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Preexposure Prophylaxis Initiative (iPrEx) Trial Results

Results of the Preexposure Prophylaxis Initiative (iPrEx) trial were published electronically in the *New England Journal of Medicine* on November 23rd (<http://www.nejm.org.proxy.cc.uic.edu/doi/full/10.1056/NEJMoa1011205#t=article>). This randomized, double-blind, placebo-controlled, multinational (South Africa, United States, South America, and Thailand) clinical trial evaluated the safety and efficacy of emtricitabine/tenofovir for prevention of human immunodeficiency virus (HIV) infection among men and transgender women who have sex with men. Subjects were eligible if they were at least 18 years of age, HIV-negative, and at high-risk for HIV infection. Emtricitabine/tenofovir (n=1224) or placebo (n=1217) was given by mouth once daily, and subjects had HIV testing and received condoms, risk-reduction counseling, and management of sexually transmitted diseases. Subjects were seen every 4 weeks to obtain study drug/placebo, undergo a pill count and adherence counseling, rapid HIV testing, and medical history. Anyone who reported unprotected exposure to an HIV-infected partner was referred for postexposure prophylaxis. The primary outcome measure was development of HIV seroconversion. A subgroup analysis was conducted to determine if serum drug levels correlated with protective effect.

Twenty-nine percent of subjects reported their gender identity as female, and the groups were similar at baseline with the exception of a slightly older population in the treatment group (27.5 vs. 26.8 years, $p=0.04$). Median follow-up time was 1.2 years (3324 person-years). Blinding appeared to be maintained as subjects who guessed their treatment assignment were evenly distributed between groups. Self-reported adherence (mean) was lower for active therapy at weeks 4 (89% vs. 92%, $p<0.001$) and 8 (93% vs. 94%, $p=0.006$), but did

not differ thereafter. According to dispensing records/dates, adherence decreased from 99% to 91% during the first year, which conflicted with self-reported adherence and pill count data. Subjects in both groups reported a decrease in the number of sexual partners with whom they had receptive anal intercourse and reported an increase in the use of condoms for this practice.

A total of 110 subjects experienced HIV seroconversion, but 10 had HIV subsequently detected in the sample they provided at enrollment. Of these 10 subjects, 2 of 2 in the active therapy group and 1 of 8 in the placebo group had emtricitabine-resistant infections. Of the remaining 100 subjects who developed HIV during the course of the trial, 36 were in the emtricitabine/tenofovir group compared to 64 in the placebo group (relative risk reduction 44%, 95% confidence interval [CI] 15 to 63, $p=0.005$). Among the treatment group, study drug was detected in 22 (51%) of seronegative subjects and 3 (9%) of 34 who became infected ($p<0.001$). The risk of HIV infection was reduced by a factor of 12.9 (95% CI 1.7 to 99.3, $p<0.001$) among subjects with emtricitabine/tenofovir detected by assay. In terms of safety, elevated serum creatinine (1.1 times the upper limit of normal or 1.5 times baseline) was found more frequently with active drug (2% vs. 1%, $p=0.08$), but the difference did not reach statistical significance. Nausea (22 vs. 10 events, $p=0.04$) and weight loss of at least 5% (34 vs. 19 events, $p=0.04$) were also more frequent with active therapy.

The authors concluded that emtricitabine/tenofovir provided protection against HIV infection among men and transgender women who have sex with men. Detectable levels of the drug in the blood correlated with the prophylactic effect.

Editorial Comments

In an accompanying editorial, Dr. Michael suggests some

points for consideration regarding the iPrEx study. He points out one of the primary challenges of the trial was the discrepancy between self-reported adherence and detection of study drug in the blood. The lack of adherence would likely carry over to clinical practice if this intervention were implemented since patients in clinical practice may not have the benefit of intensive adherence counseling as done in the study.

