even larger amount of drugs is taken inadvertently, with food, herbal remedies and over-the-counter medications, and without any medical control and prescription. This causes a widespread toxicity that is difficult to detect, often unsuspected and potentially very dangerous. As most drugs are excreted by the kidney, it is reasonable to assume that the kidney itself could be a privileged target of their toxic actions. In this paper, we shall review the renal effect of the use, misuse and abuse of pharmacologic agents. The kidney alterations will be presented according to their pathophysiologic mechanisms, i.e. immuno-related toxic effects, analgesic nephropathy, drug-induced glomerular disease, direct toxic effects of drugs, nephrogenic systemic fibrosis, selective toxic effects, herbal medications, renal hemodynamics-related renal failure and crystalline nephropathy. Table 1 displays a glossary of the abbreviations used.

1.1 Immunologic reactions caused by drugs involving the kidney
We recognize immunocomplex diseases and hapten-mediated mechanisms.

A. IC disease caused by drugs.
- Drugs can be contained in IC, causing drug-mediated IC renal disease, AGN or AIN usually secondary to a spillover mechanism: the excess IC which does not bind to glomerular structures "spills over" into the interstitial microcirculation, binding to tubular BM, triggering interstitial inflammation [1]. This recalls Goodpasture syndrome, when the excess Ab spills over into the interstitium, causing AIN beside AGN.
- Drugs can cause systemic immunologic reactions, causing microangiopathic vasculitis, which can injure the kidney. The most typical is HITP, where progressive renal failure with an elusive urinary sediment (accounted for by a pathogenic microthrombotic reaction affecting arterioles and interstitium, while mostly sparing the glomerulus) is the hallmark of the disease [2]. The picture can occur with clopidogrel and congeners, and when the conversion of macro- into micro-aggregates of von Willebrand factor is blocked [2].
- Drugs primarily affecting the immune system cause almost exclusively glomerular disease and, to a minor extent, interstitial disease. They trigger a lupus-like syndrome [3], reported with alpha-methyl-dopa, D-penicillamine, interferon, levamisole [4], procainamide and many other substances exerting blockade of immune recognition [5].

B. Hapten-mediated disease.
Pathophysiology
Haptens are epitopes represented by drugs, part of drug molecules, or biologic substances transformed into immunogenic epitopes by drugs or other processes. The immunologic reaction to haptens causes disease by the inflammatory effect of Ab-hapten interaction. This occurs mainly in the renal interstitium, where haptens bind to tubular BMs or interstitial matrix, leading to AIN. The disease can subside after discontinuation of the offending agent, with prednisone treatment, or proceed to chronic interstitial nephritis ending in CRF [6]. In many circumstances, the reaction is IgE or IgG4 mediated, with eosinophils infiltrating the interstitium, attended by eosinophiluria: this is called "allergic" AIN, even

E-mail address: ettore.bartoli@hotmail.it.

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Table 1
The acronyms used and their explanation.

Glossary		
AA = amino acids	DAIN = drug-induced acute interstitial nephritis	NSF = nephrogenic systemic sclerosis
AGN = acute glomerulo-nephritis	DM = diabetes mellitus	PCr = plasma creatinine concentration (mg/dL)
AIN = acute interstitial nephritis	ESRD = end-stage renal disease	PG = prostaglandins
ARF = acute renal failure	FENa = fraction of filtered Na excreted	PK = plasma potassium concentration (mEq/L)
ATN = acute tubular necrosis	GFR = glomerular filtration rate	PNa = plasma sodium concentration (mEq/L)
BP = blood pressure	HAART = highly active antiretroviral therapy	PT = proximal tubule
BW = body weight	HITP = heparin-induced thrombocytopenic purpura	PTCA = percutaneous coronary angiography
BM = basement membrane	IC = immune complex	RTA = renal tubular acidosis
CAT = computerized axial tomography	LC = liver cirrhosis	TGF = transforming growth factor
CAD = coronary artery disease	NDI = nephrogenic diabetes insipidus	TTP = thrombotic thrombo-cytopenic purpura
CHF = congestive heart failure	NMR = nuclear magnetic resonance	
CIN = contrast-induced nephropathy	NSAID = non-steroidal anti-inflammatory drugs	
CRF = chronic renal failure		
ECV = extra-cellular volume		

