ED Nurses Should Give Meds in Acute Asthma

BY MIRIAM E. TUCKER
Elsevier Global Medical News

BOSTON – Emergency department administration of oral corticosteroids by a triage nurse prior to physician assessment significantly reduced the time to clinical improvement, total time in the ED, and risk of inpatient admission in a study of 644 children who presented with moderate to severe asthma exacerbations. Medical directives allowing triage nurses to administer bronchodilator therapy are common, but nurse administration of oral corticosteroids has not previously been studied, even though earlier use of these agents in asthma patients with severe exacerbations has been shown to directly affect the risk of hospital admission. “We know that written clinical pathways improve physician ordering of oral steroids in acute asthma exacerbations, but delays to steroid administration are still long,” said Dr. Roger L. Zemek, a pediatric emergency physician at Children’s Hospital of Eastern Ontario, Ottawa.

The controlled trial used a “before-after” design, in which a 4-month phase of physician-ordered oral corticosteroids was compared with a 4-month period in which triage nurses administered them. The study was done in a tertiary children’s hospital ED, with an annual patient population of about 60,000 visits a year, of which about 2,500 are for asthma, Dr. Zemek said at the annual meeting of the Society for Academic Emergency Medicine. Eligible children were those aged 2-17 years who presented to the pediatric ED with a moderate to severe acute asthma exacerbation, with a Pediatric Respiratory Assessment Measure (PRAM) of 4 or greater. The PRAM is a validated scoring system that measures asthma severity based on the patient’s symptoms on a scale of 1-12, with 12 being most severe. It has good nurse-to-nurse and nurse-to-physician interuser reliability, he said.

See Nurses • page 4

Maintenance Rx Slowed NSCLC Progression

BY PATRICIE WENDLING
Elsevier Global Medical News

CHICAGO – Pemetrexed maintenance therapy after pemetrexed plus cisplatin induction reduced the risk of progression by 38% in patients with advanced nonsquamous non-small cell lung cancer in the phase III PARAMOUNT trial.

The study’s primary end point of investigator-assessed progression-free survival was 4.1 months for pemetrexed (Alimta) plus best supportive care and 2.8 months for placebo plus best supportive care (log rank P = .00006; unadjusted hazard ratio, 0.62).

Independent review, completed in 88% of patients, confirmed the robustness of the primary end point, revealing a progression-free survival of 1.9 months for pemetrexed vs. 2.6 months for placebo (log rank P = .0002; HR, 0.64), lead author Dr. Luis Paz-Ares said at the annual meeting of the American Society of Clinical Oncology. Overall survival data were not mature enough at the time of the analysis, with just 16 deaths.

“The magnitude of the benefit shown on progression-free survival, a 38% decrease in the risk of progression, is in favor of saying this is an effective treatment for patients with advanced nonsquamous non-small cell lung cancer,” he said.

A previous trial (Lancet 2009;374:1432-40) showed that switching patients to pemetrexed maintenance improved the time free of cancer, but until now, it was unclear whether patients initially treated with pemetrexed would benefit from maintenance. “This trial answers that,” Dr. Mark Kris, FACP, chief of thoracic oncology at Memorial Sloan Kettering Cancer Center and the Society for Academic Medicine will promote the ‘cross-fertilization of ideas’ between specialties. • 21

Secondary Infection Risk Higher in COPD

BY SUSAN LONDON
Elsevier Global Medical News

DENVER – The majority of patients with chronic obstructive pulmonary disease who acquire a rhinovirus infection develop a secondary bacterial infection shortly thereafter, suggesting that early antiviral therapy might do double duty.

In a study reported at the International Conference of the American Thoracic Society, 60% of patients with COPD who were experimentally infected with rhinovirus and who gave serial sputum samples developed a bacterial infection as well, approximately a week later. This rate was six times higher than the rates seen among smokers with normal lung function and among nonsmokers.

Temporal patterns of pathogen loads and molecular markers suggested that the virus may incite inflammation that, in turn, results in degradation of key defense peptides in the airways, leaving patients vulnerable to bacteria.

The findings raise the possibility that “dual infection is a lot

See COPD • page 11

Have a QR code app? Use your smartphone to view videos from major medical meetings.
DENVER — An intensive care unit telemedicine intervention was associated with lower hospital and ICU mortality and shorter hospital and ICU lengths of stay in a prospective, unblinded study conducted at one academic medical center over a 2-year period.

The intervention also was associated with significantly higher rates of adherence to critical care best practices and lower rates of complications. More rapid responses to alerts for physiologic instability and off-hours, off-site intensive care plan reviews were facilitated as critical care process elements that may have contributed to the lower mortality and shorter lengths of stay associated with the tele-ICU intervention.

The study was published online in *JAMA* (2011;305:E1-9).

## Major Finding
Unadjusted ICU mortality was significantly lower in the tele-ICU group, compared with the preintervention group (10.7% vs. 8.6%). Hospital mortality also was reduced with tele-ICU (13.6% vs. 11.8%). Both ICU and hospital mean length of stay were significantly shorter with tele-ICU (hospital stay, 9.8 days vs. 13.3 days; ICU stay, 4.5 vs. 6.4 days).

## Data Source
Prospective study of 6,290 adult patients admitted over 2 years to seven ICUs in an academic medical center.

## Disclosures
All study authors reported having no conflicts of interest.

## Other Studies
Unlike previous studies of the effects of tele ICU programs, this one focused on changes in the process of care rather than the ICU structure. Prior to the study start, best practices were standardized for the prevention of venous thromboses, cardiovascular complications, ventilator-associated pneumonia, and stress ulcers. For the primary analysis, a representative sample of preintervention cases was obtained by identifying consecutive hospita l discharges from an administrative database for cases managed in each of the seven ICUs (three medical, three surgical, and one mixed cardiovascular). Admission, discharge, and laboratory information was abstracted electronically.

The off-site team included an intensivist and used tele-ICU workstations. The tele-ICU team serially reviewed the care of individual patients, performed real-time audits of best practice adherence, performed work-station-assisted care plan reviews for patients admitted at night, monitored system-generated electronic alerts, audited bedside clinician responses to in-room alarms, and intervened when the responses of bedside clinicians were delayed and patients were deemed physiologically unstable. The off-site team was able to communicate with bedside clinicians or directly manage patients by recording clinician orders for tests, treatments, consultations, and management of life-support devices. Dr. Lilly said.

A total of 6,290 qualifying adult patients were identified from 6,465 electronic admission registrations to any of the seven ICUs, with 1,529 admitted during the preintervention period and 4,761 during the tele-ICU intervention period (the periods were staggered between 2005 and 2007).

Unadjusted ICU mortality was significantly lower in the tele-ICU group compared with the preintervention group (10.7% vs. 8.6%). When adjusted for acuity, locus of care, physiologic parameters, laboratory values, and time trend, the odds ratio was 0.37. Hospital mortality also was reduced with tele-ICU (13.6% vs. 11.8%). The unadjusted difference was not statistically significant, but hospital mortality was significantly lower with tele ICU after adjustment for acuity, locus of care, physiologic parameters, laboratory values, and time trend, with an odds ratio of 0.40.

Both ICU and hospital mean lengths of stay were significantly lower with tele ICU. The intervention group had a mean hospital stay of 9.8 days, compared with 13.3 days in the preintervention group. After adjustment for acuity, time trends, physiologic parameters, laboratory values, and locus of care, the hazard ratio was 1.44. For ICU stay, the mean was 4.5 days in the tele-ICU group vs. 6.4 days in the preintervention group. After adjustment for acuity and the previously listed factors, that hazard ratio was 1.26. Results for medical, surgical, and cardiovascular ICUs were similar, Dr. Lilly said.

## To Understand How Tele ICU Team Activities Affected Care Processes and to Evaluate the Degree to Which the Association of the Intervention with Changes in Mortality Could Be Attributed to These Process Changes, Another Analysis Examined Adherence to Best Practices, Incidence of ICU Complications, Intensivist Involvement for Cases Admitted During Nighttime Hours, Responses to Alarms, and ICU Type.

