Theophylline reduces contrast medium nephropathy risk

The adenosine receptor antagonist theophylline may lower the risk of acute kidney injury (AKI) induced by radiocontrast medium, according to a meta-analysis in *Kidney International*.

A literature review identified 16 randomized controlled trials comparing adenosine antagonists with control treatments to prevent contrast medium–induced AKI. In both arms, treatment could be with or without N-acetylcysteine. Data on 1412 participants were pooled to compare contrast medium–induced AKI rates, change in serum creatinine, dialysis requirement, and in-hospital mortality.

On the basis of data from 13 trials (1412 patients), theophylline reduced the risk of contrast medium–induced AKI by about half: risk ratio 0.48. Theophylline also had a protective effect on absolute change in serum creatinine: standardized mean difference −0.31 mg/dL, based on 13 trials (1170 patients). It did not appear beneficial in patients with serum creatinine of 1.5 mg/dL or higher.

On metagression analysis, the risk of contrast medium–induced AKI was related to baseline serum creatinine level. There was no consistent effect on rates of dialysis or in-hospital death, both of which were infrequent.

Animal studies have suggested that theophylline and aminophylline have the potential to protect kidney function after the injection of contrast medium. However, clinical studies of adenosine receptor antagonist treatment have yielded conflicting results.

Existing data suggest that theophylline reduces the risk of contrast medium–induced AKI, with a modest but significant improvement in kidney function after exposure to contrast medium. The authors call for high-quality randomized trials, including patients at different levels of baseline risk and evaluation of long-term outcomes [Bai B, et al. Effect of theophylline on prevention of contrast-induced acute kidney injury: a meta-analysis of randomized controlled trials. *Am J Kidney Dis* 2012; 60:360–370].

Late episodes of acute rejection carry higher risk of graft loss

Acute rejection events become less frequent with time since transplantation, but later events may have a greater impact on graft survival, suggests a report in *Transplantation*.

The researchers analyzed U.S. Renal Data System data on 48,179 kidney transplantations from 2000 to 2007. The Organ Procurement and Transplant Network was used to gather data on acute rejection events, which were classified as antibody-treated or not. Acute rejection was analyzed for association with all-cause graft loss, by use of a time-varying Cox regression approach.

The rate of non–antibody-treated acute rejection events (per 100 graft-years at risk) decreased from 9.93 months after transplantation to 8.43 at 12 months, 5.71 at 24 months, and 4.70 at 36 months. The rate of non–antibody-treated acute rejection was more than double the rate of antibody-treated events, across risk periods and donor types. Antibody-treated events were associated with a higher risk of graft loss than were non–antibody-treated events.

For antibody-treated acute rejection, the relative risk of graft loss increased with the time between transplantation and the rejection event. By contrast, the risk from non–antibody-treated events was highest 13 to 24 months after transplantation. Regardless of when acute rejection occurred, the associated risk of graft loss was higher in the first 89 days after the event, compared with 90 days and later.

This large study helps to clarify the rates and clinical impact of acute rejection after...
kidney transplantation. Acute rejection occurring a longer time after transplantation may return to the risk of graft loss, with risk being highest less than 90 days after the event [Lenentine KL, et al. The implications of acute rejection for allograft survival in contemporary U.S. kidney transplantation. Transplantation 2012; 94:360–376].

Peritransplantation NGAL and IL-18 predict 1-year graft function

Two biomarkers of kidney injury measured shortly after transplantation are associated with allograft function after 1 year, reports a study in the *Clinical Journal of the American Society of Nephrology*. The prospective, multicenter study included 154 patients, mean age 54 years, undergoing deceased-donor kidney transplantation. The levels of neutrophil gelatinase-associated lipocalin (NGAL) and interleukin-18 (IL-18) were measured in early posttransplantation urine specimens. These biomarkers were evaluated for association with poor allograft function—defined as an estimated GFR of less than 30 mL/min/1.73 m²—at 1 year.

There was a 42 percent rate of delayed graft function. At 1 year, 16 percent of recipients met the study criteria for poor allograft function. Elevated levels of both biomarkers were significantly associated with the 1-year outcome. For patients with upper median values on the first day after transplantation, the adjusted odds ratios were 6.0 for NGAL and 5.5 for IL-18. The net reclassification index was 36 percent for urine NGAL and 45 percent for IL-18. There was no significant interaction between the biomarkers and delayed graft function. Changes in biomarker levels over consecutive days showed a moderate trend with 1-year allograft function.

New approaches are needed to predict outcomes after kidney transplantation. This study suggests that elevated levels of urine NGAL and IL-18 are both associated with poor allograft function 1 year after transplantation. The biomarkers may have "potential for identifying patients for therapies that minimize the risk of additional injury," the investigators conclude [Hall IE, et al. Association between peritransplant kidney injury biomarkers and 1-year allograft outcomes. *Clin J Am Soc Nephrol* 2012; 7:1224–1235].

Colonoscopy for screening after kidney transplantation?

