Mechanisms of Drug-Induced Interstitial Nephritis

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Drug-induced acute interstitial nephritis (DI-AIN) is a drug hypersensitivity reaction (DHR) that manifests 7 to 10 days after exposure to the culprit drug. DHRs account for fewer than 15% of reported adverse drug reactions. The kidneys are susceptible to DHR because: (1) the high renal blood flow whereby antigens are filtered, secreted, or concentrated, and (2) it is a major site of excretion for drugs and drug metabolites. More than 250 different drugs from various classes have been incriminated as causative agents of DI-AIN, the third most common cause of acute kidney injury in the hospital. DI-AIN must be differentiated from drug-induced nephrotoxic acute tubular necrosis because of their differing pathophysiology and treatment. DI-AIN begins with antigen processing and presentation to local dendritic cells. The dendritic cells activate T cells, and the subsequent effector phase of the immune response is mediated by various cytokines. Incriminated antigenic mechanisms include response to a conjugation product of the drug or its metabolite with a host protein (eg, beta-lactam or sulfonamide antibiotic) or the direct binding of the drug to a particular host allele to elicit a hypersensitivity response (eg, certain anti-epileptic drugs). If the offending drug is not identified and discontinued in a timely manner, irreversible fibrosis and chronic kidney disease will occur. The core structure of each drug or its metabolite is an antigenic determinant, and the host interaction is termed the structure-activity relationship. Differing structure-activity relationships accounts for effect, hypersensitivity, and cross-reactivity among and between classes. The essence of management of DI-AIN lies with the four sequential steps: anticipation, diagnosis, treatment, and prevention. Corticosteroids are used in the treatment of DI-AIN because of their potent anti-inflammatory effects on T cells and eosinophils. Anticipation and prevention require notifying the patient that DI-AIN is an idiosyncratic, hypersensitivity reaction that recurs on re-exposure, and the drug should be avoided.

Key Words: Interstitial Nephritis, Drug-Induced, Acute Kidney Injury, Drug Hypersensitivity Reaction

INTRODUCTION

The first clear identification of acute interstitial nephritis (AIN) was in an 1898 autopsy study of patients with various, but principally streptococcal, infections. It is now well recognized as a common cause of acute kidney injury (AKI) but resulting from diverse etiologies.[1] Ironically, drugs, including the very antibiotics used to eradicate streptococcal infections, are now responsible for 70% of AIN cases.[1-3] Drug-induced AIN (DI-AIN) is the third most common cause of AKI in hospitalized patients.[1] The diagnosis of DI-AIN is based on its clinical and laboratory manifestations, characteristic morphologic features of the kidney on biopsy, and the identification of a causative agent. In practice, satisfying all three criteria is fraught with limitations, particularly in patients exposed to multiple potentially incriminated drugs.

AIN and acute tubular necrosis (ATN) are both inflammatory reactions with similar clinical presentations that result from an adverse reaction to a drug. ATN causes direct tubular epithelial cell injury and a rather rapid deterioration of kidney function, whereas AIN is more insidious in onset and is associated with interstitial edema and cellular infiltration.

DI-AIN is an idiosyncratic systemic hypersensitivity reaction to a drug, which by definition means it is specific to the affected individual rather than just to the implicated agent. More than 250 different drugs from multiple classes have been reported as causative agents of DI-AIN (Table 1), and it is impossible to predict which individual exposed to any of them will develop AIN. This article addresses three major questions related to DI-AIN. First, what constitutes a drug hypersensitivity reaction and which individuals are at increased risk of DI-AIN? Second, what is the mechanism of the hypersensitivity reaction that affects the kidney? Third, what are the structural features of implicated drugs that may account to their detrimental immune response from the host?

DRUG HYPERSENSITIVITY REACTIONS

An adverse drug reaction (ADR) is an undesired and unintended response to a drug that occurs at usual therapeutic doses of the drug. An allergic drug hypersensitivity reaction (DHR) is a rare and specific type of ADR that occurs in fewer than 15% of cases exposed to an agent.[4] Despite its rarity, the term "drug allergy" is mistakenly applied to any ADR because of the concern of subjecting exposed patients to anaphylactic shock. This results in the choice of alternate medications that may be less effective and more expensive with consequent potential of greater morbidity and economic cost.

The features of an ADR that support an allergic DHR are[4]:

1. Presence of a known immunologic manifestation: eg, rash, urticaria, anaphylaxis, or serum sickness.
2. No other explanation on the basis of known pharmacologic or idiosyncratic effects of the drug(s).
3. Timeline of occurrence, which is usually within 7 to 10 days of initial exposure to a drug. Re-exposure to the same agent will result in a faster (<4 days) and more severe DHR.

Additionally, the new onset of a maculopapular skin rash, peripheral eosinophilia, and fever in an otherwise well subject support the diagnosis of a DHR.