In addition the trend toward development of renal insufficiency with emtricitabine/tenofovir was concerning and could signal a safety problem if the intervention becomes widespread in clinical practice. Monitoring of renal function may be necessary, especially if adherence is superior to that found in iPrEx. Dr. Michael was also concerned about the finding of emtricitabine resistance in the patients found to have had HIV at baseline who subsequently received treatment with combination therapy (2 of 2). If the intervention becomes widespread in practice, increased emtricitabine resistance may be seen in patients with undiagnosed HIV at therapy initiation. Finally, the author raises some questions that need to be evaluated such as the role of preexposure prophylaxis in patients at lower risk for HIV acquisition and long-term safety issues of administering emtricitabine/tenofovir to healthy persons.

Centers for Disease Control and Prevention Response

According to a fact sheet released the same day as the iPrEx trial, the Centers for Disease Control and Prevention (CDC) plans to collaborate with stakeholders to fully review the data and develop public health guidelines on the safe and effective use of preexposure prophylaxis. The CDC has urged practitioners to await the guidelines prior to using preexposure prophylaxis in clinical practice. However, since emtricitabine/tenofovir is currently marketed, the agency has released some immediate cautions for patients and practitioners (available at: <http://www.cdc.gov/nchhstp/newsroom/PrEPforHIVFactSheet.html>). The key points of the cautions include:

- Trial results apply to men and transgender women who have sex with men; no data exist for heterosexuals or injection drug users.
- Preexposure prophylaxis is only for HIV negative patients; initial and regular testing during use is required.
- Preexposure prophylaxis is not the first line of defense against HIV infection; it was partially effective when used with regular testing, condoms, and other methods.
- Men who have sex with men should continue to use condoms, know their HIV status as well as that of their partner(s), get tested and treated for sexually transmitted diseases that can facilitate HIV transmission, reduce drug use and sexual risk behavior, and reduce the number of sexual partners.

- If preexposure prophylaxis is used, daily use is crucial; protection was garnered for those who took the drug regularly. Poor adherence negatively affected efficacy.

Healthcare providers are encouraged to visit the CDC's website for additional information on preexposure prophylaxis and the iPrEx trial: <http://www.cdc.gov/hiv/prep/>.

Prevention of HIV is a global priority, and it appears that preexposure prophylaxis with emtricitabine/tenofovir in men and transgender women who have sex with men reduces the rate of transmission. However, it is prudent to await further guidance from CDC on the role of this drug combination in clinical practice and to review follow-up data from iPrEx when available (data regarding subjects with concurrent hepatitis B virus infection are expected). Practitioners should continue to emphasize the role of condoms and safe sexual practices as the cornerstone of HIV prevention.

N-acetylcysteine (NAC) and contrast-induced nephropathy: results from the ACT study

Introduction

Contrast-induced nephropathy (CIN) is a condition associated with significant morbidity and prolonged hospitalization; CIN occurs more commonly among individuals with risk factors such as existing renal failure, diabetes mellitus, or advanced age (> 70 years). N-acetylcysteine (NAC) became a popular therapy for prevention of CIN over 10 years ago after publication of a prospective, randomized study by Tepel and colleagues. In that landmark study, prophylactic NAC administration, in combination with hydration, resulted in a significant reduction in the incidence of CIN as compared to hydration alone. These results had a significant impact on clinical practice with use of NAC widely implemented.

Over the decade since the Tepel publication, more than 40 individual studies and approximately 15 meta-analyses have been performed examining the efficacy of NAC in CIN. Many of the completed trials were of low quality (i.e. non-blinded, no intention-to-treat analysis performed), low statistical power (i.e. median trial size approximately 80 patients), and lacked standardized dosing for NAC and any co-interventions. In response to the poor design and inconsistent results observed with prior published studies, Berwanger and colleagues conducted the Acetylcysteine for Contrast-Induced Nephropathy Trial (ACT). The results of ACT were recently presented at the annual American Heart Association meeting.