The tele-ICU intervention was linked with significantly better adherence to DVT prevention best practices and cardiovascular protection best practices, as well as lower rates of catheter-related bloodstream infection and ventilator-associated pneumonia. These factors also were linked with significantly lower ICU and hospital mortality. The proportion of the tele-ICU intervention with lower mortality that could be attributed to adherence to these best practices and complication measures was estimated to be 23% for hospital mortality and 30% for ICU mortality.

The study “suggests that the introduction of a tele-ICU program that collaborates with and supports bedside clinicians is one way” to provide better care and cut costs, Dr. Lilly said.

## CHEST Physician Is Online
CHEST Physician is available on the Web at www.chestnet.org/acp.chest.physician.
Thrombolyis May Reduce Survival in Acute PE

BY MIRIAM E. TUCKER
Elsevier Global Medical News

DENVER – Adding thrombolytic therapy to standard anticoagulation with heparin did not significantly improve overall survival at 3 months in patients with acute symptomatic pulmonary embolism – and reduced survival rates for some normotensive patients, according to a large international retrospective cohort study.

Thrombolytic therapy as initial treatment did produce a nonsignificant trend toward survival among patients who presented with symptomatic hypotension, according to a subgroup analysis of the study data, while significantly worsening survival among normotensive patients.

However, thrombolytic had no significant impact on survival among normotensive patients when researchers accounted for differences in troponin and the presence of right ventricular dysfunction.

“Based on these findings, we cannot recommend thrombolysis in normotensive patients without more data from randomized controlled trials. We need to better determine how to risk stratify these patients,” said Dr. David Jimenez of the Ramon y Cajal Hospital and Alcala de Henares University, Madrid.

Current guidelines from the American College of Chest Physicians recommend thrombolysis in addition to anticoagulation for patients with evidence of hemodynamic compromise (grade 1B evidence) and for “selected high-risk patients without hypotension who are judged to have a low risk of bleeding (grade 2B).” The guidelines advise physicians to base that decision on the severity of the pulmonary embolism (PE), the patient’s prognosis, and risk of bleeding (Chest 2008;133:434S-54S).

The current study was done to fill in the evidence gap for those recommendations, explained Dr. Jimenez, who presented the study results at an international meeting of the American Thoracic Society. He and his colleagues from Spain and the United States analyzed data from 15,944 patients with acute pulmonary embolism enrolled in the Spanish registry Registro Informatizado de la Enfermedad Tromboembolica. Thrombolytic therapy had been used in 2.7% (430) of the patients.

In general, those patients were younger, with fewer comorbid conditions and more signs of clinical severity. To overcome that bias, a propensity analysis was conducted to match patients for those differences.

Patients were also grouped into those with systolic blood pressure less than 100 mm Hg (hypotensive) and those with 100 mm Hg and higher (normotensive).

Comparing 94 propensity score-matched patients with symptomatic hypotension receiving thrombolysis with 94 patients who did not, there was a trend in reduction in all-cause mortality with thrombolytic therapy, with an odds ratio of 0.70 (95% confidence interval 0.36-1.46).

For two groups of 217 normotensive patients each who received or did not receive thrombolysis, there was a statistically significant increased risk of death for those patients who received thrombolysis with 94 patients who did not, there was a trend in reduction in all-cause mortality with thrombolytic therapy, with an odds ratio of 0.70 (95% confidence interval 0.36-1.46).

However, because the risk of dying from pulmonary embolism is low among normotensive, hemodynamically stable PE patients, those patients’ risk of dying from thrombolysis is therefore elevated by comparison and approaches that of hypotensive patients, Dr. Jimenez speculated. Only half of all patients with pulmonary embolism actually die of the embolism, he noted.

Indeed, there has been only one previous randomized clinical trial showing benefit from thrombolysis in patients with PE, Dr. Jimenez said, and that was in 10 patients with life-threatening PE (J. Thromb. Thrombolysis 1995;2:227-9).

“Thrombolysis is only useful for those who are at high risk for dying from PE,” Dr. Jimenez said. “I think we have to test in a randomized, controlled trial whether thrombolysis is helpful in a subgroup of normotensive patients who have high risk due to right ventricular dysfunction and elevated troponin,” Dr. Jimenez said.

Such a trial is now underway. The prospective, double-blind, placebo-controlled Pulmonary Embolism Thrombolysis Study (PEITHO) will examine the particular subgroup of normotensive patients with acute PE who have echocardiographic and laboratory evidence of right ventricular dysfunction.

The study investigators want to enroll 1,000 patients at 12 European centers, and they hope to have data by the end of 2012, said Dr. Jimenez, whose hospital is one of the study centers.

Risk of PE Higher in Patients With Traumatic Chest Injury

BY BRUCE JANCIN
Elsevier Global Medical News

BOCA RATON, FLA. – Severe chest injury constitutes a newly recognized independent risk factor for pulmonary embolism in trauma patients.

“At our trauma center, we have a new venous thromboembolic algorithm, and patients with injury now go into the high-risk category. You have to give these patients some type of chemical prophylaxis as early as you feel safe, because if you’re developing a pulmonary embolism without a deep vein thrombosis, the methods used to prevent DVT [such as a prophylactic inferior vena cava filter] are not going to prevent the pulmonary embolisms,” Dr. Mary M. Knudson said at the annual meeting of the American Surgical Association.

This lack of benefit for prophylactic IVC filters in preventing pulmonary embolism (PE) was another one of the key findings in her study, in which she examined risk factors and outcomes for PE and DVT in 888,652 patients who were treated at 326 level I or II trauma centers that were included in the American College of Surgeons’ National Trauma Data Bank (NTDB) for 2007-2009.

The incidence of DVT in this very large group of trauma patients was 1.06%, and for PE it was 0.42%. Only 20% of patients with PE also had a reported DVT, but because of how the data in the national registry are collected, it is unknown which came first.

The risk factors for PE and DVT were not the same. For example, patients with severe chest injury (defined as an Abbreviated Injury Scale score of 3 or higher) were 42% more likely to develop PE than were trauma patients with other injuries, but they were not at increased risk for DVT. In contrast, patients with severe traumatic brain injury were 34% more likely to have DVT than were those without traumatic brain injury, but they were also 13% less likely to be diagnosed with a PE. And patients with a cardiac injury dependent longer than 3 days were at a 5.3-fold increased risk for DVT, but they were at a 3.8-fold increased risk for PE.

In contrast, several other significant predictors had overlapping risks for both PE and DVT, including shock, spine injury, and neurologic injury, the lead author, Dr. Knudson, reported. She also noted that patients with acute PE dropped from 0.21% in 1994-2001 to 0.49% in the same trauma centers in 2007-2009. Meanwhile, mortality in trauma patients with PE dropped from 15% in the earlier period to 11% more recently. In 1994-2001, PE was associated with an adjusted fourfold increased risk of mortality, whereas in 2007-2009 PE conferred a 2.4-fold increase in mortality.

Dr. Knudson concluded that prophylactic IVC filters are ineffective in preventing trauma-related PE because the use of such filters doubled between her first and second studies, even as the PE incidence rate more than doubled. “I am not suggesting that prophylactic IVC filters use pulmonary embolism, but they certainly aren’t preventing them,” she said.

Severely injured patients who arrive at a trauma center in shock are already coagulopathic even before they receive transfusions. During the next 2-3 days, as they receive multiple transfusions, their protein C becomes depleted and they become hypercoagulable. At that point, patients with a chest injury (with its attendant profound inflammation) are more at risk for PE, whereas those with traumatic brain injury have stasis and may be more at risk for DVT, she explained.

Discussant Dr. David B. Hoyt, executive director of the American College of Surgeons, said that Dr. Knudson’s identification of severe chest injury as a novel contributor to PE is a major new observation that will be of importance to military surgeons. He and colleagues are assessing a trauma patient’s overall risk.

Dr. Knudson reported having no relevant conflicts.
DENVER – When you prescribe a long-acting beta-agonist for a child with asthma, you may want to consider adding an inhaled corticosteroid as well, according to a meta-analysis conducted by Food and Drug Administration investigators.

"Overall, there was an increased risk of asthma-related hospitalizations, intubation, or death to asthmatics of all ages using long-acting beta-agonists (LABAs)," said Dr. Ann W. McMahon at the meeting.

Dr. McMahon and her colleagues also found an age effect, with asthmatics aged 4-11 years at greater risk, compared with older patients. "Children are at increased risk, primarily of hospitalization, from asthma with LABA use compared to the overall population."

