Drug-Induced Glomerulopathy: A Selective Review

Francis Dumler

Follow this and additional works at: https://scholarlycommons.henryford.com/hfhmedjournal

Part of the Life Sciences Commons, Medical Specialties Commons, and the Public Health Commons

Recommended Citation

Available at: https://scholarlycommons.henryford.com/hfhmedjournal/vol31/iss2/10

This Article is brought to you for free and open access by Henry Ford Health System Scholarly Commons. It has been accepted for inclusion in Henry Ford Hospital Medical Journal by an authorized editor of Henry Ford Health System Scholarly Commons.
Drug-Induced Glomerulopathy: A Selective Review

Francis Dumler, MD*

The pathogenesis of drug-induced glomerular disease is becoming better understood because of recent advances in the study of glomerular physiology and metabolism. Various classes of drugs may produce nephrotoxicity. This review is limited to types of drugs whose use may result in glomerular functional and metabolic abnormalities leading to proteinuria and/or renal insufficiency. Drugs which cause tubular necrosis are excluded. Nonsteroidal anti-inflammatory agents are examples of drugs that induce glomerular proteinuria and minimal change nephropathy. Gold, penicillamine, and captopril produce drug-induced glomerular proteinuria in association with membranous nephropathy. Finally, semustine and mitomycin are examples of drugs that induce glomerular sclerosis and microangiopathy.

Recent advances in the study of glomerular physiology and metabolism have increased our understanding of the pathogenesis of drug-induced glomerular disease. Various types of therapeutic agents are associated with renal dysfunction. Nephrotoxicity that results in acute renal failure is usually dramatic in its clinical presentation, is well recognized, and has been comprehensively reviewed (1,2). By contrast, drug-induced glomerulopathy is clinically more insidious, and progressive proteinuria or renal insufficiency develop gradually. The nonsteroidal anti-inflammatory agents and the angiotensin converting enzyme inhibitor captopril have been selected as examples of drugs that induce proteinuria. Although they have been used in general clinical practice for a relatively short time, their use is increasing. Gold and penicillamine are drugs that induce membranous glomerulopathy, and semustine and mitomycin C are chemotherapeutic agents that induce glomerular sclerosis.

To better understand the pathogenesis of drug-induced proteinuria, a brief description of the normal filtration of plasma proteins by the glomerulus is in order. Plasma proteins that appear in the urine must be transferred across the glomerular filter through a pathway consisting of the endothelial fenestrae, the glomerular basement membrane, and the slit diaphragm of the epithelial cell. A polyanion coating of sialic acid renders a highly negative charge on the endothelial and epithelial cell coats and to the glomerular basement membrane (3). Molecular size and charge are important determinants of the glomerular filtration of proteins. As the effective molecular radius increases, the fractional clearance of proteins decreases, reaching very low values when the size of albumin (36Å) is approached. Neutral dextrans with a molecular size similar to that of albumin have a significantly higher fractional clearance than albumin. However, negatively charged sulphated dextrans have a lower clearance than neutral dextrans of similar size, and approach that of albumin (4,5). Drugs or drug metabolites which affect glomerular metabolism and disrupt the structural or molecular integrity of the glomerular filtration barrier may also cause glomerulopathy and significant proteinuria. For example, in rats, the parenteral administration of puromycin aminonucleoside induces proteinuria, hypoalbuminemia, hypercholesterolemia, and a renal lesion similar to that of human minimal change nephropathy (6-8). In this experimental model, a diminution of the electrostatic barrier function of the glomerular capillary wall (9,10) and loss of glomerular polyanionic sites (11,12) have been well documented. Cellular metabolic damage induced by this agent results in a loss of polyanion coating and subsequent proteinuria.

Nonsteroidal Anti-inflammatory Drugs

Currently, at least 14 nonsteroidal anti-inflammatory agents are available in the United States to treat arthritis and musculoskeletal pain of various etiologies. These drugs share the ability to block prostaglandin synthesis in various tissues (13). The use of these agents may be

Submitted for publication: October 11, 1982
Accepted for publication: May 9, 1983
*Department of Internal Medicine, Division of Nephrology, Henry Ford Hospital
Address reprint requests to Dr. Dumler, Henry Ford Hospital, 2799 W Grand Blvd, Detroit, MI 48202.

110
associated with decreased renal function due to inhibition of prostaglandin synthesis, which results in a predominance of vasoconstrictor effects on the glomerular microcirculation of patients treated with these drugs. At particularly high risk for acute renal failure are those with preexisting renal disease, volume depletion (especially following diuretic therapy), or cardiac insufficiency; these conditions result in decreased renal perfusion pressure and increased renal vasoconstrictor activity from activation of the renin-angiotensin system (14-17). Hyperkalemia may be quite prominent even when loss of renal function is not severe (18,19), perhaps due to a concomitant decrease in renin-aldosterone production (20). In some patients, histological evidence of acute tubulo-interstitial nephritis has been reported during acute renal failure (21,22).

