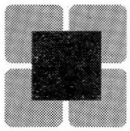

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Drugs for the prevention and treatment of acute renal failure

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SUMMARY Certain preventive measures might decrease the incidence or severity of acute renal failure, including vigorous hydration before the administration of radiocontrast agents, and use of mannitol, loop diuretics, dopamine, and calcium antagonists. However, the pharmacologic agents should be used judiciously, and clinicians should not accept blindly that they are indicated in all clinical situations involving acute renal failure until further studies are available.

KEY POINTS Mannitol, loop diuretics, dopamine, and calcium antagonists show promise in most experimental animal studies, although their effects depend on the type of experimental model studied. These agents have found wide acceptance in clinical practice, even though their efficacy has not been adequately demonstrated in prospective, randomized clinical trials involving adequate sample sizes. As we learn more about the pathophysiology of ischemic and toxic acute renal failure, we will be able to selectively use these medications in a more rational fashion, minimize their unnecessary use, and reduce their potential for adverse effects.

INDEX TERMS: KIDNEY FAILURE, ACUTE; MANNITOL; FUROSEMIDE; ETHACRYNIC ACID; BUMETANIDE; DOPAMINE; CALCIUM CHANNEL BLOCKERS
CLEVE CLIN J MED 1995; 62:248–253

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ACUTE RENAL FAILURE (ARF) can be devastating, especially when it occurs in critically ill patients with other failed organ systems. The mortality rate depends on the clinical setting in which ARF occurs, ranging from 76% in critically ill patients who develop ARF requiring dialysis, to as low as 10% in nonsurgical patients with uncomplicated ARF not requiring dialysis.[1–3]

Medical or surgical procedures often precipitate ARF, and certain measures may prevent it. Vigorous hydration effectively prevents radiocontrast-induced nephropathy, especially in high-risk patients. Other prophylactic measures are also used, but many of them have not been rigorously evaluated for effectiveness and therefore remain unproven.

Drugs used to prevent ARF or alleviate its severity either blunt the reduction in renal blood flow, prevent tubular-cell damage and intratubular obstruction, or minimize intracellular calcium accumulation and reperfusion injury. This report focuses on mannitol, loop diuretics, dopamine, and calcium antagonists, as they are the most

commonly used. Other agents are currently under investigation, but because they are not yet used routinely, we will not discuss them further.

MANNITOL

Diuretics were the first agents to be evaluated for the prevention and treatment of ARF, and mannitol was one of the first diuretics studied. A metabolically inert sugar, mannitol exerts a diuretic and natriuretic effect throughout the entire tubular system by osmosis. In 1945, Selkurt[4] reported that infusion of mannitol before total occlusion of the renal artery in dogs prevented anuria following release of the clamp. Since then, 20 similar reports have been published, and 19 of them showed that mannitol reduces the severity of ARF.[5]

Mannitol does not prevent tubular necrosis but exerts vascular and tubular effects that may lessen the severity of ARF. Mannitol can act as a vasodilator and therefore can increase renal blood flow and glomerular capillary hydraulic pressure; it also reduces intratubular obstruction. Which effect predominates probably depends on the type of experimental model studied. For example, in a study involving norepinephrine-induced ARF in dogs, the protective effect of mannitol seemed to correlate with an enhancement of solute excretion and an increase in intratubular pressure.[6] This suggests that mannitol works primarily by increasing solute excretion, thereby decreasing intratubular obstruction by removing intratubular debris.

Mannitol in clinical trials

Most clinical trials of mannitol have suffered from the lack of a control group, small numbers of subjects, or ill-defined endpoints. In most, urine output was greater in mannitol-treated patients, but renal function was not better, and the incidence of ARF was not lower, perhaps because the overall incidence of ARF in these studies was remarkably low.[5]

In early ARF, oliguria will reverse in approximately two thirds of patients given 12.5 to 25 g of mannitol.[5,7] Renal function usually improves commensurately with urine output. However, most studies have been uncontrolled, and it is difficult to tell if the mannitol actually had an effect or if the patients had less severe renal injury and would have improved regardless.

The potential toxic effects of mannitol consist primarily of volume overload and fluid shifts.