The elevated overall and age-related risks are no longer statistically significant, however, when patients are prescribed an inhaled corticosteroid (ICS) along with a LABA as part of a study protocol, Dr. McMahon said at the annual meeting of the Pediatric Academic Societies.

"Although further study is indicated, simultaneous use of inhaled corticosteroids and LABAs may mitigate this risk in children," said Dr. McMahon, deputy director of the division of pharmacovigilance at the FDA’s Office of Surveillance and Epidemiology.

In a previous meta-analysis, LABA use was associated with a higher overall risk for adverse outcomes, a risk difference estimate of 2.80 for an asthma composite index of asthma-related hospitalizations, intubations, and deaths. In a 2008 meta-analysis that included 60,954 patients of all ages from 110 trials, Mark Levenson, Ph.D., one of Dr. McMahon’s FDA colleagues, found the highest risk associated with LABA therapy was among those aged 4-11 years, who had a risk difference estimate of 14.83/1,000 participants.

Dr. McMahon presented a secondary analysis of the 2008 meta-analysis in which she and her associates assessed a subset of patients assigned an ICS as part of their study regimen. Using a forest plot analysis, they compared 7,862 patients also treated with a LABA versus 7,130 who did not receive a LABA.

"What we see here is no overall risk for this subset of patients and no particular age trend either," Dr. McMahon said. The overall risk difference was 0.2/1,000 patients.

"This is a smaller group of patients, so whether we can conclude this is definitive, I would say probably not," Dr. McMahon said. "But it is very intriguing that this subgroup that took assigned inhaled corticosteroids really did not have an age effect or an overall increased risk."

In contrast, when all users and nonusers of inhaled corticosteroids were combined, overall risk associated with LABA use was 6.3 additional adverse events per 1,000 patients.

Another analysis of the data looked at all patients who took some concomitant ICS therapy (those intentionally prescribed an ICS and those noted to be taking an ICS at baseline). This analysis "looks very similar, with a slight increased risk overall" of 6.1 events per 1,000 patients, Dr. McMahon said.

Age again made a difference, with a point estimate risk of 19.8 per 1,000 participants for those aged 4-11 years, a statistically significant higher risk compared with that of patients aged 12-17 years, 18-64 years, and 65 years and older.

"Children are at increased risk primarily of [asthma-related] hospitalization," Dr. McMahon said. Data on intubations and deaths were insufficient to calculate these outcomes among children, she added.

Dr. McMahon’s findings concur with those of other published studies. For example, the Salmeterol Multicenter Asthma Research Trial (SMART) and the Sterevent Nationwide Surveillance (SNS) study "both gave similar results to the extent that there was a three- to fourfold increase in risk of serious asthma outcomes such as asthma-related death and intubation" associated with LABA use (Chest 2006;129:15-26; BMJ 1993;306:1034-7).

However, these trials did not include children younger than 12 years and did not include enough adolescents for investigators to be able to analyze those data separately, she added.
Salivary Markers May Help Assess Asthma Severity

By Doug Brunk

SAN FRANCISCO—In the future, physicians may look no further than to a sample of saliva to assess asthma disease activity in children.

In a poster session at the annual meeting of the American Academy of Allergy, Asthma, and Immunology, Dr. Frederic F. Little, of the department of medicine at Boston University, presented findings from a study that explored the efficacy of salivary inflammatory biomarkers as markers of disease activity in asthmatic children.

“It’s premature to make any definitive clinical conclusions, but we have some insights that some of the traditional markers of allergic inflammation that are seen in blood, induced sputum, and nasal lavage, and correlate with disease control, can be readily detected in saliva,” Dr. Little said in an interview.

For the study, which was conducted in collaboration with Dr. Elizabeth C. Matsui of Johns Hopkins University, Baltimore, 58 children aged 5-17 years who had moderate to severe asthma underwent measurements of exhaled nitric oxide, serum IgE quantification, and aeroallergen skin testing and filled out symptoms questionnaires. The researchers collected whole masticatory saliva, which was separated by centrifugation for supernatant harvest.

Slightly more than half of the children (52%) were boys, and 88% were black. Inflammatory mediators were detected in more than 95% of participants. The researchers found that salivary levels of eosinophil-related mediators such as interleukin (IL)-5 and the chemokines CCL11/eotaxin and CCL5/RANTES were strongly and positively correlated with each other. A similar strong association was seen among non-eosinophil-related mediators such as IL-1 beta and CXCL8/IL-8.

The researchers also found that salivary levels of vascular endothelial growth factor (VEGF) were positively correlated with certain markers of clinical disease activity. Also, VEGF correlated positively with non-Th2 markers of immune activation, including CXCL8/IL-8, CCL2/MCP1, yeilding with markers of atopic burden such as exhaled nitric oxide and total serum IgE. What that disconnect means going forward “we don’t know,” Dr. Little said. “That caught us by surprise.”

In their poster, the researchers noted that “saliva profiling may offer complementary noninvasive assessment of disease activity beyond current markers of allergic inflammation.”

Inner-City Families Struggle With Asthma Tx Compliance

By Mitchell L. Zoler

It’s challenging enough to control chronic asthma in children, but youngsters who live in low-income, inner-city households face some special barriers to optimal asthma management, including their family’s difficulty paying for medication, lack of family understanding about optimal treatment, and denial by the family about treatment compliance.

The best way to deal with that at least some of these issues may be a new approach to educating families about their child’s persistent asthma, said Dr. Marina Reznik, a pediatrician at the Children’s Hospital at Montefiore Medical Center in New York. She has launched a study to test the ability of community health workers to improve family understanding of optimal asthma therapy and to see if this improves patient outcomes.

The study involves randomizing Bronx families who have a child with persistent asthma to receive either standard education materials or to get six visits from a community health worker every other week for 10 weeks. The health workers will instruct parents on optimal asthma therapy, teach them how to administer an inhaled corticosteroid to their young child, and continue to monitor the therapy for 10 weeks to make sure correct treatment continues. Dr. Reznik will compare the results between the intervention and control groups over the subsequent year.

She and her associates gained insight into the problems parents face with administering correct asthma treatment to their children from the results of a pair of studies they reported in March at the annual meeting of the Eastern Society for Pediatric Research in Philadelphia.

In one study, Dr. Reznik and associates tested parents’ perceived compliance with their child’s inhaled corticosteroid regimen, compared with their actual compliance. They recruited 40 parents of a child aged 2-9 years with persistent asthma who required twice-daily therapy with an inhaled corticosteroid, a total of four puffs per day. All children were patients of the community health care center run by Montefiore. The participating parents averaged 33 years old, two-thirds were Hispanic, and 29% had not graduated high school.

Each parent received an inhaled corticosteroid actuator with an attached dose counter that recorded the number of puffs delivered. The researchers surveyed the parents about their adherence to the two-puffs twice-daily regimen and checked the dose counter on the family’s actuator.

Sixteen of the 40 parents (40%) claimed they had been 100% compliant with the regimen, while the dose counters revealed that only two families (5%) had achieved complete compliance. Only one parent (3%) owned up in a interview to being completely nonadherent, while the dose counters showed that four parents (10%) had actually failed to administer any treatment.

The results showed that parental self-reporting is “nonreliable” for assessing compliance with an asthma regimen, Dr. Reznik said. “The results may have implications for physicians using parental self-reports in managing children with persistent asthma.”

The disparity between perceived and actual adherence may derive in part from parents’ concerns about the safety of this treatment, she suggested. “They see improved symptoms (in their children), but they are terrified of the drugs. They have misconceptions.”

The second set of results that her group presented at the meeting came from a study that focused on caregiver knowledge of inhaled corticosteroid delivery. Again, the study used parents of children aged 2-9 years old seen at the hospital’s community outpatient pediatric clinic. This time, they enrolled 66 caregivers, who averaged 32 years old, with 96% of the study group comprising mothers; 27% of the parents had not finished high school, 95% were unemployed, and 59% were Hispanic and 26% were black.