Kidney transplant recipients have high rates of advanced colorectal neoplasia and cancers, which are better detected by colonoscopy than by fecal hemoglobin screening, suggests a study in the *British Medical Journal*. The cross-sectional study included 229 Australian kidney transplant recipients, mean 9.0 years since transplantation. All were at least 50 years old and, aside from kidney transplantation, at average risk of colorectal cancer. The patients underwent fecal immunochemical testing for hemoglobin followed by colonoscopy with histologic examination of biopsy specimens. The two tests were compared for detection of advanced colorectal neoplasia: adenoma at least 10 mm in diameter, villous features, high-grade dysplasia, or colorectal cancer. Advanced colorectal neoplasias were detected by colonoscopy in 13 percent of patients and by fecal hemoglobin in 12 percent. Colonoscopy detected colorectal cancer in five patients, three of whom had abnormal results on fecal hemoglobin testing. The fecal test had 31 percent sensitivity and 90.5 percent specificity for the detection of advanced colorectal neoplasia; positive and negative predictive values were 52.1 percent and 90.1 percent, respectively. One additional case of advanced neoplasm would be detected for each eight colonoscopies performed.

Important Safety Information: (cont)

- Pregnancy Exposure Prevention and Planning: FRP must be made aware of the increased risk of first trimester pregnancy loss and congenital malformations, and must be counseled regarding pregnancy prevention and planning. (See additional important Pregnancy Testing, Contraception, and Pregnancy Planning Information below.)
- Lymphoma and Other Malignancies: Patients receiving Immunosuppressive regimens involving combinations of drugs, including myfortic, as part of an Immunosuppressive regimen are at increased risk of developing lymphomas and other malignancies, particularly of the skin.
- Infections: Suppression of the immune system can also increase susceptibility to infection, fatal infections, and sepsis.
- Polymavirus Infections: Immunosuppressed patients are at increased risk for opportunistic infections, including Polymavirus-associated graft rejection in transplant recipients as well as infections in patients may have serious as well as sometimes fatal outcomes. These include cases of JC virus-associated progressive multifocal leukoencephalopathy (PML) and Polymavirus-associated nephropathy (PVAN), especially due to BK virus infections, which have been observed in patients receiving myfortic. PVAN, typically due to BK virus infection, is associated with serious outcomes, including deteriorating renal function and renal graft loss. Patient monitoring should help detect patients at risk for PVAN.
- Cases of PML have been reported in patients treated with MPA derivatives including MMF and mycophenolate sodium. PML, which is sometimes fatal, commonly presents with hemiparesis, apathy, confusion, cognitive deficiencies, and ataxia. Risk factors for PML include treatment with immunosuppressant therapies and impairment of immune function. In immunosuppressed patients, physicians should consider PML in the differential diagnosis in patients reporting neurological symptoms, and consultation with a neurologist should be considered as clinically indicated. Reduction in immunosuppressive should be considered for patients who develop evidence of PML or PVAN. Physicians should also consider the risk that reduced immunosuppression represents to the graft.
- Blood Dyscrasias Including Pure Red Cell Aplasia: Cases of pure red cell aplasia (PRCA) have been reported in patients treated with MPA in combination with other immunosuppressive agents. In some cases, PRCA was found to be reversible with dose reduction or cessation of therapy with MPA derivatives. In transplant patients, however, reduced immunosuppression may place the graft at risk. Patients receiving myfortic should be monitored for blood dyscrasias (eg, neutropenia or anemia). If blood dyscrasias occur (eg, neutropenia develops [ANC <1.3 x 103/L]), dosage of myfortic should be interrupted or the dose reduced, appropriate diagnostic tests performed, and the patient managed appropriately.
- Pregnancy Testing: To prevent unplanned exposure during pregnancy, FRP should have a serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL, immediately before starting myfortic. Another pregnancy test with the same sensitivity should be done 8 to 10 days later. Repeat pregnancy tests should be performed during routine follow-up visits. Results of all pregnancy tests should be discussed with the patient. In the event of a positive pregnancy test, females should be counseled with regard to whether the maternal benefits of mycophenolate mofetil treatment may outweigh the risks to the fetus in certain situations.
- Contraception: FRP taking myfortic must receive contraceptive counseling and use acceptable contraception during the entire myfortic therapy, and for 6 weeks after stopping myfortic, unless the patient chooses abstinence. Patients should be aware that myfortic reduces blood levels of the hormones that maintain contraception in the oral contraceptive pill, and could theoretically reduce its effectiveness. (Please see package insert for acceptable contraceptive methods for females).
- Pregnancy Planning: For patients who are considering pregnancy, consider alternative immunosuppressants with less potential for reproductive toxicity. Risks and benefits of myfortic should be discussed with the patient.
- Gastrointestinal Disorders: Gastrointestinal bleeding (requiring hospitalization) has been reported in de novo renal transplant patients (1.0%) and maintenance patients (1.3%) treated with myfortic (up to 12 months).
- Patients with Renal Impairment: Subjects with severe chronic renal impairment (GFR <25 mL/min/1.73 m²) may present higher plasma MPA and MPAG AUC relative to subjects with lesser degrees of renal impairment or normal healthy volunteers. No data are available on the safety of long-term exposure to these levels of MPAG.
- Concomitant Medications: Caution should be used with drugs that interfere with enteralhepatic recirculation because of the potential to reduce efficacy.
- Hypoxanthine-guanine phosphoribosyl-transferase (HPRT) Deficiency: myfortic should be avoided in patients with HPRT deficiency such as Lesch-Nyhan and Kelley-Seegmiller syndrome.
- Immunizations: Use of live attenuated vaccines should be avoided.
- The principal adverse reactions associated with the administration of myfortic include constipation, nausea, and urinary tract infection in de novo patients and nausea, diarrhea, and nasopharyngitis in maintenance patients.


Please see Brief Summary of Prescribing Information, including Boxed WARNINGs, on adjacent pages.