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In This Issue:

- ***N-Acetylcysteine for the Prevention of Contrast-Induced Nephropathy***
- ***Proton Pump Inhibitor Use and the Risk of *C. difficile* Infections***

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Should N-Acetylcysteine Be Used for Contrast-Induced Nephropathy?

By: Amanda McDavid, Pharm.D. Candidate

Introduction: Contrast-induced nephropathy (CIN) is a potential adverse outcome of iodinated contrast media administration. Contrast media is thought to induce nephropathy through vasoconstriction-induced renal ischemia, direct tubular cell toxicity, and generation of oxygen free radicals.^{1,2} Contrast-induced nephropathy occurs in fewer than 5% of patients with normal renal function, but has an incidence of up to 25% in patients with risk factors such as pre-existing renal impairment, diabetes mellitus, advanced age, congestive heart failure, or hypovolemia.¹⁻⁵ Contrast-induced nephropathy is characterized by an increase in serum creatinine (SCr) of at least 0.5 mg/dl or 25% over baseline within 48 hours of contrast administration.¹ Although usually nonoliguric and transient in nature, some cases of CIN result in significant renal dysfunction and may necessitate dialysis. Due to the association of CIN with prolonged hospital stays, increased costs, and morbidity and mortality, various strategies to reduce the incidence of CIN have been investigated.^{1,5,6}

Despite conflicting results from numerous clinical trials, N-acetylcysteine (NAC) is commonly utilized off-label to reduce the incidence of CIN due to its vasodilatory and antioxidant properties.^{2,7} A prior shortage of the drug had jeopardized its availability for use in indications approved by the Food and Drug Administration (FDA) such as prevention of liver toxicity in acetaminophen overdose and spotlighted the

lack of definitive evidence for the use of NAC in prevention of CIN.⁸ Two recent clinical trials have attempted to clarify the true efficacy of NAC for CIN prophylaxis.

The Acetylcysteine for Contrast-Induced Nephropathy Trial (ACT):

This prospective, randomized, double-blind, placebo-controlled study conducted at 46 sites in Brazil evaluated the efficacy of high-dose prophylactic oral NAC in the prevention of CIN from September 2008 to July 2010.⁹ It included over 2300 patients undergoing diagnostic coronary angiography (67.2%), percutaneous coronary intervention (PCI) (28.8%), or peripheral vascular angiography (2.8%) with at least one risk factor for CIN (see Table 1). Subjects received two 1200 mg doses of oral NAC (n=1153) or placebo (n=1119) the day before and the day after the procedure, and all patients received intravenous (IV) hydration. The primary endpoint was the incidence of CIN, defined as an increase of $\geq 25\%$ in SCr from baseline within 48-96 hours of the procedure. Secondary endpoints included a composite of death or need for dialysis in 48-96 hours and at 30 days, individual components of the composite outcome; frequency of elevation in SCr of 0.5 mg/dl between 48-96 hours, and rates of various adverse events such as cardiovascular deaths. Comparison of baseline characteristics showed no significant differences between groups. The average age of the

study participants was 68.0 ± 10 years. Approximately 50% of the subjects had an estimated creatinine clearance of ≤ 60 ml/min and 60% had diabetes mellitus. Ninety-eight percent of patients received hydration with sodium chloride with or without bicarbonate for a median of 6 hours before and 6 hours after the procedure. Seventy-five percent received low-osmolar contrast media; the median volume of contrast received was 100 ml. Intention-to-treat analyses showed no significant difference in the incidence of CIN between the placebo and treatment groups (12.7% versus 12.7%, respectively; $p=0.97$). Similarly, no significant differences in the rates of CIN were found within any evaluated subgroup, including patients with diabetes ($p=0.42$), those who were >70 years of age ($p=0.52$), those who received >140 ml of contrast media ($p=0.79$), or those with a baseline glomerular filtration rate of <30 ml/min ($p=0.73$). No differences were found between groups among the secondary endpoints. Based on the results of this trial, the authors concluded that high-dose oral NAC does not reduce the incidence of CIN.