Among the 66 participants, 92% said that they had used a spacer when delivering the inhaled corticosteroid to their child, and 87% said they used the spacer for every treatment and 5% said they never used a spacer. In addition, 97% of the caregivers said that a physician or nurse had taught them how to use the metered-dose inhaler and spacer, 91% said that a physician or nurse had demonstrated the correct technique, and 49% said that at some point a physician or nurse had watched their technique “before administering the drug.”

A researcher then watched each caregiver deliver two puffs of the inhaled corticosteroid to a doll. Only one of the participants (2%) correctly performed every step of drug administration with the metered-dose inhaler and spacer. Although 97% correctly formed a tight seal with the inhaler, the most problematic steps involved waiting the appropriate interval between puffs, done by 23%, and instructing the recipient to exhale before the treatment inhalation, done by 24%. Other steps scored on the assessment involved shaking the inhaler for at least 5 seconds before administering a puff, pressing the inhaler just once for each puff, and administering the correct number of puffs.

Dr. Reznik and her associates concluded that this highlighted the need for repeated training of caregivers to ensure ongoing, proper delivery of inhaled corticosteroids.

Most physicians don’t have the time to properly teach parents on the correct delivery of inhaled corticosteroids, Dr. Reznik said. In addition, many parents favor treatment with an inhaled, short-acting beta-agonist, such as albuterol, because of the immediate symptom relief it provides. “They don’t see the role of preventive treatment, compared with acute treatment,” she said in an interview.

There is a discrepancy between what physicians say and what parents hear, and there is more to this than education. Parents face the financial challenge of paying for the medications, and they fear the side effects of inhaled corticosteroids. “Physicians don’t educate the family as much as possible, but with limited time, that may not be possible.”

The community health worker approach under development by Dr. Reznik features a user-friendly format in which the health worker goes to the family’s home, a format that she hopes will lead to improved caregiver education and reinforcement, improved drug delivery, and better outcomes.

Dr. Reznik said that she had no disclosures.
Risk Factors Identified for Patients Weaned From VAD

NEW ORLEANS – Patients with chronic cardiomyopathy can be successfully weaned from ventricular assist devices, and certain parameters can predict long-term cardiac stability after explantation, according to German investigators.

“Unloading-promoted reversal of heart failure allows for long-term transplant-free outcomes after patients are removed from VADs. However, few patients with chronic cardiomyopathy have been weaned from VADs, and the majority only recently,” said principal investigator Dr. Michael Dandel of the German Heart Institute Berlin. “The long-term outcomes of patients, therefore, and the reliability of the criteria for making weaning decisions, are not well known.”

At his clinic, 91 patients with chronic cardiomyopathy (CCM) as the underlying cause of heart failure were weaned from VADs between 1995 and 2010, including 75 weaned from right ventricular assist devices, 13 weaned from left ventricular assist devices, and 3 weaned from right ventricular assist devices. Before VAD implantation, the patients had left ventricular ejection fraction (LVEF) values of 10%-20%. These patients were evaluated as to the feasibility of weaning and to establish criteria that could predict long-term cardiac stability after VAD removal.

“With this information, we can improve future weaning decisions and post-weaning patient management,” Dr. Dandel said at the annual meeting of the American College of Cardiology. A total of 47 patients were evaluated. Of these 41 (87.2%) had idiopathic cardiomyopathy, 4 (8.5%) had histologic evidence of chronic myocarditis before VAD implantation, and 2 (4.3%) had chronic ischemic cardiomyopathy with severe left ventricular dilation.

Before VAD insertion, all patients had irreversible end-stage heart failure and required continuous positive inotropic support. No attempts were made to use VADs electively with the aim of myocardial recovery only. Dr. Dandel said.

Postweaning Results
Cardiac stability lasting at least 15 years was achieved by 2 patients, while 10 patients have been stable at least 10 years and at least 5 years, he reported.

“At 5 years, only five patients, 10.6%, had died due to heart failure recurrence or weaning-related complications. Several patients died of other causes,” he said.

Postweaning freedom from heart failure recurrence for all evaluated patients was 74% at 3 years and 66% at 5 years, but these results included nine patients at very high risk for poor outcomes. After 2002, when the investigators tightened their criteria for weaning, freedom from heart failure recurrence reached 100% at 3 years, he noted.

Pre-Explantation Variables Predictive of Outcomes
“Echo data obtained during off pump trials proved to be reliable for detection of recovery during mechanical unloading,” Dr. Dandel said. “In particular, off-pump [left ventricle] size, geometry, and ejection fraction were predictive of outcome after weaning, especially when history of heart failure was also considered.”

For cardiac stability lasting at least 5 years, pre-explantation “off pump” LVEF of 50% or more was associated with a positive predictive value of 91.7%, while LVEF of 45% or more had a positive predictive value of 79.1%.

The positive predictive value of LVEF of 45% or more was approximately 90% if additional parameters were considered: pre-explantation left ventricle size and geometry, stability of unloading-induced cardiac improvement before VAD removal, and heart failure duration before implantation.

Time to cardiac recovery seemed important, Dr. Dandel said. “Patients who had recurrences needed more time to show an improvement. They needed twice the duration of VAD support as patients who did not have a recurrence,” he said.

“Definite cutoff values for certain parameters— including tissue Doppler-derived LV wall motion velocity – allowed us to formulate weaning criteria with high predictability for postweaning stability,” he said.

Risk Factors for Heart Failure Recurrence
Dr. Dandel and his colleagues also identified several risk factors that predicted heart failure recurrence during the first 3 years after VAD removal. These factors, and their associated probability for recurrence, were:

- Preweaning off-pump LVEF less than 45% plus history of heart failure longer than 5 years (100%).
- Preweaning LVEF less than 45% (88.9%).
- Preweaning off-pump LVEF less than 90% plus left ventricular internal diastolic diameter greater than 55 mm (90%).
- Pre-explantation LVEF less than 50% and preexisting alteration of greater than 10% best value (87.5%).
- LVEF less than 50% plus relative wall thickness decrease of less than 10% during final off-pump trial (83.3%).

Of these, Dr. Dandel emphasized the importance of the final off-pump trial values.

‘WITH THIS INFORMATION, WE CAN IMPROVE FUTURE WEANING DECISIONS AND POSTWEANING PATIENT MANAGEMENT.’

“An off-pump ejection fraction less than 43% in patients with a history of heart failure for more than 5 years is an absolute contraindication for VAD removal,” he noted. “All such patients in our study had a recurrence of heart failure,” he said.

Early instability of ejection fraction and unstable geometry confer a high probability of recurrence. “A wall thickness increase by more than 10% means the reverse in modeling is not stable enough,” he added.

“The notion that we can actually wean patients from VADs is still a fairly new concept, and the European experience is larger than that of the United States. This is still a field that is wide open for determining patient selection and predictors of outcome after VAD removal,” session moderator Dr. Gregory A. Ewald, medical director of heart transplantation at Barnes-Jewish Hospital, St. Louis, commented in an interview.

“Clearly, the echocardiographic appearance of the heart on and off support is a good predictor,” Dr. Ewald said, but he noted that non-echocardiographic factors such as exercise tolerance were not studied.

He also noted that the field has moved to continuous-flow pumps rather than pulsatile pumps, which constituted much of the German experience. It remains to be determined if the same parameters are completely applicable to the newer-generation devices.

Dr. Dandel and Dr. Ewald both reported having no relevant conflicts of interest.
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SAN DIEGO – Ventricular assist de-

cices appear to be a “reasonable strategy”

for supporting certain patients who have

failing cardiac grafts and are waiting for

a new heart, concludes a retrospective re-

view of more than 1,500 patients who

had a second transplant.

In the group who had retransplant-

ation at least 1 year after their first trans-

plantation, median survival was about 7

years. There was no difference between

patients bridged with a ventricular assist

device (VAD) and those who did not

have any type of mechanical circulatory

support (MCS), according to results re-

ported at the annual meeting of the In-

ternational Society for Heart and Lung

Transplantation.

But survival was poor for those who

were bridged after any interval with ex-

tacorporeal membrane oxygenation

(ECMO) and former patients who did not

receive MCS as a bridge to transplantation.

Regardless of MCS, patients retrans-

planted for primary graft failure or hy-

peracute rejection do not do well,” Dr.

Morales commented. Specifically, in pa-

tients with these indications for retrans-

plantation, the 1-year mortality rate was

83%, with essentially no difference ac-

cording to whether they received bridging

or the type received.