Mannitol: recommendations

In early ARF, it is reasonable to give a single dose (12.5 to 25 g) if there has been no response to the correction of prerenal factors. Mannitol may have a prophylactic role in conditions where intratubular precipitation may occur, such as intravascular hemolysis, hemoglobinuria, and extreme hyperuricemia. Mannitol may also prevent radiocontrast-induced nephropathy in nondiabetic patients, but may cause more harm compared with normal saline hydration in diabetic patients.[8] In these situations, a trial of small doses of mannitol seems warranted if other routine measures for supporting the circulation have not maintained normal urine flow.

LOOP DIURETICS

Furosemide, ethacrynic acid, and bumetanide act primarily in the thick, ascending limb of the loop of Henle, where they inhibit active transport of chloride and sodium. They have minimal effects on other areas of the nephron. They also cause renal vasodilation and stimulate prostaglandin synthesis.

Loop diuretics in animal studies

In experiments in animals, loop diuretics have been most beneficial in ARF induced by the vasoconstrictors norepinephrine or epinephrine.[5] The diuretics were usually given before or immediately after the vasoconstrictor and had a beneficial effect on the glomerular filtration rate (GFR).[5,9,10] Although furosemide has multiple effects, it primarily protects against ARF in these models by increasing solute excretion and thereby decreasing intratubular obstruction.[9,11]

On the other hand, the loop diuretics have had very inconsistent effects in various nephrotoxic models of ARF[5] and provide no benefit in experimental ischemic ARF.[12,13] They may protect against radiocontrast-induced nephropathy in rats.[10]

Loop diuretics in clinical trials

Prophylactic use. Clinical trials of loop diuretics given prophylactically to prevent ARF are limited. One controlled trial demonstrated that patients given furosemide before open heart surgery had greater GFR values afterwards than did controls, but only if cardiopulmonary bypass lasted longer than 60 minutes.[14] In a study of radiocontrast-induced nephropathy, Weinstein and colleagues[15] concluded that

TABLE 1
EFFECT OF LOOP DIURETICS IN HUMAN STUDIES

Endpoint	Number of trials	Results
Urine output	19	Increased (25% to 75% of patients)
Renal function	18	Positive effect (7 studies) No effect (9 studies) Equivocal (2 studies)
Dialysis requirement	14	Positive effect (7 studies) No effect (5 studies) Equivocal (2 studies)
Mortality rate	15	No reduction (14 studies) Reduction (1 study)

prophylactic furosemide administration may be deleterious because it induces volume depletion.

In early ARF. Most studies of loop diuretics in the early phase of ARF have been uncontrolled. Levinsky and Bernard[5] combined these uncontrolled trials and found that of 108 patients whose urine output increased, 76% survived; of 53 patients who remained oliguric, 58% survived ($P < .05$). However, this analysis has limited validity because it involved patients from multiple trials and centers, who differed as to severity and cause of ARF.

In established ARF. Overall, 19 studies have evaluated loop diuretics in established ARF, and furosemide was used in all but one of them (*Table 1*). Although urine output increased in 25% to 75% of patients, whether renal function improves or dialysis requirements decrease is unclear. Of the 15 trials that evaluated mortality, 14 showed no improvement with the use of loop diuretics.

Rare toxic reactions include ototoxicity and acute interstitial nephritis.[16] Diuretic-induced deafness may be irreversible in some patients. The risk of deafness is enhanced when the diuretic is combined with other ototoxic drugs such as aminoglycosides or when given in high doses. Bumetanide may be less ototoxic than furosemide.

Loop diuretics: recommendations

Because of a lack of consensus regarding the effects of loop diuretics in ARF, clinicians must individualize their approach to using these agents. In early or established ARF, it seems reasonable to try a single dose of a loop diuretic in an effort to increase urine output. This should be done only after ensuring that all prerenal and postrenal factors have been corrected. If urine output does not increase within 1 hour, the dose can be doubled until a ceiling dose is reached. An appropriate ceiling dose for furosemide is 400 to 1000 mg; for bumetanide, 8 to 10 mg. If the urine output fails to respond to a ceiling dose, it probably will not respond to additional doses, and the diuretic should be discontinued. High doses of furosemide should be administered no faster than 4 mg/minute to minimize the risk of ototoxicity.