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There are five principal mechanisms by which a seemingly inert drug can elicit an autoimmune or hypersensitivity response in the host. One, the host tissue may become immunogenic after being altered by the drug. Two, the host may develop an antibody to the drug and then this complex elicits the immune reaction; eg, procainamide and hydralazine are capable of eliciting reactions with positive antinuclear antibodies that mimic lupus. Methicillin-induced AIN has been reported along with granular immune complex deposits along the anti-TBM, although this is rare and not the typical mechanism for DI-AIN.[5] Three, the unchanged drug itself may be immunogenic in individuals with a particular T-cell receptor or major histocompatibility complex (MHC) protein. This is termed the pharmacologic interaction with immune receptors or p-i concept. For example, carbamazepine has a high affinity for HLA-B*15:02 and flucloxacillin for HLA-B*57:01 class II receptors.[6,7]

Four, the drug may be metabolized into a reactive antigen or immunogen that can stimulate the innate immune response. Kidney proximal tubular cells have the capacity to hydrolyze and metabolize exogenous antigens and present them to the MHC antigen-presenting cells in the kidney.[3] Five, haptenization (from the Greek verb, "to fasten") is the process by which low-molecular weight compounds, such as drugs or their metabolites, bind irreversibly to self-proteins to create an immunogenic compound termed "hapten." An individual drug may be deemed incapable of triggering a specific response because of its size of <1000 Da. After haptenization in peripheral circulation, larger and more immunologically active compounds can become "trapped" in the kidney. Haptenization can also occur in the kidney during filtration, after the drug or its metabolite binds to specific tubulointerstitial proteins to elicit the AIN response.[8] Beta-lactam antibiotics bind to lysine residues on circulating proteins, particularly albumin, to form an immunogenic complex. Sulfamethoxazole (SMX) acts a "prohapten" because it is modified by the CYP2C9 isoenzyme in the liver before spontaneously converting to the toxic nitroso-SMX.[9] The toxic compound then binds to cysteine residues on intracellular and extracellular proteins to form a hapten which then elicits the immune response.[10]

CLINICAL SUMMARY

- Drug-induced AIN (DI-AIN) is a delayed T-cell-mediated hypersensitivity reaction.
- The host immunogenic response is elicited by: (1) a drug or its metabolite (hapten) with a carrier protein (haptenization) or (2) direct interaction of the drug with a specific host protein (p-i concept).
- The core structural component of each drug acts as an antigenic determinant and similar drug structures from different functional classes result in cross-reactivity.
- Successful management of DI-AIN involves anticipation, diagnosis, treatment, and prevention.

DELAYED HYPERSENSITIVITY MECHANISMS IN THE KIDNEY

Regardless of the mechanism by which a hypersensitivity response is elicited, the host response is either immediate and immunoglobulin-E mediated (type I reaction) or delayed and T-cell mediated (type IV reaction). The most common clinically encountered DHRs are type I hypersensitivity reactions, which present within 24 hours of drug exposure. The skin is commonly reported as a DHR because this organ is immunologically active and even a mild skin rash is readily visible; common symptoms include urticarial and maculopapular skin eruptions.[11] The prevalence of cutaneous drug eruptions has been noted to be 3.6 per 1000 hospitalized patients and antibiotics accounted for 55% of the observed cases.[12]

DHRs by definition occur 48 to 72 hours after antigen exposure and any organ can be affected.[11] In DI-AIN, T cells have a central role as evidenced by the predominantly lymphocytic infiltrate in the kidney.[3] Laboratory markers of kidney involvement (eg, electrolyte abnormalities, sterile pyuria) occur at 72 hours after exposure but often go undetected or missed until a rise in serum creatinine or blood urea nitrogen is reported, usually 7 to 10 days after exposure. The cutaneous reaction that appears in 50% of cases DI-AIN occurs 24 to 96 hours after drug exposure and, therefore, cannot be considered a type I reaction.[1] The kidneys are susceptible to DHR for two principal reasons. First, there is a high blood flow to the kidneys where potential antigens are filtered, processed, secreted, and concentrated. Second, the kidney is a major excretory route of many drugs and their metabolites.

The bulk of the available information about the kidney inflammatory reaction in AIN derives from studies in experimental animals.[13,14] A principal limitation of human studies is that the data derived from kidney biopsies or serologic data provide information only at fixed moments in the course of an evolving lesion, usually when the lesion is well established and often at its worst, with limited or no data available on the onset or resolution phases of the lesion.

For simplicity, the pathogenesis of DI-AIN occurs as three successive but overlapping phases: an "antigen recognition" and presentation phase, an "integrative" or regulatory (primarily cellular) phase, and an "effector" or mediator (primarily humoral) phase (Fig 1).[1] The first phase begins when freely filtered antigens or haptens are endocytosed by the resident peritubular interstitial cells or tubular epithelial cells. These cells function as antigen presenters displaying the antigenic stimulus to dendritic cells.[1] Dendritic cells (DCs) are resident monocytes that function as the body's immunologic sentinels. DCs have stellate-like projections throughout the kidney which are in direct contact with the basolateral facets of tubular epithelial cells (Fig 1).[15-17] The normally quiescent DCs become activated when exposed to antigens or damage signals and express the antigenic compounds as peptides on their surface MHC II molecules. Once activated, DCs