PREDISPOSING FACTORS FOR NSAID-INDUCED ACUTE RENAL FAILURE

Severe heart disease (congestive heart failure)
Severe liver disease (cirrhosis)
Nephrotic syndrome (low oncotic pressure)
Chronic renal disease
Age 80 years or older
Protracted dehydration (several days)

FIGURE 11-18

Conditions associated with risk for nonsteroidal anti-inflammatory drugs (NSAID)-induced acute renal failure. NSAIDs can induce acute renal decompensation in patients with various renal and extrarenal clinical conditions that cause a decrease in blood perfusion to the kidney [32]. Renal prostaglandins play an important role in the maintenance of homeostasis in these patients, so disruption of counter-regulatory mechanisms can produce clinically important, and even severe, deterioration in renal function.

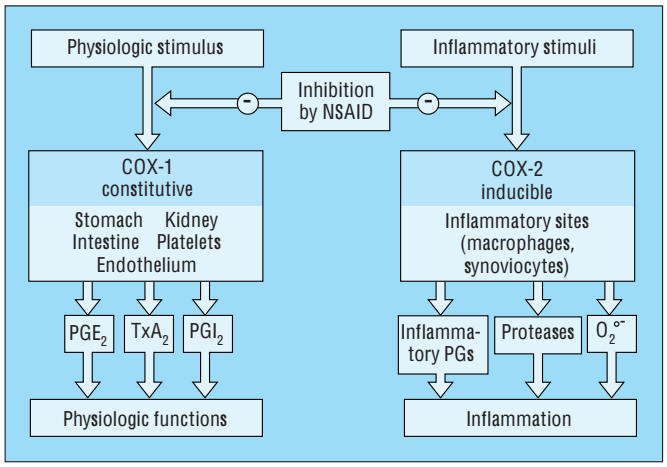

FIGURE11-19

Inhibition by nonsteroidal anti-inflammatory drugs (NSAIDs) on pathways of cyclo-oxygenase (COX) and prostaglandin synthesis [33]. The recent demonstration of the existence of functionally distinct isoforms of the cox enzyme has major clinical significance, as it now appears that one form of cox is operative in the gastric mucosa and kidney for prostaglandin generation (COX-1) whereas an inducible and functionally distinct form of cox is operative in the production of prostaglandins in the sites of inflammation and pain (COX-2) [33]. The clinical therapeutic consequence is that an NSAID with inhibitory effects dominantly or exclusively upon the cox isoenzyme induced at a site of inflammation may produce the desired therapeutic effects without the hazards of deleterious effects on the kidneys or gastrointestinal tract. PG—prostaglandin; TxA_2—thromboxane A_2.

EFFECTS OF NSAIDS ON RENAL FUNCTION

Renal Syndrome	Mechanism	Risk Factors	Prevention/Treatment [34]
Sodium retension and edema	↓ Prostaglandin	NSAID therapy (most common side effect)	Stop NSAID
Hyperkalemia	↓ Prostaglandin ↓ Potassium to distal tubule ↓ Aldosterone/renin-angiotensin	Renal disease Heart failure Diabetes Multiple myeloma Potassium therapy Potassium-sparing diuretic	Stop NSAID Avoid use in high-risk patients
Acute deterioration of renal function	↓ Prostaglandin and disruption of hemodynamic balance	Liver disease Renal disease Heart failure Dehydration Old age	Stop NSAID Avoid use in high-risk patients
Nephrotic syndrome with: Interstitial nephritis	↑ Lymphocyte recruitment and activation	Fenoprofen	Stop NSAID Dialysis and steroids (?) Stop NSAID
Papillary necrosis	Direct toxicity	Combination aspirin and acetaminophen abuse	Avoid long-term analgesic use

FIGURE 11-20

Summary of effects of nonsteroidal anti-inflammatory drugs (NSAIDs) on renal function [31].

