Acetaminophen Improves Kidney Function in Severe Sepsis

Written by Emma Hitt Nichols, PhD

Administration of acetaminophen to patients with severe sepsis and detectable plasma levels of cell-free hemoglobin (CFH) improved kidney function but did not appear to reduce oxidative injury. David R. Janz, MD, Vanderbilt University, Nashville, Tennessee, USA, presented data from the Phase 2a randomized controlled trial of Acetaminophen for the Reduction of Oxidative Stress in Severe Sepsis trial [ACROSS; NCT01739361; Janz DR et al. *Am J Respir Care Med* 2014.]

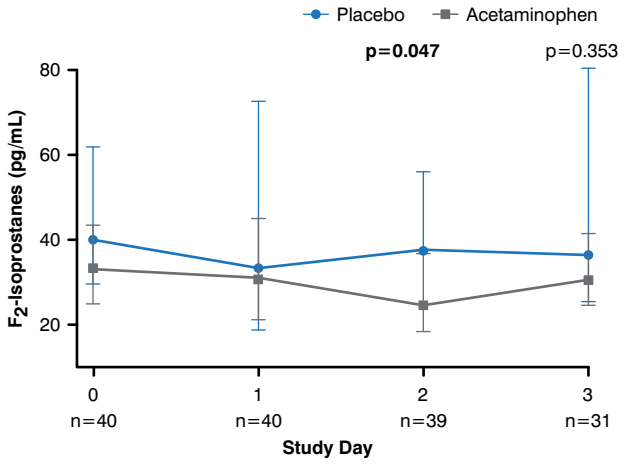
Sepsis is associated with increased plasma levels of CFH, which causes oxidative injury to the kidney [Janz DR et al. *Crit Care Med* 2013]. Previous observational studies have suggested that acetaminophen can decrease detectable CFH plasma levels, reduce oxidative damage caused by CHF, and improve outcomes in patients with severe sepsis and detectable plasma CFH [Janz DR et al. *Crit Care Med* 2013]. The hypothesis of the ACROSS trial was that oxidative injury would decrease and renal function would improve by treatment with acetaminophen in patients with severe sepsis and detectable CFH.

In the Phase 2a trial, 45 patients with severe sepsis were randomly assigned to receive enteral acetaminophen (1 g every 6 hours for 3 days) or placebo within 24 hours of admittance to the intensive care unit. Patients were ineligible if they had taken acetaminophen within the past 48 hours, had no enteral access, had acute or chronic liver disease, were pregnant, or if death was imminent. Before randomization, blood was collected at baseline and Days 1, 2, and 3 and analyzed for CFH, F_2-isoprostanes, F_2-isofurans, and acetaminophen levels. Forty patients completed the trial (acetaminophen, n=18; placebo, n=22).

The primary outcome of the ACROSS trial was the concentration of F_2-isoprostanes on Day 3, a measure of oxidative injury. Secondary outcomes included F_2-isoprostanes levels on Day 2, F_2-isofuran levels on Day 3, and serum creatinine levels on Day 3.

The results were negative for the primary end point, with no significant decrease in F_2-isoprostanes levels on Day 3 (p=0.353) for patients who received acetaminophen compared to placebo (Figure 1). F_2-isofurans tended to decrease with acetaminophen treatment compared with placebo. Creatinine levels were significantly lower in the acetaminophen arm compared with the placebo arm beginning on Day 3 (p=0.039) and continuing to discharge or death (p=0.03; Figure 2).

Figure 1. Effect of Acetaminophen on F_2-isoprostanes Levels in Patients With Severe Sepsis



Square/circle=median; Upper and lower caps=interquartile range.
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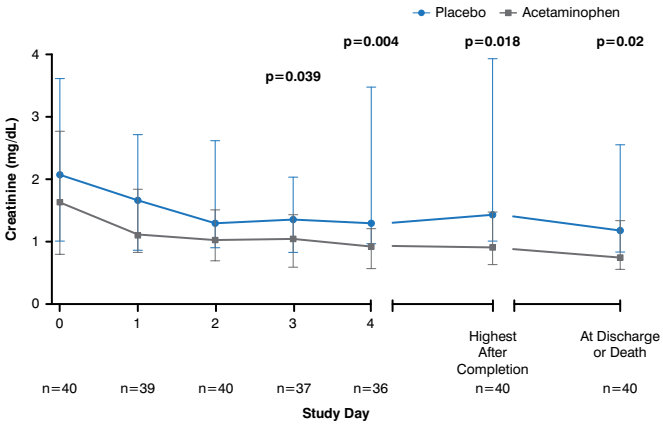
Figure 2. Effect of Acetaminophen on Kidney Function in Patients With Severe Sepsis



Square/circle=median; Upper and lower caps=interquartile range.
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Adverse events included elevation of aspartate and alanine aminotransferase above 400 units/L in 6.8% of the study population, with 9.5% occurring in the acetaminophen arm and 4.3% occurring in the placebo arm. Aspartate aminotransferase levels were greatest on Day 1 of the study, whereas alanine aminotransferase levels were highest on Day 2 of the study.