VAD to bridge patients with primar

y transplantation does not

support.

Although MCS is widely accepted for

bridging patients to initial heart trans-

plantation, its use for bridging to re-

transplantation has not been well

studied. The investigators therefore took

a closer look at this issue, analyzing data

from the United Network for Organ

Sharing database for 1,535 patients who

underwent cardiac retransplantation dur-

ing 1982-2009.

Results showed that just 8% of the pa-

tients were bridged to retrans-

plantation, with a VAD in

about two-thirds of cases and

ECMO in the other third. The

mean age was 41 years in the

former and 35 years in the

latter, with children (younger

than age 18) comprising 15%

and 35%, respectively.

The patients bridged to re-

transplantation were signifi-

cantly more likely than were

their nonbridged counterparts

to have primary graft failure or

hyperacute rejection (54% vs.

11%) and significantly less likely to have

chronic rejection (16% vs. 63%).

And the bridged patients by and large

underwent retransplantation early, with

64% in the VAD group and 76% in the

ECMO group retransplanted within 3

months of their primary transplantation,

compared with just 12% of their non-

bridged peers.

“Regardless of MCS, patients retrans-

planted for primary graft failure or hy-

peracute rejection do not do well,” Dr.

Morales commented. Specifically, in pa-

tients with these indications for retrans-

plantation, the 1-year mortality rate was

83%, with essentially no difference ac-

cording to whether they received bridging

or the type received.

Major Finding: Among patients retrans-

planted last year after an initial trans-

plantation, median survival was 7 years

and did not differ between those bridged

with a VAD and those who did not receive

any mechanical circulatory support.

Data Source: A retrospective review of

1,535 patients who underwent cardiac


Disclosures: Dr. Morales disclosed hav-

ing relationships with Berlin Heart, Synca-

rdia Systems, and CircuLite as an investiga-

tor and/or consultant.

In the entire study population, medi-
an overall survival after retransplantation

was 61 years in nonbridged patients,
significantly longer than the 1.5 years in

VAD-bridged patients and the 30 days in

ECMO-bridged patients.

But when analyses were restricted to

patients who underwent retransplant-

ation at least 1 year after primary trans-

plantation, median survival was similar

in nonbridged and VAD-bridged patients,

at 7.0 and 6.9 years. Compared with

those groups, however, survival was sig-

ificantly shorter — just 6 months — in the

ECMO group.

“Patients bridged to retransplant with

ECMO have poor outcomes regardless of

timing or indication,” Dr. Morales con-

cluded of the findings. “And all patients

retransplanted for hyperacute rejection

or primary graft failure do poorly, re-

gardless of MCS,” he said.

“However, patients who are bridged

with a VAD to retransplant that is done

a year post primary transplant do have

similar outcomes as compared to re-

transplant patients without MCS,” he

commented.

As for study limitations, “it is very im-

portant to note that we do not know the

number of patients placed on MCS as a

bridge to transplant who died while on

support,” he pointed out.
Biomarker Testing Key to MetMAb in Lung Cancer

**By Patrice Wendling**

Elsenior Global Medical News

CHICAGO—Final efficacy results from the phase II, OAM4458g trial confirm that the success of MetMAb in previously treated lung cancer lies in accurately testing for c-Met.

Some patients gained a striking survival advantage when given the investigational monoclonal antibody as second-line therapy for non-small-cell lung cancer (NSCLC). However, the study group as a whole did not benefit, and others actually did worse with the antibody. This difference appears to be expression of the c-Met receptor.

MetMAb targets hepatocyte growth factor and its receptor, c-Met. Expression of c-Met is associated with a worse prognosis in many cancers, including NSCLC. Met activation by hepatocyte growth factor is thought to decrease sensitivity to erlotinib (Tarceva), hence the interest in combining MetMAb with erlotinib. In this trial, patients received either a combination of the two drugs or erlotinib with a placebo.

In NSCLC patients whose tumors were classified as Met-positive, the addition of MetMAb to erlotinib nearly doubled the median time that they were free of disease from 1.5 months to 2.9 months (HR, 1.09; P = .04) and tripled median overall survival from 3.8 months to 12.6 months (HR, 0.37; log rank P = .002). This was said at the annual meeting of the American Society of Clinical Oncology. When MetMAb plus erlotinib was given to patients with Met-negative tumors, however, median progression-free survival was significantly lower at 1.4 months, compared with 2.7 months in the control arm given erlotinib plus placebo (HR, 1.82; P = .05).

Median overall survival was also shorter with the combination in the Met-negative group—8.1 months vs. 15.3 months with erlotinib and placebo—although the difference did not reach statistical significance (HR, 1.78; P = .158), Dr. Spigel said. Dr. Spigel, director of lung cancer research at the Sarah Cannon Research Institute in Nashville, Tenn., concluded that the combination of MetMAb and erlotinib in Met-positive patients was really needed to improve survival and that particularly small subpopulations benefit.

"Outcomes in the diagnostic substudies and inten
to-treat populations. In the latter, the combination of MetMAb and erlotinib failed to significantly improve median time to progression over erlotinib (2.2 months vs. 2.6 months; HR, 1.09; P = .04) and tripled median overall survival from 8.9 months to 7.4 months (HR, 0.80; P = .34), he said.

The researchers performed additional analyses in key subpopulations, suggesting that the benefit from MetMAb is not related to epidermal growth factor receptor (EGFR) mutation or fluorescence in situ hybridization (FISH) status.

Although the patient numbers were small, an overall survival advantage was seen with MetMAb for patients with high Met expression (at least 5 copies) by FISH (HR, 0.60; P = .35), and was maintained in FISH-negative/Met diagnostic-positive patients (HR, 0.37; P = .01). Dr. Spigel said. Patients who were Met diagnostic positive and did not have an EGFR mutation also gained a survival advantage (HR, 0.42; P = .01).

"Outcomes in the diagnostic substudies and inten
to-treat populations highlight the importance of developing tools to identify patients who might best benefit from this treatment," he said, adding that immunohistochemistry appears to be more sensitive than FISH in determining benefit from combination MetMAb/erlotinib.

The study confirmed that Met expression by immunohistochemistry is associated with worse outcomes. An analysis of the 68 patients treated with erlotinib plus placebo confirmed that Met expression revealed that progression-free survival was worse among Met diagnostic-positive vs. Met diagnostic-negative patients (1.5 vs. 2.7 months; HR, 1.71; P = .06), as was overall survival (3.8 vs. 15.3 months; HR, 2.61; P = .004).

In response to audience questions, Dr. Spigel said it is unknown whether metastatic sites have different Met expression than primary tumor sites or why outcomes are worse in low Met tumors.

No new safety concerns emerged in the trial, although patients treated with Met diagnostic-positive had more peripheral edema that was largely low grade, reversible, and manageable, he said.

A phase III study testing MetMAb plus erlotinib for Met diagnostic-positive patients is expected to start enrolling this year, he said.

**Continued Therapy Beneficial**

Memorial Sloan-Kettering Cancer Center in New York, told reporters in a press briefing at the meeting, "I think it’s very important in that it's an example of how we can achieve an incremental ben
efit with the optimal use of drugs that are already available.”

Pemetrexed (Eli Lilly) is approved in combination with cisplatin as first-line therapy for advanced nonsquamous non-small-cell lung cancer (NSCLC) and in the second line as maintenance therapy in patients initially treated with chemotherapy.

Standard treatment for nonsquamous NSCLC is continuous pemetrexed until disease progression, but on the basis of these results, clinicians will likely give pemetrexed with pemetrexed, Dr. Kris said in an interview.

"The guidelines don’t say that because they didn’t have any data, but this will be the data that I’m pretty confident will change the guidelines," said Dr. Kris, who also is the William and Joy Ruane Chair in Thoracic Oncology at Sloan-Kettering.

During the formal presentation of the data, invited discussant Dr. Martin Edelman, director of solid tumor oncology at the University of Maryland Greenebaum Cancer Center in Balti
tmore, described the use of maintenance therapy as a contentious issue. He noted that many questions remain regarding maintenance trials, including the value of progression-free survival as an end point, how and when control patients are crossed over to active treatment, and whether the RECIST criteria should be used to determine progression.