Table 1. ACT Inclusion and Exclusion Criteria⁹

Inclusion Criteria	Exclusion Criteria
At least one of the following risk factors for CIN: Age >70 years Chronic renal failure (SCr >1.5 mg/dl) Diabetes mellitus Congestive heart failure Left ventricular ejection fraction <0.45 Hypotension	Dialysis ST-segment myocardial infarction Women who were: Pregnant Breastfeeding <45 years of age and not using contraceptive methods

ACT=Acetylcysteine Contrast-Induced Nephropathy Trial CIN=Contrast-Induced Nephropathy SCr=Serum Creatinine

The Leipzig Immediate Percutaneous Coronary Intervention Acute Myocardial Infarction (LIPSIA-N-ACC)

Trial: The LIPSIA-N-ACC trial was a prospective, randomized, single-blind, placebo-controlled study conducted at a single center in Germany between November 2006 and February 2008.¹⁰ It evaluated the effects of high-dose intravenous (IV) NAC on CIN and reperfusion injury in ST-segment myocardial infarction patients undergoing primary angioplasty with moderate volumes of iopromide (Ultravist[®] 3%), a low-osmolar contrast media. Inclusion and exclusion criteria are presented in Table 2. Patients were randomized to receive high-dose NAC 1200 mg IV bolus before angioplasty, followed by 1200 mg IV twice daily for 48 hours ($n=120$) or placebo ($n=125$). All patients received hydration with normal saline. Patients and investigators assessing outcomes were blinded to the treatment assignment. The two primary outcomes of the LIPSIA-N-ACC trial were: 1) the occurrence of CIN, defined as an increase in SCr of $\geq 25\%$ from baseline within 72 hours of PCI and 2) reperfusion injury, measured as the myocardial salvage index (MSI). Because oxidative stress is thought to contribute to reperfusion injury, the researchers speculated that NAC might prevent this outcome. No significant difference was found between the placebo and treatment groups in the rate of CIN (20% versus 14% respectively; $p=0.28$) or reperfusion injury (51.5% versus 43.5%, respectively; $p=0.36$). Although this trial did not achieve 80% power, the authors felt that any undetected potential benefit of NAC on CIN was likely to be small and clinically irrelevant. The authors concluded that high-dose IV NAC does not reduce nephropathy or myocardial reperfusion injury in patients undergoing primary PCI with moderate volumes of a low-osmolar contrast media.

Table 2. LIPSIA-N-ACC Inclusion and Exclusion Criteria¹⁰

Inclusion Criteria	Exclusion Criteria
Patients with acute myocardial infarction undergoing primary PCI if: Symptoms lasted <12 hours with either ST-segment elevation of ≥ 0.1 mV in ≥ 2 extremity leads or ≥ 0.2 mV in ≥ 2 pre-cordial leads	Previous fibrinolysis within <12 hours Known NAC allergy Chronic dialysis

LIPSIA-N-ACC=The Leipzig Immediate Percutaneous Coronary Intervention Acute Myocardial Infarction
 PCI=Percutaneous Coronary Intervention NAC=N-acetylcysteine mV=Millivolt

Discussion: The ACT and LIPSIA-N-ACC trials provide evidence that NAC is ineffective for prevention of CIN.^{9,10} The ACT trial showed that high-dose oral NAC did not reduce the risk of CIN in moderate- to high-risk patients. Similarly, the LIPSIA-N-ACC trial failed to show a reduction in CIN or myocardial reperfusion injury with high-dose IV NAC in patients undergoing primary PCI. Based on the results of these two trials, the American Heart Association (AHA) Guidelines for Percutaneous Coronary Intervention now specifically recommend against the use of NAC for the prevention of CIN.⁷ Additionally, the AHA recommends that providers should focus on proven preventive measures such as hydration and minimization of contrast volumes.

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Is There an Association Between Proton Pump Inhibitors and *Clostridium difficile*?

By: Natalie V. Parc, Pharm.D. Candidate

Introduction: The Food and Drug Administration (FDA) issued a safety announcement for proton pump inhibitors in February 2012:¹

“The use of stomach acid drugs known as proton pump inhibitors (PPIs) may be associated with an increased risk of *Clostridium difficile*-associated diarrhea (CDAD). A diagnosis of CDAD should be considered for patients taking PPIs who develop diarrhea that does not improve.”