All NSAIDs can cause another type of renal dysfunction that is associated with various levels of functional impairment and characterized by the nephrotic syndrome together with interstitial nephritis.

Characteristically, the histology of this form of NSAID–induced nephrotic syndrome consists of minimal-change glomerulonephritis with tubulointerstitial nephritis. This is an unusual combination of findings and in the setting of protracted NSAID use is virtually pathognomic of NSAID-related nephrotic syndrome.

A focal diffuse inflammatory infiltrate can be found around the proximal and distal tubules. The infiltrate consists primarily of cytotoxic T lymphocytes but also contains other T cells, some B cells, and plasma cells. Changes in the glomeruli are minimal and resemble those of classic minimal-change glomerulonephritis with marked epithelial foot process fusion.

Hyperkalemia, an unusual complication of NSAIDs, is more likely to occur in patients with pre-existing renal impairment, cardiac failure, diabetes, or multiple myeloma or in those taking potassium supplements, potassium-sparing diuretic therapy, or intercurrent use of an angiotensin-converting enzyme inhibitor. The mechanism of NSAID hyperkalemia—suppression of prostaglandin-mediated renin release—leads to a state of hyporeninemic hypoaldosteronism. In addition, NSAIDs, particularly indomethacin, may have a direct effect on cellular uptake of potassium.

The renal saluretic response to loop diuretics is partially a consequence of intrarenal prostaglandin production. This component of the response to loop diuretics is mediated by an increase in renal medullary blood flow and an attendant reduction in renal concentrating capacity. Thus, concurrent use of an NSAID may blunt the diuresis induced by loop diuretics.

Contrast Medium–Associated Nephrotoxicity

RISK FACTORS THAT PREDISPOSE TO CONTRAST ASSOCIATED NEPHROPATHY

Confirmed	Suspected	Disproved
Chronic renal failure	Hypertension	Myeloma
Diabetic nephropathy	Generalized atherosclerosis	Diabetes without nephropathy
Severe congestive heart failure	Abnormal liver function tests	
Amount and frequency of contrast media	Hyperuricemia	
Volume depletion or hypotension	Proteinuria	

FIGURE 11-21

Risk factors that predispose to contrast-associated nephropathy. In random populations undergoing radiocontrast imaging the incidence of contrasts associated nephropathy defined by a change in serum creatinine of more than 0.5 mg/dL or a greater than 50% increase over baseline, is between 2% and 7%. For confirmed high-risk patients (baseline serum creatinine values greater than 1.5 mg/dL) it rises to 10% to 35%. In addition, there are suspected risk factors that should be taken into consideration when considering the value of contrast-enhanced imaging.