Dr. Edelman described progression-free survival as an arbitrary end point sub
tected to testing interval and considerable bias. To the credit of the PARAMOUNT investigators, he pointed out that there was use of independent review for this end point, but he said it still does not an
er the question of overall survival.

"If one is supposed to change practice based on progression-free survival, we really need to know if particularly small differences are really beneficial," Dr. Edelman said. "That is where quality of life analysis can help us.”

The PARAMOUNT investigators assessed health-related quality of life using the EuroQol-5D at baseline, day 1 of each cycle of induction or maintenance therapy, and at the 30-day postdiscon
tinuation visit. Compliance at all times during the phase III trial was very high, but no statistical differences in the EQ-5D index score or VAS score (0–100 scale) between treatment arms, said Dr. Paz-Ares of the Hospital Universitario Virgen del Rocio, Seville, Spain.

A total of 939 patients were enrolled in the trial. They received pemetrexed 500 mg/m² on day 1 of a 21-day cycle plus cisplatin 75 mg/m² induction, followed by maintenance MetMAb 15 mg/kg IV every 4 weeks with cisplatin until disease progression or progression-free survival doubled from 2.7 months to 5.4 months (HR, 0.37; P = .01), Dr. Paz-Ares said. Patients who were Met diagnostic positive and did not have an EGFR mutation also gained a survival advantage (HR, 0.42; P = .01).

"Outcomes in the diagnostic substudies and inten
to-treat populations highlight the importance of developing tools to identify patients who might best benefit from this treatment,” he said, adding that immunohistochemistry seems to be more sensitive than FISH in determining benefit from combination MetMAb/erlotinib.

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**By Dr. W. Michael Alberts, FCCP**

**Comments: The ACCP Evidence-Based Clinical Practice Guidelines on the Diagnosis and Management of Lung Cancer**

Dr. Paz-Ares disclosed no relevant relationships. Several coauthors reported relationships with industry including stock ownership, honoraria, and consultancy with Lilly, which markets pemetrexed. ■

Dr. W. Michael Alberts, FCCP, comments: The ACCP Evidence-Based Clinical Practice Guidelines on the Diagnosis and Management of Lung Cancer recommend that the duration of first-line therapy in patients with stage IV disease should be brief, consisting of three to four cycles. The study reviewed here and a number of other similarly positive recent articles will no doubt prompt changes in the recommendations in the next edition. Maintenance chemotherapy and so-called “early second-line” chemotherapy appear to provide significant benefit in some patients.
Rituximab Safe in RA Patients With Lung Disease

BY ELIZABETH MECHCATIE
Elsevier Global Medical News

To date, no new significant safety signals associated with rituximab therapy in patients with severe rheumatoid arthritis and lung disease have been identified in an ongoing observational study, Dr. Shouvik Dass said at the annual European Congress of Rheumatology.

He and his associates reviewed the records of 67 patients with RA and concomitant lung disease who were treated with rituximab between 2004 and 2010 at their center, which he said has one of the largest single cohorts of RA patients treated with rituximab.

The patients’ mean age was 60 years, and most (56) were female. The most common pulmonary diagnosis was interstitial lung disease, in 48 patients; 14 had COPD, and 5 had bronchectasis; 2 also had a previous pulmonary empyema. All patients received two infusions of 1,000 mg rituximab with methylprednisolone per course, which was repeated when RA became active again, at intervals of no less than 6 months.

Half of the patients received at least two treatment cycles. Over a median of about 2 years of follow-up (range, 8 months to 6.5 years) after treatment with rituximab, 2 of the 48 patients with ILD and 1 of the 14 patients with COPD died. The patient with COPD died of an infective COPD exacerbation 12 months after the third cycle of rituximab. One of the patients with ILD died of pneumonia and possible acute progression of ILD. Dr. Dass said, noting that clinical and CT changes attributable to either condition were observed 4 weeks after the patient had been treated with the first cycle of rituximab.

Suicide was the cause of death in another patient with ILD, 3 months after treatment with the first course of rituximab.

Another three patients had a single episode of serious respiratory tract infection that required hospital admission or treatment with intravenous antibiotics.

Based on these cases, no definite new significant safety signals were observed “beyond that which might be expected in this group of patients.”

DR. DASS

No significant safety signals were observed “beyond that which might be expected in this group of patients.”

It was observed in an additional 22 patients 12 to 17 years of age who were treated with DULERA in another clinical trial. The safety and efficacy of DULERA have not been established in children less than 12 years of age.

Controlled clinical studies have shown that inhaled corticosteroids may cause a reduction in growth velocity in pediatric patients. In these studies, the mean reduction in growth velocity was approximately 1 cm per year (range 0.3 to 1.1 cm per year) and appears to depend upon dose and duration of exposure.

This effect was observed in the absence of laboratory evidence of hypothalamic-pituitary-adrenal (HPA) axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The long-term effects of this reduction in growth velocity associated with orally inhaled corticosteroids, including the impact on final adult height, are unknown. The potential for “catch up” growth following discontinuation of treatment with orally inhaled corticosteroids has not been adequately studied.

The growth of children and adolescents receiving orally inhaled corticosteroids, including DULERA, should be monitored routinely (e.g., via stadiometry). A child or adolescent on any corticosteroid appears to have growth suppression, the possibility that he/she is particularly sensitive to this effect should be considered. The potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the risks associated with alternative therapies. To minimize the systemic effects of orally inhaled corticosteroids, including DULERA, each patient should be treated to the lowest possible effective dose (see Dosage and Administration [2.2]).

6.5 Geriatric Use

A total of 77 patients 65 years of age and older (of which 11 were 75 years and older) have been treated with DULERA in 3 clinical trials up to 52 weeks in duration. Similar efficacy and safety results were observed in an additional 28 patients 65 years of age and older who were treated with DULERA in another clinical trial. No overall differences in safety or effectiveness were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

As with other products containing beta-adrenergic agents, special caution should be observed when using DULERA in geriatric patients who have concomitant cardiovascular disease that could be adversely affected by beta, agonists. Based on available data for DULERA or its active components, no adjustment of dosage of DULERA in geriatric patients is warranted.

6.6 Hepatic Impairment

Concentrations of mometasone furoate appear to increase with severity of hepatic impairment (see Clinical Pharmacology [12.3]).

10 OVERDOSAGE

10.1 Signs and Symptoms

DULERA, DULERA contains both mometasone furoate and formoterol fumarate; therefore, the risks associated with overdosage for the individual components described below apply to DULERA.

Mometasone Furoate: Chronic overdosage may result in signs/symptoms of hypercorticism (see Warnings and Precautions [5.3]). Single oral doses up to 3200 mg of mometasone furoate have been studied in human volunteers with no adverse reactions reported.

Formoterol Fumarate: The expected signs and symptoms with overdosage of formoterol are those of excessive beta-adrenergic stimulation and/or overactivation or exaggeration of any of the following signs and symptoms: angina, hypertension or hypotension, tachycardia, with rates up to 200 beats/min., arrhythmias, nervousness, headache, tremor, seizures, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, hypokalemia, hyperglycemia, and insomnia. Metabolic acidosis may also occur. Cardiac arrest and even death may be associated with an overdose of formoterol.

The minimum acute inhaled induction dose of formoterol fumarate in rats is 115 mg/kg (approximately 63,000 times the MRHD on a mcg/m L basis). The median lethal oral doses in Chinese hamsters, rats, and mice provide even higher multiples of the MRHD.

10.2 Treatment

DULERA: Treatment of overdosage consists of discontinuation of DULERA together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if diazepam is beneficial for overdosage of DULERA. Cardiac monitoring is recommended in cases of overdosage.

Manufactured by 3M Health Care Ltd., Dunwoody, United Kingdom. Manufactured for Schering Corporation, a subsidiary of MERCK & CO., INC.

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327041077-JBS
DENVER — Exacerbations of COPD show distinctly different temporal patterns of onset and resolution, which may have implications for treatment and prognosis, researchers reported.

In a prospective cohort study in patients with COPD who kept daily diaries for at least 2 years, 56% of exacerbations started suddenly, the rest began gradually.

The sudden-onset type were 18% shorter in duration than were the gradual-onset type, reported presenting author Gavin C. Donaldson, Ph.D., a senior lecturer and respiratory medicine specialist at University College London.