On March 6, 2012, the Centers for Disease Control and Prevention (CDC) reported the incidence of, deaths associated with, and excess health care costs resulting from *C. difficile* infections (CDIs) in hospitalized patients are at historic highs.² Based on multiple cause-of-death data from 1999 to 2000, there were an estimated 3000 deaths attributed to CDIs in individuals ≥ 65 years of age. The number of estimated deaths increased to 14,000 from 2006 to 2007. Additionally, the recent national health care costs for hospital-onset CDIs have reached an annual estimate of \$897 million to \$1.3 billion. Currently, the FDA is reviewing the association between CDAD and stomach acid suppressors, which includes histamine H₂ receptor antagonists (H₂RAs) and PPIs (See Table 1 for a select list of PPIs).¹

Table 1. Select Proton Pump Inhibitors^{1,3}

Generic Name	Proprietary Name	Over-the-Counter (OTC) Name
Dexlansoprazole	Dexilant [®]	
Esomeprazole magnesium	Nexium [®]	
Esomeprazole magnesium and naproxen	Vimovo [®]	
Lansoprazole	Prevacid [®]	Prevacid [®] 24 HR
Omeprazole	Prilosec [®]	Omeprazole [®] Prilosec OTC [®] (omeprazole magnesium)
Omeprazole and sodium bicarbonate	Zegerid [®]	Zegerid OTC [®]
Pantoprazole sodium	Protonix [®]	
Rabeprazole sodium	AcipHex [®]	

The association of PPI use and CDAD is a controversial issue that stems from case reports and observational studies of patients who had chronic and/or underlying conditions, were elderly, or were concomitantly taking broad-spectrum antibiotics.¹ These conditions have been identified as risk factors for *C. difficile*-related infections; however, the association between CDAD and PPI use cannot be ruled out. Having one or more risk factors for CDAD with concomitant use of PPIs may even contribute to more serious outcomes from CDAD.

Proton pump inhibitors have been widely used and overused.⁴ They are often prescribed for inappropriate indications (e.g., peptic ulcer disease prophylaxis in non-intensive care unit patients); see Table 2 for a list of FDA-approved and appropriate off-label indications. Excessive use of PPIs is believed to be due to their perceived tolerability and safety. However, with the current FDA alert, there is increasing concern with the adverse drug reaction (ADR) profiles of these agents.¹ The incidence of ADRs with PPIs is associated with high doses and prolonged use.⁴ Minor adverse events have an incidence of 1 to 5% and include headache, diarrhea, constipation, nausea, and rash.^{3,4} The most alarming ADRs associated with PPIs include bone fractures, altered gastric function, and increased susceptibilities to infections such as CDAD.

Table 2. FDA-Approved and Appropriate Off-Label Indications for Proton Pump Inhibitors⁵

Heartburn/regurgitation*	Aspirin and NSAID-Related Ulcers and Complications
Uninvestigated GERD	Risk of Duodenal Ulcer Recurrence
Healing of NSAID-associated Gastric Ulcers	Barrett's Esophagus
Treatment of Symptomatic GERD	<i>Helicobacter pylori</i> Eradication
Maintenance of GERD Symptom Relief	Non-Variceal GI Bleeding
Maintenance of Healing of Erosive Esophagitis	Bleeding Ulcers
Hypersecretory Conditions	Prophylaxis of Upper GI Bleeding in Critically Ill
Treatment of Symptomatic NERD	Dyspepsia
Extra-Esophageal Manifestations of GERD	Nocturnal GERD
Refractory Heartburn	Esophageal Strictures
Peptic Ulcer Disease	

GERD=Gastroesophageal reflux disease NSAID=Nonsteroidal anti-inflammatory agent NERD=Non-erosive reflux disease

GI=Gastrointestinal

*Over-the-counter indication

Mechanism: The associated mechanism of action between PPI use and CDAD is based on the natural biological gradient.^{4,6,7} *Clostridium difficile* is a spore-forming, gram-positive, fastidious anaerobic bacillus agent. Signs and symptoms of CDIs are most commonly mild-to-moderate watery diarrhea, fever, abdominal pain/tenderness, nausea, loss of appetite, and colitis.^{1,2,8} The mechanism of action of PPIs is to suppress gastric basal and stimulated acid secretion through the inhibition of the H⁺/K⁺ ATP pump in parietal cells; however, gastric acid is an effective host defense and functions to sterilize gastric content before it enters the small intestine.^{3,6,7} With alkalinization of the gut, there is an associated increased risk of enteric and systemic infections. Ultimately, the *Clostridium* spore survives in the GI tract and subsequently may proliferate in the colon. Thus, in this case, the risks of PPIs may actually outweigh their therapeutic benefits.