Table 1. ACT Trial Results.

Study Endpoint	NAC	Placebo	Relative Risk
Incidence of CIN	12.7%	12.7%	1.00 (95% CI: 0.81 to 1.25); p = 0.97
Total mortality	2.0%	2.1%	0.93 (95% CI: 0.53 to 1.64); p = 0.80
Cardiovascular mortality	1.5%	1.6%	0.97 (95% CI: 0.51 to 1.85); p = 0.93
Need for dialysis	0.3%	0.3%	0.97 (95% CI: 0.20 to 4.80); p = 0.97
Serum creatinine doubling	1.1%	1.5%	0.74 (95% CI: 0.36 to 1.52); p = 0.41
Elevation in serum creatinine of ≥ 0.5 mg/dL	3.9%	3.8%	1.04 (95% CI: 0.69 to 1.57); p = 0.85

ACT Trial

ACT is the largest, randomized, placebo-controlled, multicenter study of NAC for the prevention of CIN performed to date. The study enrolled 2,308 patients from 46 separate hospitals in Brazil between September 2008 and July 2010. All enrolled patients had at least 1 of the following risk factors for CIN: age > 70, chronic renal failure, diabetes, heart failure or ejection fraction < 45%, or shock. Patients were randomized to receive either NAC 1200 mg orally twice daily for 2 doses before and 2 doses after an angiographic procedure or placebo. The primary endpoint of ACT was the incidence of CIN defined as a $\geq 25\%$ elevation of serum creatinine above baseline 48 to 96 hours after angiography. Secondary endpoints included 30-day clinical endpoints such as total mortality, cardiovascular mortality, and need for dialysis. The extent of serum creatinine elevations and adverse effects were also evaluated. All enrolled patients were included in the intention-to-treat analysis.

Results from the ACT trial are summarized in Table 1. Overall, NAC administration had no significant effect on the primary endpoint of CIN or any of the secondary endpoints as compared to placebo.

The overall incidence of adverse events was similar between the groups: 7.6% NAC vs. 7.0% placebo; $p = 0.61$. Vomiting occurred significantly more frequently among patients receiving placebo (1.2% vs. 0.3%; $p = 0.01$). Other reported adverse events included nausea, angina, fatigue, and diarrhea. Serious adverse events including stroke, pneumonia, sepsis, and acute pulmonary edema occurred more frequently in the placebo group (2.2% vs. 1.3%), but this difference was nonsignificant ($p = 0.09$).

Berwanger and colleagues also performed a sub-group

analysis of the ACT data as well as a meta-analysis of other “high-quality” NAC studies for the prevention of CIN. Results of the subgroup analysis revealed no benefit of NAC therapy in any patient population including those stratified by age, presence of diabetes, sex, serum creatinine levels, or type of contrast administered prior to angiography. Results of the meta-analysis were in line with ACT trial results (i.e. no benefit observed with NAC therapy).

Summary

The ACT trial represents the largest investigation of the efficacy of NAC for the prevention of CIN. Results of ACT revealed that NAC therapy provided no significant benefit for the prevention of CIN nor did NAC improve any of the evaluated secondary endpoints. These results may significantly impact current clinical practice in the catheter lab and cause a necessary reduction in the use of NAC therapy going forward.

AHA Guidelines for Cardiopulmonary Resuscitation: Update

Since the 1960s the American Heart Association (AHA) has authored guidelines for healthcare providers on appropriate management of cardiopulmonary arrest. The first guideline focused on use of cardiopulmonary resuscitation (CPR); today the guidelines encompass all aspects of emergency cardiovascular care including basic life support (BLS), electrical therapies such as defibrillation and cardioversion, adult and pediatric advanced cardiac life support (ACLS), acute coronary syndrome, and stroke. The 2010 update to the AHA Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care contain several important changes from previous versions, which are summarized on the following page.