The nature of onset of an exacerbation “is of particular interest because it is the prodrome that is reported to the physician when the patient comes into the clinic and dictates the course of therapy,” he noted at an international conference of the American Thoracic Society. Hence, a better understanding of these events could help physicians to time therapy more appropriately.

Study results additionally showed that patients frequently had episodes of symptom worsening that resolved without ever turning into exacerbations. Participants recorded peak flow readings and various symptoms — including major (dyspnea, sputum purulence, and sputum volume) and minor (nasal discharge/congestion, wheeze, sore throat, and cough) symptoms — on a daily basis.

The investigators used the diary data to identify episodes of worsening symptoms and to identify exacerbations (defined as an increase in at least two symptoms, one of them major, on 2 consecutive days).

Results were based on 212 patients with an average age of 68 years. In all, 64% were men; 33% were current smokers. Their mean forced expiratory volume in 1 second (FEV1) was 45% of predicted. All patients had at least 2 years of follow-up.

The patients experienced 4,439 episodes of worsening symptoms, slightly more than half of which resolved spontaneously and the rest of which resulted in a defined COPD exacerbation. The median number of exacerbations was 2.33 per patient per year.

Analyses revealed two distinct patterns of exacerbation onset. With the sudden-onset pattern (seen in 56%), the median time between initial worsening of symptoms and exacerbation was 0 days. With the gradual-onset pattern (seen in 44%), the time to exacerbation was 4 days.

In addition, the time between the start of an exacerbation and recovery to baseline health status was a significant 18% shorter for sudden-onset vs. gradual-onset exacerbations (11 days vs. 13 days; P less than .001).

Treatment did not seem to affect these onset or recovery patterns, Dr. Donaldson noted.

Multiple logistic regression analyses showed that certain factors predicted the nature of onset and recovery, Dr. Donaldson said. Exacerbations were more likely to have a sudden onset in patients who were current smokers (odds ratio, 1.28), had cold symptoms (OR, 1.27), or had purulent sputum (OR, 1.47). There was less likelihood of a sudden onset in patients with a higher body mass index (OR, 0.98) or cardiovascular disease (OR, 0.78), or if the exacerbations occurred during the spring (OR, 0.71).

Exacerbations were more likely to have a long recovery time (defined as taking more than 12 days) if they had a gradual onset (OR, 1.39), and also if patients were male (OR, 1.27) or had cold symptoms (OR, 1.30), and if they occurred in the winter (OR, 1.56). There was less likelihood of a long recovery time in patients with purulent sputum (OR, 0.91).

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COPD Exacerbations Half as Common in Summer

BY SUSAN LONDON

DENVER—Exacerbations and deaths among patients with COPD follow a pronounced pattern of seasonal variation, according to an analysis of data from a randomized, controlled trial presented at an international conference of the American Thoracic Society.

The rate of exacerbations requiring treatment was about twice as high during the winter as during the summer, according to the analysis of data from the Prevention of Exacerbations With Tiotropium (POET) in COPD trial, which enrolled 7,376 patients with moderate to very severe COPD.

The rate of death from any cause followed a similar pattern, with about twice the rate of all-cause deaths occurring in the winter. In all, 142 of the patients died from any cause during the trial, said Dr. Thomas Glaab, head of respiratory medicine at Boehringer Ingelheim.

The randomized, double-blind trial enrolled patients from 25 countries and assigned them to treatment with tiotropium or salmeterol. Main results have been previously reported (N. Engl. J. Med. 2011;364:1093-1103).

The participating patients had a mean age of 63 years, and 48% were current smokers. Most had stage II (49%) or stage III disease (43%), according to GOLD criteria. On average, their FEV1 was 49% of that predicted.

During the 1-year trial, the patients had a total of 4,411 exacerbations that were moderate (defined as requiring treatment with systemic corticosteroids and/or antibiotics) or severe (requiring hospitalization).

Results showed that such exacerbations were twice as common during the winter versus summer months. Specifically, there were nearly 50% more monthly exacerbations between December and February, compared with about 25% more monthly exacerbations between June and August.

On an individual basis, the mean rate was 0.073-0.081 exacerbations per patient per month during the winter months, compared with 0.033-0.037 during the summer months, regardless of treatment group.

The pattern was stronger for exacerbations treated with antibiotics—likely reflecting the role of respiratory infection—than for exacerbations treated with steroids, Dr. Glaab commented.

The 2009 H1N1 influenza pandemic occurred during the middle of the study, he noted. “We expected a slight to moderate increase in exacerbations during this time,” he said. But surprisingly, the rate was half as high during a period after the first documented case of H1N1 flu (April 2009 to March 2010) as during a period before (April 2008 to March 2009).

The investigators did not have data on the patients’ immunization status. “One thing we have learned from POET and H1N1 is [that] it’s very important to have the vaccination status for influenza at baseline,” he commented. “We should have [these] data because we have problems explaining the difference in exacerbations between H1N1 versus H1N1 without any vaccination status.”

“Impressive of the efficacy results of large COPD trials such as POET . . . we can learn much from studies like this,” Dr. Glaab added. “And perhaps this may have an impact on how we plan and design studies on exacerbations moving forward and more efficiently in the future.”

Dr. Glaab is an employee of Boehringer Ingelheim. The trial was funded by Boehringer Ingelheim and Pfizer.

Dr. Marcos Restrepo, FCCP, comments: This is a very clever study with an important observation that may impact the future of the diagnosis, management, and prevention of acute exacerbations of COPD. The study authors showed that a significant number of rhinovirus-infected COPD patients developed secondary bacterial infection before or at the time when bacterial load peaked. In contrast, levels remained the same or rose slightly in those who did not develop bacterial infection. Furthermore, lower levels of the peptides were correlated with higher bacterial loads. “This would suggest that bacterial infection is a consequence of low SLPI and elafin levels in the airways,” Dr. Mallia said.

Finally, sputum levels of neutrophil elastase (an enzyme that could degrade the protective peptides) rose in rhinovirus-infected COPD patients who developed bacterial infection but remained essentially at baseline levels in their counterparts who did not.

“We hypothesize that possibly you have a sequence of events—viral infection, high neutrophil elastase levels, and degradation of SLPI and elafin—and that may progress to secondary bacterial infection,” he said.

The study gives rise to several potential, related avenues of research. “Certainly, one of the things we are interested in is, are there markers that can identify those people who are going to go on to develop bacterial infections?” he said. And some evidence suggests that in addition to having antibacterial activity, macrolide antibiotics also have antiviral activity, which the investigators plan to test using their model.

Dr. Mallia reported previously having received research grants from Pfizer and GlaxoSmithKline, and currently receiving a travel grant from Boehringer Ingelheim. The study was funded in part by Pfizer and GlaxoSmithKline.

Bacterial Follows Viral Infection

more common than has been reported in previous studies,” said lead investigator, Dr. Patrick Mallia, a U.K. National Institute for Health Research clinical lecturer at the Imperial College London.

In terms of therapeutics, this may suggest that antiviral drugs may not only be effective against virus-induced exacerbations, but also potentially prevent or reduce secondary bacterial infection, he commented.

At his institution, COPD patients with an exacerbation are not routinely tested for viruses. But that may change, given the advent of rapid PCR (polymerase chain reaction) assays for detecting viruses and their potential expansion of the indications for antiviral agents. Interest in the role of viruses and of dual viral-bacterial infection in COPD exacerbations has intensified recently, according to Dr. Mallia. As both types of infections are common in this population, one might expect that dual infection is common as well; yet, on average, studies have found dual infection in only 13% of exacerbations.

“There are a number of reasons why these studies may have underestimated the rate of dual infection, “he said, such as their cross-sectional or retrospective nature, and one-time testing for pathogens.

Studies using a single sampling point during exacerbation will probably underestimate the true prevalence of co-infection, and also tell us what the sequence of infection is,” he explained.

To get around these issues, the study investigators used their newly developed model of experimental rhinovirus-induced COPD exacerbation. “These patients catch a cold, get lower respiratory symptoms, and get an exacerbation with increased airflow obstruction and airway inflammation,” he said.