Differing degrees of glomerular proteinuria have been reported with the nonsteroidal anti-inflammatory drugs indomethacin, naproxen, fenoprofen, tolmetin, and sulindac (15,16,21-25), and histological changes are consistently similar to those of minimal change nephropathy (lipoid nephrosis). No systematic studies have been carried out on the glomerular polyanion content in these patients, and little data are available on the effects of nonsteroidal anti-inflammatory drugs on glomerular metabolism other than on prostaglandin synthesis. In one study, indomethacin was found to decrease glomerular basement membrane collagen synthesis (26). Thus, these agents may induce proteinuria by a toxic effect on the cells responsible for the integrity of the glomerular filtration barrier.

Patients who receive these agents, particularly those at high risk because of diuretic therapy, volume depletion, preexisting renal disease, high renin hypertension volume depletion, or congestive heart failure, should have regular evaluation of their renal function and routine urinalysis during therapy. Gradually progressive renal insufficiency, sudden increases in serum creatinine or potassium, or the presence of proteinuria greater than 500 mg/day are sufficient indications to discontinue therapy. If no adequate alternatives are present, continuation of therapy may be reasonable in rare instances, provided close monitoring of renal function and proteinuria are concomitantly carried out. If renal insufficiency or proteinuria develop while the patient is under treatment with one of these agents, it is possible that similar complications may be encountered when another nonsteroidal anti-inflammatory drug is used.

Gold and Penicillamine

Proteinuria may occur in up to 7% of individuals who receive parenteral gold therapy for rheumatoid arthritis, and the nephrotic syndrome may develop in as many as 3% of patients (27). The renal histological lesion is usually that of membranous nephropathy with granular deposits of IgG and IgM along the glomerular capillary wall. In addition, characteristic filamentous electron dense cytoplasmic inclusions commonly occur; in some cases, these have been demonstrated by x-ray dispersion analysis to be gold particles (28,29).

Mechanisms for development of this nephropathy are not clear. Discovery of a mechanism is hampered by the occurrence of membranous nephropathy in patients with rheumatoid arthritis who have not been exposed to gold therapy (30). Thus, a direct toxic effect of gold on the glomerulus cannot be excluded. Also, gold therapy may result in the release of renal tubular epithelial antigens (31) and subsequent immune complex formation leading to glomerular damage (32). The potential for developing the immunological response that leads to membranous glomerulopathy may well be genetically controlled, since rheumatoid arthritis patients who are HLA-DRw3 positive have a 32-times greater risk of developing proteinuria during gold therapy than patients who are HLA-DRw3 negative (33).

Nephrotic syndrome and membranous glomerulopathy have also been reported after oral gold therapy. However, the reported experience of only a few cases of mild proteinuria occurring in over 1672 patients treated for at least six months suggests that the overall prevalence of proteinuria may be less than with parenteral gold therapy (34).

In a multicenter trial, penicillamine was shown to be effective in rheumatoid arthritis (35), but the authors of this report noted that nephrotoxicity precludes the indiscriminate use of penicillamine to treat rheumatoid arthritis. The prevalence of penicillamine-induced proteinuria in rheumatoid arthritis patients is 7-20% (36,37). On renal biopsy, the lesion is usually consistent with the diagnosis of membranous glomerulopathy, and in most patients circulating immune complexes are not detected (36). These abnormalities are similar to those observed in patients receiving gold therapy. Rheumatoid arthritis patients who are HLA-DRw3 positive are also at a higher risk of nephrotoxicity from penicillamine therapy (33), as they are from gold therapy. Chelation of penicillamine by iron in the intestine reduces its absorption, and in patients taking iron supplements renal toxicity may be apparent only after discontinuation of iron therapy.
increases penicillamine absorption (38). Patients with gold-induced proteinuria are also at a higher risk of progressive proteinuria during penicillamine therapy (39).

The nephropathy associated with gold and penicillamine therapy in patients with rheumatoid arthritis is likely to be immunologically mediated. As in idiopathic membranous glomerulopathy, the lesion may result from the glomerular deposition of preformed immune complexes. These are formed from the reaction of circulating antibodies to antigens extrinsic to the glomerulus that become bound to the glomerulus during the disease process (40). The possibility that immune complexes form in situ has recently been postulated in the pathogenesis of membranous nephropathy (40).

In general, proteinuria will develop within three to 12 months of initiating therapy with gold or penicillamine (39). After therapy has been discontinued, proteinuria usually decreases, although this may take several months (27,35,36). When the drugs are discontinued, the glomerulopathy rarely progresses, and renal insufficiency is uncommon (27,35,36). Because improvement in the degree of proteinuria has been reported with steroid therapy (27), a short course of prednisone might be given to patients with gold or penicillamine-induced membranous glomerulopathy, as is currently advocated for idiopathic membranous nephropathy (41). Mild proteinuria of less than 500 mg/day is not an indication for discontinuing therapy (36), but proteinuria greater than 0.5-1.0 mg/day or declining renal function requires prompt discontinuation of therapy. On some occasions reintroduction of the drug has led to recrudescence of the nephrotic syndrome (42).