Quality cardiopulmonary resuscitation

Cardiopulmonary resuscitation refers to interventions performed on patients with cardiopulmonary arrest that aim to achieve return of spontaneous circulation (ROSC). These activities typically include chest compressions and rescue breaths for patients without a pulse and spontaneous breathing, respectively. Of the 2 interventions, chest compression is associated with better outcomes. Several studies have demonstrated an increase in survival with shorter time to chest compression or improved compression technique, which has led to a change in the 2010 guidelines in the sequence of BLS events to “C-A-B” from “A-B-C”. In addition, “look, listen, and feel”, which refers to activities in checking the airway, has been removed from the BLS protocol. The new focus on achieving adequate chest compressions prior to clearing the patient’s airway and delivering rescue breaths is an effort to decrease the time to first chest compression.

Reasons cited in the guidelines for an increased focus on chest compressions include greater willingness and ability of first responders (often non-healthcare providers) to participate in BLS, tailoring rescue efforts to the most likely cause of adult arrest (cardiac rather than respiratory), and lack of evidence suggesting harm if assisted breathing is delayed. Of note, since cardiopulmonary arrest in infants usually results from respiratory causes, “A-B-C” remains the standard BLS procedure in that population unless there is a known cardiac cause.

There are also data suggesting that out-of-hospital rescue efforts involving only chest compressions may have similar efficacy as those involving both chest compressions and rescue breaths. Survival to discharge, a common measure of efficacy in cardiopulmonary arrest studies, were not statistically different in 2 retrospective studies that compared standard CPR with continuous chest compression (no breaths). Similarly, 1-month survival did not differ between groups in another retrospective study. One prospective study found no difference in the endpoint of 1-year survival with favorable neurologic outcome when standard CPR and continuous chest compression were compared, while another demonstrated significantly better 1-year survival with continuous chest compression compared to standard CPR in patients with apnea, shockable rhythm, and CPR initiated less than 4 minutes after a witnessed arrest. These data further reinforce the value of chest compressions compared to breath support in the setting of cardiopulmonary arrest.

The quality of chest compressions remains an important focus of the 2010 guidelines. Adequate compression technique requires a depth of at least 2 inches (a change from the previous recommendation of 1.5 to 2 inches), a rapid enough rate to ensure tissue perfusion, complete recoil to allow the heart to completely fill with blood between compressions (100 per minute), and minimal interruptions in compression for breaths, defibrillation, or checking for a pulse. Any deviation from this standard of care may

decrease the effectiveness of BLS efforts. The need to achieve appropriate compression depth and rate is summarized in the new phrase “push hard, push fast”. Healthcare providers with previous BLS certification may require retraining to ensure understanding of these new CPR recommendations.

Medication use in advanced cardiac life support

Several medication-related changes have been made to the 2010 ACLS guidelines. The first change involves the pulseless electrical activity (PEA)/asystole algorithm. For several decades, the AHA has recommended alternating bolus doses of epinephrine and atropine in patients with non-shockable PEA/asystole; however, data to support the use of atropine in this setting are limited. The drug is used to reverse cholinergic effects on heart rate and atrioventricular nodal conduction, but no prospective studies examining its efficacy in this setting have been conducted and retrospective studies are conflicting. An early case series of 8 asystole cases refractory to epinephrine found that all patients achieved a regular heart rhythm after atropine therapy. Subsequent studies found no benefit with atropine, or demonstrated an association with emergency medication use (including atropine) and decreased likelihood of successful resuscitation and survival after PEA or asystole. Based on the lack of efficacy data, atropine has been removed from the PEA/asystole algorithm. In contrast, improved ROSC (but not survival) has been seen with epinephrine. According to the guidelines, multiple clinical trials have demonstrated similar efficacy of vasopressin compared to epinephrine, thus justifying its continued inclusion in the PEA/asystole protocol.