In patients with chronic renal failure, a constant infusion may cause greater natriuresis and diuresis and less tachyphylaxis than do bolus doses.[17] Although data are lacking for ARF, it may be reasonable to attempt to increase urine flow in this setting by using a continuous infusion of a loop diuretic. If there is no response to the diuretic, urine output may increase if dopamine is added to the regimen (see below).

DOPAMINE

The hemodynamic effects of dopamine are dose-dependent.[18] At low doses (0.5 to 1.0 µg/kg/minute), dopamine primarily activates D1 and D2 receptors, causing vasodilation. At intermediate doses (2 to 3 µg/kg/minute), beta-1 receptors are stimulated, resulting in an increase in cardiac output. At higher doses, alpha-1 and alpha-2 receptor stimulation occurs, resulting in vasoconstriction. These dose-dependent effects are on a continuum, and overlap may occur.[18] In addition, receptor activation varies from patient to patient: one may experience an increase in cardiac output when dopamine is infused at a very low dose, whereas another may not.[18]

Dopamine in animal studies

Most animal studies demonstrated an increase in renal blood flow with dopamine, but failed to distinguish whether it was caused by a direct vasodilatory effect or by an increase in cardiac output. In addition, the animals received general anesthesia, which itself alters renal hemodynamics by activating the sympathetic nervous system. Mechanical ventilation and surgical stress also have adverse renal effects. McGrath and colleagues[19] found no effect of dopamine on either renal blood flow or GFR at low or high doses in an isolated perfused kidney preparation, suggesting that dopamine's systemic effects (increased cardiac output) are responsible for increases in renal blood flow and GFR.

Dopamine in human studies

Studies in normal human volunteers generally show results similar to those in *Table 2*.[20] In these studies, dopamine increased renal blood flow and sodium excretion and also increased the GFR slightly.[21] However, saline was usually given concomitantly with the dopamine, and this may have contributed to the observed changes in these renal parameters. Most studies did not report the effect of dopamine on cardiac output, which may increase by as much as 20%, even when dopamine is infused at low doses.[18,22]

Few studies have evaluated the effect of dopamine in patients with ARF. Urine output increased in uncontrolled trials,[23,24] as did GFR.[23] One of the few randomized, controlled trials was performed by Lumlertgul[25] in 23 patients with ARF caused by malaria. The patients received either no treatment, furosemide alone, or a combination of dopamine and furosemide. Serum creatinine levels stabilized only in the patients who had serum creatinine levels of 2 to 4 mg/dL at baseline and who received both dopamine and furosemide; the other patients continued to exhibit an increase in serum creatinine levels and progressive ARF.

More recently, Weisberg and colleagues[8] gave either dopamine or saline alone to patients who had chronic renal failure before they underwent cardiac catheterization. Dopamine protected the nondiabetic patients from radiocontrast-induced ARF better than saline alone did, even though it did not increase renal blood flow. Interestingly, renal blood flow did increase in diabetic patients given dopamine, and these patients had a greater incidence of radiocontrast-induced nephropathy than did controls. The authors postulated that abnormal vascular reactivity resulted in an increase in renal blood flow, causing a vascular "steal" phenomenon in which blood was shunted from the medulla towards the cortex, thereby leading to renal dysfunction.

Thus, despite in vivo data suggesting dopamine can increase renal blood flow by direct vasodilation, a clinically significant direct renal vasodilatory effect remains unproven. Many of the studies were either uncontrolled or failed to take into consideration the effects of dopamine on cardiac output, which may indirectly increase renal blood flow. Dopamine probably does have a direct tubular effect resulting in natriuresis, at least in experimental animals and in normal humans. This effect seems unrelated to changes in renal blood flow.

TABLE 2
EFFECTS OF DOPAMINE INFUSION IN NORMAL SUBJECTS*

Noted effect	Percent increase	*P* value
Effective renal plasma flow	43	< .001
Glomerular filtration rate	9	< .01
Sodium clearance	128	< .001
Urine output	31	< .01
Fractional sodium excretion	105	< .001

*Data from Olsen et al, reference 20

Dopamine in low doses can produce tachyarrhythmias, increased cardiac afterload, aggravation of hypoxemia caused by depressed respiratory drive, and increased pulmonary shunting.[18] In addition, natriuresis induced by dopamine may mask hypovolemia or renal hypoperfusion and may contribute to an inappropriate diuresis, leading to hypovolemia. Dopamine may also impair tubuloglomerular feedback and, therefore, adversely affect the oxygen supply-and-demand balance, which is already jeopardized in ARF.[18]

