Acute Renal Failure and Toxic Nephropathy

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1. General Aspects

Recent prospective studies of hospital-acquired acute renal failure have revealed it to be a serious illness. The development of hospital-acquired acute renal failure is associated with a sixfold increase in risk of dying. In fact, patients who develop an elevation of serum creatinine concentration greater than 3 mg/dl have a mortality rate of 64%. Development of this condition also has a marked impact on the length of stay of a patient in hospital. One recent report demonstrated that the development of acute renal failure increased a patient’s length of stay in the hospital an average of 13–23 days. The most common etiologies of hospital-acquired acute renal failure include aminoglycoside nephrotoxicity, radiodensity exposure, volume depletion, and septic shock. These etiologies highlight the role of both toxic and ischemic processes in clinically relevant acute renal failure. Prevention of hospital-acquired acute renal failure is, therefore, critically important, not only to diminish the mortality rate associated with this disease process, but also to limit the cost of hospital care. For example, a carefully done retrospective analysis of 1756 patients receiving aminoglycosides was undertaken to determine the economic impact of aminoglycoside-associated nephrotoxicity. An incidence rate of 7% in these patients was identified for aminoglycoside-associated nephrotoxicity. In this study, the additional cost of treating this complication in these patients totaled approximately $2500 per episode.
Mechanisms responsible for development of acute renal failure in humans have recently been shown to be similar to pathophysiology of ischemic acute renal failure in experimental animal models. Ten patients who developed protracted acute renal failure after cardiac surgery were evaluated using differential clearance of various markers of glomerular filtration. Results demonstrated that human acute renal failure is characterized by transtubular backleak of glomerular filtrate and by sluggish tubular fluid flow rates, strongly supporting the existence of severe and generalized intraluminal tubule obstruction as the major nephronal determinants of excretory failure in this clinical disorder.

This chapter further examines recent literature regarding the pathophysiology and clinical aspects of the most relevant forms of clinically recognized acute renal failure, including aminoglycoside nephrotoxicity, radiocontrast nephrotoxicity, and ischemic acute renal failure. In addition, because of the developing importance in understanding cyclosporine (CsA) nephrotoxicity, detailed discussion of this clinical process is also included in this review.

2. Cyclosporine

Nephrotoxicity is the most frequent and clinically most important complication associated with CsA use. A dose-related decline in glomerular filtration rate (GFR) with elevated levels of blood urea nitrogen (BUN) and serum creatinine concentrations occurs in nearly all CsA-treated patients, including transplant recipients and those with autoimmune diseases.

2.1. Clinical Features

2.1.1. Nephrotoxicity

There are differences in the definition of CsA nephrotoxicity. These differences are summarized in Table I. In most clinical disease states in which CsA is used, there are two primary forms of nephrotoxicity: (1) acute drug-induced toxicity, which occurs within the first several months; and (2) chronic (late) drug-induced toxicity, which occurs after several months of CsA use. The acute form most often responds to CsA dose reductions, whereas the chronic form often does not. In the setting of renal transplantation there are three forms of CsA nephrotoxicity: (1) acute (initial posttransplant dysfunction); (2) subacute (early posttransplant dysfunction); and (3) chronic (late-use dysfunction). As noted in Table I, the "acute" and "subacute" forms of nephrotoxicity may, in fact, be overlapping and also properly labeled as instances of "acute drug toxicity," but certain clinical situations in the renal transplantation experience may predispose the recipient to an immediate form of CsA nephrotoxicity, which appears to be distinctly different from the less acute, or subacute, form of toxicity.

An acute decline in renal function may occur immediately following or during the first week after transplantation. This initial, acute form of nephrotoxicity in the