Adenosine continues to be the standard of care for treatment of narrow-complex tachycardia with a regular rhythm. Previous tachycardia algorithms have also recommended adenosine for regular wide-complex tachycardia thought to be due to supraventricular tachycardia (SVT) with aberrancy; however, the 2010 ACLS guideline recommends use of adenosine for any regular wide-complex tachycardia. In this case, adenosine can be used to both treat and diagnose the underlying rhythm; SVT will slow or convert to sinus rhythm with adenosine, while ventricular tachycardia will not be affected. Of note, due to the risk of ventricular fibrillation the guidelines caution against use of adenosine for irregular or polymorphic wide-complex tachycardias.

The bradycardia algorithm has also changed in terms of medication use. Symptomatic bradycardia with evidence of instability such as hypotension, acute chest discomfort, or altered mental status should be treated with atropine. If atropine is ineffective, an infusion of dopamine, epinephrine, or isoproterenol is now suggested by the guidelines as an equally effective alternative (rather than a less effective alternative, as stated in previous guidelines) to transcutaneous pacing. These infusions should be used temporarily prior to more definite treatment, such as pace-

maker placement, and may be most useful in patients with hypotension.

Post-cardiac arrest care

A new section of the 2010 AHA guidelines focuses on care of patients during the immediate post-cardiac arrest period. Following the examples of success with other critical illnesses such as sepsis and acute decompensated heart failure, the guidelines now advocate a structured, comprehensive, multidisciplinary, bundled approach to post-arrest management. A new post-arrest algorithm has been developed to help institutions implement these changes. Initial objectives of focused care in this setting include optimization of cardiac function and vital organ perfusion, transport of patients to tertiary care hospitals and critical care units with adequate post-arrest treatment facilities, and identification and treatment of the underlying cause for the cardiac arrest to prevent future arrests. Specifically, the guidelines recommend:

- Achievement of adequate body temperature for survival and neurologic recovery;
- Identification and management of acute coronary syndromes;
- Optimization of mechanical ventilation to prevent lung injury;
- Support of organ function to minimize risk of injury;
- Objective assessment of prognosis for recovery;
- Provision of rehabilitation services to survivors.

The post-cardiac arrest algorithm recommends that providers consider inducing hypothermia in patients unable to follow commands after ROSC and pulmonary and hemodynamic support, especially those presenting with ventricular fibrillation. Multiple clinical trials, including 2 randomized trials, have demonstrated an improvement in overall survival and neurologically intact survival to hospital discharge when patients were cooled after ROSC post-ventricular fibrillation. No randomized, controlled trials have compared induced hypothermia with no hypothermia in patients with other arrhythmias, though there are some preliminary data suggesting benefit. The induced hypothermia protocol involves administration of 30 mL/kg cold intravenous fluid with concurrent surface cooling. The goal core temperature is 32 to 34°C as continuously monitored by esophageal, bladder, or pulmonary artery thermometers. After 12 to 24 hours patients should be gradually rewarmed by 0.25°C per hour. Important questions remain about induced hypothermia, including the optimal time to start, duration, method of cooling, and monitoring. In addition, further information is needed regarding the potential adverse effects such as coagulopathy, arrhythmia, and hyperglycemia.

Summary

Several important changes were made to the AHA cardiopulmonary resuscitation guidelines with the 2010 update. Key changes include a greater emphasis on high-quality chest compressions with a de-emphasis on rescue breaths during CPR, removal of atropine from the PEA/asystole algorithm, an expanded role for infusion of chronotropic agents for refractory bradycardia and adenosine for regular wide-complex tachycardia, and a new algorithm for post-cardiac arrest care including a strong recommendation regarding provision of induced hypothermia to comatose post-arrest patients. Clinicians involved in cardiopulmonary arrest rescue efforts should be aware of these changes and work to ensure their implementation on the institutional level.

P&T Formulary Committee Action

Not Added:

- Everolimus (Zortress)

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