**Captopril**

Administration of captopril has rarely been associated with acute renal failure, which, when it occurs, has been attributed to a concomitant decrease in blood pressure (43). However, some investigators have suggested a direct nephrotoxic effect, because loss of renal function during captopril treatment may occur in the absence of hypotension and because histological study discloses patchy atrophy and inflammation (44). A report of eosinophilia, eosinophiluria, and acute renal failure observed simultaneously in a patient receiving captopril suggests that hypersensitivity phenomena may be important in the development of acute renal failure (45). Also, patients with bilateral renal artery stenosis or renal artery stenosis in a solitary kidney are at particular risk for developing acute renal failure during captopril therapy (46-48), probably because of inadequate autoregulation of glomerular filtration in the presence of reduced renal artery perfusion pressure.

During captopril therapy, proteinuria occurs in approximately 1.5% of patients, and nephrotic syndrome develops in 0.4% (49). On renal biopsy, the usual histological lesion is that of membranous nephropathy (49-51). The pathogenesis of captopril-induced glomerulopathy is probably similar to that of gold and penicillamine, that is, immune complex nephropathy. While these drugs share a heavy metal or a heavy metal binding site, it is not clear how the immune complex nephropathy is generated. In some patients, proteinuria may result in spite of continuous captopril therapy (49), but no data are available on how frequently this occurs. Membranous nephropathy has also been found in random renal biopsies of patients without proteinuria who have been treated with captopril for severe hypertension (51).

In patients treated with captopril, the advantages of the drug must be weighed against its potential nephrotoxicity. In patients with bilateral renal artery stenosis or a solitary kidney and renovascular hypertension, therapy should be gradual and cautious in order to minimize the risk of acute renal failure. In those patients in whom persistent proteinuria of 0.5-1.0 gm/day or greater occurs, renal biopsy should be considered and the drug should be discontinued, particularly when renal function is already impaired. In patients with renal failure, hyperkalemia due to aldosterone deficiency is also more likely to occur (52). Perhaps the use of smaller doses (i.e., 100 mg/day or less) than those currently recommended may provide comparable blood pressure control and reduce the likelihood of side effects, particularly in patients with renal insufficiency (53).

**Semustine (methyl-CCNU)**

The chlorethyl nitrosoureas are antitumor agents of particular use to treat solid tumors. Although initial studies did not show significant nephrotoxicity (54) with the use of semustine, in one study severe renal damage was reported several years later in all six children who received more than 1500 mg/m$^2$ (55). In another study, decreased renal function occurred in 26% of adult patients who received more than 1400 mg/m$^2$, and severe chronic renal failure occurred in 14% (56). Histologically, glomeruli revealed significant sclerosis, with thickening and wrinkling of the glomerular basement membrane as well as marked interstitial fibrosis and moderate lymphocytic infiltration (55,56). Since the compound is rapidly metabolized, either the active drug or a metabolite could be responsible for the nephrotoxicity, but the nature of the active drug or its metabolites is not known. Semustine should be used only when the ratio of therapeutic benefit to renal toxicity is considered to be high. Close monitoring of renal function...
including urinalysis, urea nitrogen, serum creatinine, and creatinine clearance should be carried out before each treatment and regularly after therapy is completed. All other potential nephrotoxic agents should be avoided, and therapy should be discontinued if loss of renal function is noted (56).

**Mitomycin C**

Recent reports have indicated that adjuvant therapy with 5-fluorouracil and mitomycin C for malignancy is associated with a syndrome characterized by progressive microangiopathic hemolytic anemia, disseminated intravascular coagulation, and acute renal failure (57,58). This syndrome may also occur when mitomycin C is used alone (59). Therapy with these agents may result in a hemolytic-uremic syndrome which is suddenly and markedly aggravated by the use of blood transfusions (60).* Renal histological studies have demonstrated typical microangiopathy with significant fibrin deposition in small vessels (53,54).

**Summary**

The nonsteroidal anti-inflammatory drugs, gold, penicillamine, captopril, semustine, and mitomycin C are examples of drugs whose use may be associated with the development of significant glomerular disease leading to proteinuria and renal insufficiency. Patients who undergo therapy with these drugs should be monitored with routine urinalysis and serum creatinine determinations. The appearance of persistent glomerular proteinuria requires reassessment of the benefit-to-risk ratio of the drug therapy, while loss of renal function warrants discontinuation of the drug.

**References**


*A case of the hemolytic-uremic syndrome in a patient receiving mitomycin-C and 5-fluorouracil is discussed in the article by GR Willie, et al on pp. 104-09.


52. Warren SE, O'Connor DT. Hyperkalemia resulting from captopril administration. JAMA 1980;244:2551-2.