Dopamine: recommendations

Although popular, low-dose dopamine infusions have not been conclusively proved to have a beneficial effect in ARF. Before resorting to dopamine, clinicians must first correct all prerenal and postrenal factors that may contribute to renal dysfunction, such as volume depletion. In early or established ARF, dopamine may have a role if a trial of diuretics has failed to increase urine flow. In this situation, dopamine may enhance the delivery of diuretics to nephron sites and enhance their response or provide a natriuretic-diuretic action of its own.

If there is no response to dopamine infusion, it should be discontinued. There is absolutely no benefit in maintaining a low-dose dopamine infusion unless it supports cardiac output. Even if urine output does increase after dopamine is started, the infusion should be discontinued within 24 hours to allow assessment of the patient's underlying renal function.

Lastly, one needs to be cautious when using dopamine to prevent radiocontrast-induced nephropathy in diabetic patients. However, this recommendation is based on only eight patients,[8] and additional study is required.

TABLE 3
RENAL EFFECTS OF CALCIUM ANTAGONISTS IN ACUTE RENAL FAILURE*

Vascular effects
Prevent vasoconstriction and mesangial cell contraction
Restore autoregulation of renal blood flow
Diuretic and natriuretic response
Reduce intratubular obstruction
Effects on tubular epithelial cells
Reduce intracellular calcium accumulation
Blunt reperfusion injury
Preserve mitochondrial respiration

*Summarized from Schrier, reference 26, and Epstein, reference 27

CALCIUM ANTAGONISTS

In vitro experiments have demonstrated that calcium antagonists exert separate vascular and tubular effects, both of which may protect against ischemic or toxic ARF (*Table 3*).[26–28]

Calcium antagonists in animal studies

Wetzels and colleagues[29] have reviewed the protective effects of calcium antagonists in experimental models of ischemic ARF. Most studies have used either rats or dogs with ARF induced by either renal-artery clamping or intrarenal norepinephrine infusion. In 18 reports, the calcium antagonist was given before the ischemic insult, either directly into the renal artery, by intravenous infusion, or orally (one report). The disadvantage of intravenous administration was a decrease in systemic blood pressure. Fifteen of the 18 studies demonstrated a beneficial effect.

Calcium antagonists in clinical trials

Clinical studies to date have focused on renal ischemia, radiocontrast-induced ARF, transplant-associated acute renal insufficiency, and ARF associated with nephrotoxins, particularly cyclosporine, aminoglycoside antibiotics, and cisplatin.[27]

Lumlertgul and colleagues[30] gave intrarenal infusions of verapamil to patients with ARF caused by malaria or leptospirosis. Six patients received verapamil (100 µg/minute for 3 hours) and furosemide (0.8 mg/kg/hour intravenously for 24 hours). Six additional patients served as controls and received only intravenous furosemide. Both groups were nonoliguric. The experimental group demonstrated a greater increment in creatinine clearance and urine output 24 hours after treatment; they also had a shorter course of ARF (6.5 ± 2.1 vs 13 ± 1.1 days; $P < .05$), and fewer of them required dialysis.

In a double-blind, prospective, randomized trial, 16 patients received nitrendipine (20 mg daily by mouth) starting 1 day before the administration of radiocontrast media and continuing for 2 days afterwards. Both the experimental and placebo groups (n = 19) received intravenous hydration. The baseline renal function was significantly more compromised in the experimental group, but their GFR declined less ($P < .01$).[31]

Promising applications in ARF

Although calcium antagonists show promise in preventing and treating ARF, we must await additional studies before making any definitive recommendations. To date their most promising clinical application has been in kidney transplantation, but studies in other areas are certain to follow. At least one randomized study now underway is designed to compare the effects of atrial natriuretic peptide with an intrarenal infusion of a calcium antagonist.

SUMMARY

The drugs currently used to prevent or lessen the severity of ARF have not been rigorously evaluated. Therefore, their effectiveness has not been conclusively demonstrated. Although these agents for the most part show promise, they can cause deleterious effects, and one should not accept blindly that they are indicated in all cases.

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