Clinical Studies: The FDA reviewed a total of 28 observational studies described in 26 publications; the majority demonstrated a higher risk of CDIs in patients who used PPIs.¹ Two of the most recent observational studies included in the FDA's list were published in 2010 and assessed the association of PPIs with CDAD. A multi-center, retrospective cohort study analyzed the association between PPI use and the risk of recurrent CDI. This trial used data from October 2003 to September 2008, in a total of 1166 inpatients and outpatients who had positive *C. difficile* toxin assays 15 to 90 days after the initial CDI diagnosis.⁸ Influential covariates related to recurrent CDI risks and PPI exposure were included in the analysis. Hazard ratios (HRs) were also determined in the sensitivity analysis since positive toxin results may not portray clinically relevant recurrent CDIs. Inclusion criteria consisted of individuals having a positive first *C. difficile* toxin A and/or B findings, Veterans Affairs (VA) Healthcare System use of at least 1 year, and treatment with metronidazole or vancomycin started in the VA either 3 days before or after the initial CDI diagnosis. Patients were classified as either concurrently exposed to PPIs (n=527) or not exposed to PPIs (n=639), with exposure being defined as oral PPI use during a 14-day period following the first CDI diagnosis. Baseline characteristics between the groups were similar with the exception that the PPI-exposed group had a statistically significant difference in comorbid conditions (e.g., ischemic heart disease, chronic obstructive pulmonary disease, rheumatoid arthritis, peptic ulcer disease, and esophageal disease), and received more systemic corticosteroids. The results of this study can be reviewed in Table 3.

Table 3: Recurrent CDI Results⁸

Unadjusted Analysis	PPI Exposed	Non-PPI Exposed
Incidence of recurrent toxin 15 to 90 days after initial CDI diagnosis	25.2%	18.5%
<i>PPI-exposed vs. non-PPI exposed</i>	HR (95% CI)	p-value
Kaplan-Meier recurrence-free survival	1.42 (1.11-1.82)	0.006
Adjusted Analysis[*]		
Kaplan-Meier recurrence-free survival	1.42 (1.10-1.83)	0.008
Effect Modification[†]		
Risk of recurrence during treatment and follow-up [‡]	1.44 (1.09-1.89)	0.01
Sensitivity Analysis[§]		
Recurrent CDI (n=251)	1.52 (1.15-2.01)	0.003
Control for any vancomycin exposure within the first 14 days	1.42 (1.10-1.84)	0.008

CDI=*Clostridium difficile* infection PPI=Proton pump inhibitor CI=Confidence interval

*Adjusted for age, incident CDI treatment, CDI treatment, additional antibiotic exposure, length of hospital exposure, and statistically significant baseline differences

† Potential effect modification by age, non-CDI antibiotic exposure during follow-up and PPI exposure during follow-up

‡ Patients in the PPI-exposed group (82.4%) and non-PPI exposed group (6.4%) received PPIs during the 15 to 90 day follow-up period

§ Recurrent CDI cases treated with antibiotics targeted at CDI and documented in the VA pharmacy

|| Accounts for clinical severity of disease and response failure with original CDI treatment

The authors concluded that concomitant use of PPIs during the initial CDI treatment and the follow-up period demonstrated an increased risk of CDI recurrence, 42% and 44% respectively; whereas patients prescribed a PPI in either the treatment only or follow-up only timeframes were shown to have a non-statistically significant higher risk of recurrent infection.

A single-center, large pharmacoepidemiologic cohort study performed a secondary analysis on data prospectively collected as part of the center's usual care to examine the relationship between acid suppressive agents and the initial occurrence of nosocomial acquired *C. difficile* in adult patients discharged between January 2004 and January 2008.⁷ Patients were included if they were 18 years of age or older, had a hospital length of stay of 3 days or more, and had a diagnosis of *C. difficile* for the first time. Acid suppression therapy was the primary exposure of interest. Four groups designated per treatment as no acid suppression, H₂RAs, daily PPIs, and more frequent than daily PPIs were evaluated. Antibiotics were also assessed prior to a CDI diagnosis or discharge. A propensity score adjustment technique, in addition to multivariate adjustment for comorbidities, was used to account for the systematic differences in prescribing acid suppressive therapies. Patients in the 'no acid suppression' group were considered the reference group. A total of 101,796 admissions were analyzed and 665 cases of *C. difficile* infection were identified. Patients were generally older, male, and had comorbidities such as congestive heart failure, cancer, and renal failure. There was a statistically significant association between hospital length of stay and the risk of developing *C. difficile*; hospital stay less than 7 days (0.4%) compared to hospital stay of 7 days or more (1.1%), p<0.001. Results on the risk of developing nosocomial *C. difficile* infections can be reviewed in Table 4.