though the Ag is not an "allergen", as it could be a hapten or a non-allergic, immunogenic epitope. This "allergy" is called type B idiosyncratic non-immunoglobulin-E-mediated immune reaction marked by cell-mediated immune injury to the renal tubule-interstitium, carried out by CD4+ T-lymphocytes [7,8]. The drug becomes immunogenic through antigen mimicry, haptenization, or neo-antigen formation. Dendritic cells of renal interstitium, and tubular epithelial cells can transform the injury into a chronic process. Thus, acute drug-induced AIN can progress to a chronic form attended by fibroblast activation, ending in interstitial fibrosis, tubular atrophy and, finally, ESRD [8,9]. The recruitment of T-lymphocyte immunity represents the hallmark of evolution into chronically progressive interstitial disease [10]. It is almost always caused by T-cell activation, CD4 and CD8+, which, in turn, can recruit either an IgE or IgG4-mediated pathway. The data indicate that drug-specific T cells activated locally release different cytokines responsible for renal damage [11].

- Known haptens. Methicillin nephritis was named by the initial cases reported, although all penicillins and cephalosporins can cause this through haptenic mechanisms. It is a typical interstitial nephritis [12,13], accounting for 49% of all instances [12]. Methicillin-specific anti-tubular BM antibody diseases have been reported [1].
- Other haptens causing AIN are NSAIDS [14–16], accounting for a further 11% [12], hydrogen-ion pump inhibitors [17–19] for some 14% [12], plus a number of miscellaneous other substances [20–24], to quote only a few.
- Clinical symptoms. Interstitial nephritis is characterized by back pain, caused by renal swelling, which distends the capsula, while the kidney outline remains smooth. Plasma creatinine concentration (PCr) rises slowly and progressively, urine output increases initially despite the fall in GFR, an important clue to the diagnosis. Sterile pyuria, low-grade proteinuria made up by "tubular" protein, namely, short peptides and tubular enzymes, renal tubular cell casts and leukocyte casts are observed. Eosinophiluria can be found in allergic nephritis. Urine specific gravity is low and isostenuric in advanced disease. Fever relapsing during antibiotic treatment after an initial resolution constitutes an additional clue and is more suggestive if associated with peripheral eosinophilia. The urine sediment may disclose additional findings, according to concomitant glomerular involvement, vascular and endothelial lesions, and tubular damage. The disease, if unrecognized, can progress to CRF.

  These symptoms point to interstitial involvement, as this affects the epithelial peritubular side facing the tubular BM, thus damaging transport systems. Therefore, phosphate reabsorption is impaired, resulting in increased phosphaturia. Hydrogen ion secretion is hampered, delivering more bicarbonate to the distal nephron, overwhelming its reabsorption mechanism: the excretion of alkaline urine and RTA ensue. Other PT functions, as PT accounts for the majority of peritubular sites exposed to the interstitium, are deranged, like AA and glucose resorption. PT reclamation of low molecular weight peptides is hampered, causing "tubular proteinuria", which is easily distinguished from glomerular proteinuria made up by albumin or immunoglobulins not retained by the glomerular sieve. As the countercurrent mechanism is critically dependent upon the integrity of renal medullary and papillary interstitium, urine concentration is preferentially lost in AIN with respect to AGN: polyuria occurs even in the face of reduced GFR, until its fall does not reach a point beyond which even the increased fraction of urine flow over that of filtration cannot afford a normal urine volume.
- Diagnosis. Recognition of AIN requires awareness of the disease, accurate follow-up of patients during drug treatment, continuous review of the drugs administered, knowledge of the potential offending agents, appropriate questioning of patients about symptoms, sequential PCr measurement and urinalysis with careful examination of urinary sediment.

  Diagnosis can be reached clinically on the grounds of the above symptoms, and confirmed, when necessary, by renal biopsy. This can be avoided in most circumstances by prompt drug withdrawal, prednisone administration [25], continuous follow-up of renal function and clinical conditions.
- Treatment. Treatment consists of PDN administration, 1 mg/kg either i.v. or p.o. at 8 am for 7–20 days according to response, with tapering in a variable time, from one up to six months, guided by the evaluation of remission versus persistent disease [25]. There are patients requiring dialysis for ARF or CRF. PDN is given as 50% of the total at breakfast, 25% at lunch and at 5 p.m. Tapering is accomplished by withdrawing the afternoon and lunch administrations. After one month, a double daily dose should be given every other day.

1.2 Analgesic nephropathy

This is a chronic process which leads slowly over many years to CRF by causing an interstitial nephropathy [26]. The toxic effect is dose related, and requires the continuous daily intake of analgesics for decades. In many circumstances, the interstitial changes disrupt the vascular system, causing ischemic alterations that