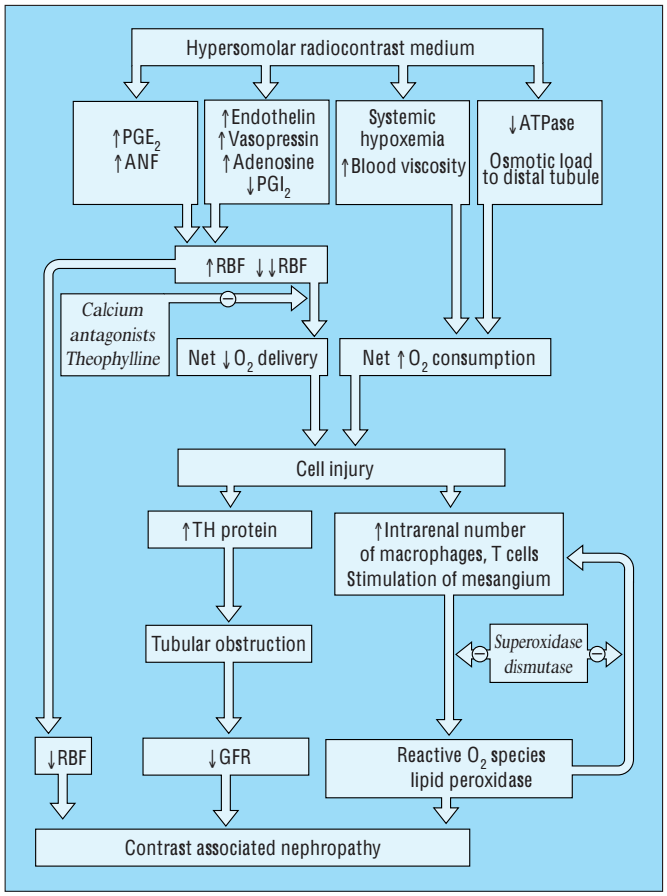

FIGURE 11-22

A proposed model of the mechanisms involved in radiocontrast medium–induced renal dysfunction. Based on experimental models, a consensus is developing to the effect that contrast-associated nephropathy involves combined toxic and hypoxic insults to the kidney [35]. The initial glomerular vasoconstriction that follows the injection of radiocontrast medium induces the liberation of both vasoconstrictor (endothelin, vasopressin) and vasodilator (prostaglandin E_2 [PGE_2], adenosine, atrionatiuretic factor {ANP}) substances. The net effect is reduced oxygen delivery to tubule cells, especially those in the thick ascending limb of Henle. Because of the systemic hypoxemia, raised blood viscosity, inhibition of sodium-potassium–activated ATPase and the increased osmotic load to the distal tubule at a time of reduced oxygen delivery, the demand for oxygen increases, resulting in cellular hypoxia and, eventually cell death. Additional factors that contribute to the acute renal dysfunction of contrast-associated nephropathy are the tubule obstruction that results from increased secretion of Tamm-Horsfall proteins and the liberation of reactive oxygen species and lipid peroxidation that accompany cell death. As noted in the figure, calcium antagonists and theophylline (adenosine receptor antagonist) are thought to act to diminish the degree of vasoconstriction induced by contrast medium.

The clinical presentation of contrast-associated nephropathy involves an asymptomatic increase in serum creatinine within 24 hours of a radiographic imaging study using contrast medium, with or without oliguria [36].

We have recently reviewed the clinical outcome of 281 patients with contrast-associated nephropathy according to the presence or absence of oliguric acute renal failure at the time of diagnosis. Of oliguric acute renal failure patients, 32% have persistent elevations of serum creatinine at recovery and half require permanent dialysis. In the absence of oliguric acute renal failure the serum creatinine value does not return to baseline in 24% of patients, approximately a third of whom require permanent dialysis. Thus, this is not a benign condition but rather one whose defined risks are not only permanent dialysis but also death. GFR—glomerular filtration rate; RBF—renal blood flow; TH—Tamm Horsfall protein.

PREVENTION OF CONTRAST ASSOCIATED NEPHROPATHY

Hydrate patient before the study (1.5 mL/kg/h) 12 h before and after.
Hemodynamically stabilize hemodynamics.
Minimize amount of contrast medium administered.
Use nonionic, iso-osmolar contrast media for patients at high risk (*see* Figure 11-21).

FIGURE 11-23

Prevention of contrast-associated nephropathy. The goal of management is the prevention of contrast-associated nephropathy.

Thus it is important to select the least invasive diagnostic procedure that provides the most information, so that the patient can make an informed choice from the available clinical alternatives.

Since radiographic contrast imaging is frequently performed for diabetic nephropathy, congestive heart failure, or chronic renal failure, concurrent administration of renoprotective agents has become an important aspect of imaging. A list of maneuvers that minimize the risk of contrast-associated nephropathy is contained in this table. The correction of prestudy volume depletion and the use of active hydration before and during the procedure are crucial to minimizing the risk of contrast-associated nephropathy. Limiting the total volume of contrast medium and using nonionic, isoosmolar media have proven to be protective for high-risk patients. Pretreatment with calcium antagonists is an intriguing but unsubstantiated approach.

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