Table 4. Risk of Developing Nosocomial *C. difficile* Infection Results⁷

Unadjusted Analysis		
Type of Therapy	Odds Ratio, 95% CI	p-value
No acid suppression	0.3 (0.2-0.31)	NR
H ₂ RAs	0.6 (0.49-0.79)	NR
Daily PPI	0.9 (0.8-0.98)	NR
More than daily PPI	1.4 (1.15-1.71)	NR
Adjusted Analysis*		
Type of Therapy	Odds Ratio, 95% CI	p-value
H ₂ RAs	1.53 (1.12-2.10)	0.008
Daily PPI	1.74 (1.39-2.18)	<0.001
More than daily PPI	2.36 (1.79-3.11)	<0.001
Sensitivity Analysis†		
Type of Therapy	Odds Ratio, 95% CI	p-value
H ₂ RAs	1.29 (0.94-1.67)	NR
Daily PPI	1.47 (1.18-1.84)	NR
More than daily PPI	1.98 (1.51-2.59)	NR

CI=Confidence interval NR=Not reported H₂RAs=Histamine₂ receptor antagonists PPI=Proton pump inhibitor

*Adjusted analyses performed for antibiotic therapy, comorbid conditions, age, and propensity score

†Excluded psychiatric and obstetric service patients

Although exposure to antibiotics and length of hospital stay were strongly associated with CDIs, the unadjusted and adjusted analyses indicated the risk of CDI increased as the level of acid suppression increased. Once daily PPI use compared to no acid suppression demonstrated an association of greater than 70% to CDIs. The authors of this study concluded there is a clinically and statistically significant association existing between the level of pharmacologic acid suppression and the risk of nosocomial CDIs.

Recommendation: Documented ADRs associated with PPIs are mostly derived from observational studies and postmarketing data, which further supports the need for completion of randomized controlled trials to identify the cause linking PPIs to CDAD.^{1,4} In the meantime, controlling for known and speculated CDAD risk factors is crucial in reducing the incidence of CDIs.

The following recommendations from the FDA and the American Society of Health-System Pharmacists (ASHP) should be considered for implementation into clinical practice^{1,9}:

1. Consider CDAD in patients taking PPIs who develop diarrhea without improvement and experience symptoms of CDAD (watery persistent stool, abdominal pain and fever while taking PPIs).
2. Use lowest dose and shortest duration of PPI therapy appropriate to condition/diagnosis.
3. Proton pump inhibitors and H₂RAs should be used based on their appropriate indications and in accordance with the ASHP therapeutic guidelines for gastrointestinal stress ulcer prophylaxis in hospitalized patients.
4. The ASHP guidelines recommend PPI use for gastrointestinal stress ulcer prophylaxis for:
 - a. **Patients in the intensive care unit (ICU) with one of the following:**
 - Mechanically ventilated for >48 hours
 - Coagulopathy
 - Recent history of GI ulceration or hemorrhage within the past year
 - Two or more of the following risk factors:
 - Sepsis
 - ICU stay ≥1 week
 - Occult bleeding ≥6 days
 - Use of high-dose corticosteroid (>250 mg/day of hydrocortisone or equivalent)
 - b. **Special populations in the ICU:**
 - Head injury (Glasgow Coma Score ≤10)
 - Serious burns (>35% of body surface area)
 - Partial hepatectomy
 - Multiple trauma with injury (Injury Severity Score ≥16)
 - Transplantation (during perioperative period)
 - Spinal cord injury
 - Hepatic failure

Conclusion: Proton pump inhibitors have been identified as a probable risk factor for a clinically significant infection caused by *C. difficile*. By implementing the FDA and ASHP recommendations into clinical practice, the incidence of CDIs associated with PPIs may be reduced, thus potentially improving the morbidity, mortality, and health care costs related to CDIs.

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