In conclusion, Dr. Janz stated that the results from the ACROSS trial suggest that treatment of patients with severe sepsis and detectable CFH levels with

acetaminophen did not result in a reduction in oxidative injury, the primary outcome; however, renal function was improved, as measured by serum creatinine. Overall, acetaminophen was well tolerated. Although further studies are needed to confirm the findings of the ACROSS trial, Dr. Janz stated that acetaminophen may improve renal outcomes of patients with severe sepsis and detectable CFH plasma levels.

Bisoprolol Improves RVEF and Heart Rate in PAH

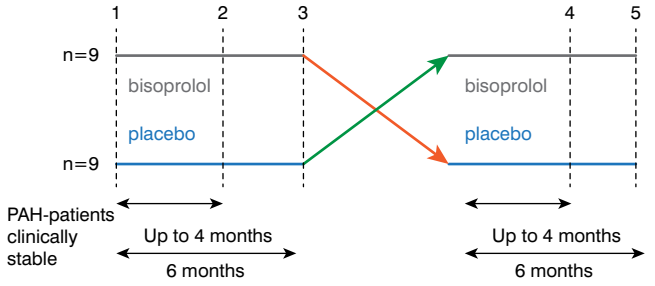
Written by Emma Hitt Nichols, PhD

Treatment of idiopathic pulmonary arterial hypertension (PAH) with the β-blocker bisoprolol resulted in decreased heart rate, increased right ventricular ejection fraction (RVEF), and improved quality of life (QoL). J.S.J.A. Van Campen, MD, VU Medical Center, Amsterdam, The Netherlands, presented data from the Beta-Blocker Therapy in Idiopathic Pulmonary Arterial Hypertension trial [NCT01246037; Van Campen JSJA et al. *Am J Respir Crit Care* 2014].

The sympathetic nervous system is excessively active in PAH; however, blockade by β-blockers was thought to be contraindicated because of the acute negative inotropic and chronotropic effects. Despite similar thinking, blockade of β-adrenergic receptors in patients with left heart failure has been shown to reduce left ventricular remodeling and mortality by about 30% [Dickstein K et al. *Eur Heart J* 2008]. In addition, data from recent preclinical animal studies suggest that low-dose β-blocker therapy may be beneficial in PAH [De Man FS et al. *Circ Heart Fail* 2012]. The purpose of this study was to determine if bisoprolol is safe and effective in patients with PAH.

In this double-blind, crossover, Phase 1 and 2 trial, 18 patients with optimally treated, stable idiopathic PAH received an escalating dose of up to 10 mg of bisoprolol or placebo for up to 6 months, then crossed over to the opposite treatment for up to an additional 6 months (Figure 1). Patients were assessed every 2 weeks by physical examination with blood pressure and heart rate measurements. Every month, patients underwent electrocardiography, 6-minute walking distance (6MWD) tests, and the Minnesota Living With Heart Failure Questionnaire assessing QoL. In addition, at baseline, crossover, and end of the study, patients were evaluated by magnetic resonance imaging (MRI), echocardiography, heart rate variability measurements, cardiopulmonary exercise testing, and positron emission tomography.

Figure 1. Trial Design of the Beta-Blocker Therapy in Idiopathic PAH Trial



PAH=pulmonary arterial hypertension.

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The primary end point of the study was RVEF, as measured by cardiac MRI. The secondary end points included assessments of sympathetic overdrive, maladaptive remodeling of the right ventricular wall, perfusion, mechanical efficiency, and exercise capacity.

Patients who received bisoprolol (mean dose, 4.4 ± 3.2 mg) demonstrated an improvement in RVEF by 3%, which was not statistically significant. However, bisoprolol treatment resulted in a significant decrease in heart rate ($p=0.0001$), with most patients (15 of 18) experiencing reductions of 10 beats/min. Significant decreases were also seen in cardiac output ($p=0.02$) and cardiac output, as measured by the 6-minute walk test ($p<0.02$). There were no significant differences in maximal oxygen consumption or QoL.

Of 18 patients, 5 experienced serious adverse effects; however, 4 events were determined to not be associated with the study drug. One patient experienced fluid retention at the beginning of bisoprolol treatment that required intravenous diuretics. Two patients did not tolerate bisoprolol, secondary to hypotension, bradycardia, or fatigue. Syncope was not reported during the study.

In conclusion, Prof. van Campen stated that data from this trial indicated that treatment of PAH with a β-blocker is safe and well tolerated. In addition, β-blocker treatment can reduce heart rate and improve RVEF and QoL, without significantly affecting exercise capacity.