The study included 30 patients with GOLD stage II COPD who were using only short-acting bronchodilators, 28 smokers with normal lung function, and 18 nonsmokers. They were experimentally inoculated with rhinovirus, the virus most commonly detected in COPD exacerbations. Induced sputum was collected before inoculation and at 5, 9, 12, 15, 21, and 42 days afterward. A sample was taken from the small intestine under anesthesia one day before inoculation to assess bacterial activity, which the investigators measured as sputum levels of antivirally active interferon (SLPI) and elafin.

Levels of both peptides fell in rhinovirus-infected COPD patients who developed bacterial infection before or at the time when bacterial load peaked. In contrast, levels remained the same or rose slightly in those who did not develop bacterial infection. Furthermore, lower levels of the peptides were correlated with higher bacterial loads. “This would suggest that bacterial infection is a consequence of low SLPI and elafin levels in the airways,” Dr. Mallia said.

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Dr. Darcy Marciniuk, FCCP, comments: These results objectively confirm our clinical suspicion that acute exacerbations of COPD requiring therapy, as well as death from AECOPD, are twice as common in the winter compared to the summer. Antibiotic use demonstrated a similar pattern, suggesting a more frequent possible infective etiology. The results highlight the importance of instituting measures known to reduce the likelihood of exacerbations in this population, including optimal pharmacologic therapies, pulmonary rehabilitation, and vaccination.
**Important safety information**

Because of the risks of liver injury and birth defects, Tracleer may be prescribed and dispensed only through the Tracleer Access Program (T.A.P.), a restricted distribution program, by calling 1-866-228-3546. Only prescribers and pharmacies registered with T.A.P. may prescribe and distribute Tracleer. Tracleer may be dispensed only to patients who are enrolled in and meet all conditions of T.A.P.

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Elevations of liver aminotransferases (ALT, AST) and liver failure have been reported with Tracleer. In a setting of close monitoring, rare cases of liver failure and unexplained hepatic cirrhosis were observed after prolonged treatment. In general, avoid using Tracleer in patients with elevated aminotransferases (>3 × ULN). Measure liver aminotransferases prior to initiation of treatment and then monthly. Discontinue Tracleer if aminotransferase elevations are accompanied by signs or symptoms of liver dysfunction or injury or increases in bilirubin ≥2 × ULN.

**Teratogenicity**

Based on animal data, Tracleer is likely to cause major birth defects if used during pregnancy. Exclude pregnancy before and during treatment. To prevent pregnancy, females of childbearing potential must use 2 reliable forms of contraception during treatment and for 1 month after stopping Tracleer unless the patient has a tubal sterilization or Copper T 380A IUD or LNG-20 IUS inserted, in which case no other contraception is needed. Monthly pregnancy tests should be obtained.

**Contraindications**

Tracleer is contraindicated with cyclosporine A, glyburide, in females who are or may become pregnant, or in patients who are hypersensitive to bosentan or any component of Tracleer.

**Warnings and precautions**

In clinical trials, Tracleer caused ALT/AST elevations (>3 × ULN) in 11% of patients accompanied by elevated bilirubin in a few cases. The combination of hepatocellular injury (increases in aminotransferases of >3 × ULN) and increases in total bilirubin (≥3 × ULN) is a marker for potential serious liver injury. Liver aminotransferase levels must be measured prior to initiation of treatment and then monthly. Avoid using Tracleer in patients with moderate or severe liver impairment or elevated ALT/AST >3 × ULN.

If clinically significant fluid retention develops, with or without associated weight gain, the cause, such as Tracleer or underlying heart failure, must be determined. Patients may require treatment or Tracleer therapy may need to be discontinued.

Preclinical data and an open-label safety study (N=25) showed a decline in sperm count of ≥50% in 25% of Tracleer-treated patients after 3 or 6 months. After 6 months, sperm count remained in normal range, with no changes in sperm morphology or motility, or hormone levels. Endothelin receptor antagonists such as Tracleer may adversely affect spermatogenesis.

Treatment with Tracleer can cause a dose-related decrease in hemoglobin (Hgb) and hematocrit. Hgb should be checked after 1 and 3 months, and then every 3 months. Upon marked decrease in Hgb, determine the cause and need for specific treatment.

If signs of pulmonary edema occur, the possibility of associated pulmonary veno-occlusive disease should be considered. Tracleer should be discontinued.

**Adverse events**

In Tracleer pivotal trials, the most common adverse events occurring more often in Tracleer-treated patients than in patients taking placebo (≥2%) were respiratory tract infection, edema, hypotension, sinusitis, arthralgia, liver function test abnormal, palpitations, and anemia.
Indication
Tracleer is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability and to decrease clinical worsening. Studies establishing effectiveness included predominantly patients with NYHA Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%), and PAH associated with congenital systemic-to-pulmonary shunts (18%). Patients with WHO class II symptoms showed reduction in the rate of clinical deterioration and a trend for improvement in walk distance. Physicians should consider whether these benefits are sufficient to offset the risk of liver injury in WHO class II patients, which may preclude future use as their disease progresses.

Please see accompanying brief summary of prescribing information, including BOXED WARNING about liver injury and pregnancy, on following pages.

*Patients ineligible for the Tracleer Patient Coupon Program include any patients whose prescriptions are paid for by the government, Medicare, Medicaid, VA/DOD (Tricare), or Indian Health Service, patients in Massachusetts and Puerto Rico, or where prohibited by law.
WARNING: RISKS OF LIVER INJURY and TERATOGENICITY

Because of the risk of liver injury and birth defects, Tracleer is available only through a special restricted distribution program called the Tracleer Access Program (TAP), by calling 1-866-220-2546. Only prescribers and pharmacies registered with TAP may purchase and distribute Tracleer. In addition, Tracleer may be dispensed only to patients who are enrolled in and meet all conditions of TAP [see Warnings and Precautions].

Liver Injury

In clinical trials, Tracleer caused at least a 3-fold higher limit of normal of total AL and ALT in about 11% of patients, accompanied by elevated bilirubin in a small number of cases. Because these changes are a marker for potential hepatic injury, alanine and aspartate aminotransferase (ALT and AST) levels must be measured prior to initiation of treatment and then (see Dosage and Administration, Warnings and Precautions). In the post-marketing period, in the setting of close monitoring, new cases of abnormal liver function have been reported in less than 0.1% of patients treated for 12 months therapy with Tracleer in patients with no multiple co-morbidities or drug therapies. There have also been reports of liver failure. The contribution of Tracleer in these cases cannot be excluded.

In at least one case, the initial presentation (after >20 months of treatment) included pronounced elevations in aminotransferases with bilirubin elevations, all of which resolved completely despite the continuation of Tracleer. This case reinforces the importance of strict adherence to the monthly/monitoring schedule for the duration of treatment with bosentan. If during bosentan therapy, there is a loss of aminotransferases accompanied by symptoms of liver dysfunction (see Dosage and Administration).

Elevations in aminotransferases require close observation (see Dosage and Administration). Tracleer should generally be avoided in patients with chronic liver disease, and bosentan should be stopped if ALT/AST levels are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigues) or increases in bilirubin ≥ 2 x ULN with treatment Tracleer should be stopped. There is no experience with the re-introduction of Tracleer in these circumstances.

Teratogenicity

Tracleer is likely to cause major birth defects if used by pregnant females based on animal data [see Contraindications]. Therefore, pregnancy must be avoided before the start of treatment with Tracleer. Throughout treatment and for one month after stopping Tracleer, females of childbearing potential must use two reliable methods of contraception or be sterilized unless the patient has a tubal sterilization or Copper T 380A IUD or Cu 2000 IUD inserted, in which case no other contraceptive is needed. Hormonal contraceptives, including oral, injectable, transdermal, and implantable contraceptives should not be used as the sole means of contraception because these may not be effective in patients receiving Tracleer [see Drug Interactions]. Monthly pregnancy tests should be obtained.

INDICATIONS AND USAGE

Pulmonary Arterial Hypertension

Tracleer is indicated for the treatment of pulmonary arterial hypertension (PAH) WHO Group I to improve exercise ability and to decrease clinical worsening. Studies establishing effectiveness included predominantly patients with NYHA Functional Class II to IV symptoms, PAH associated with connective tissue diseases (11-15%), and PAH associated with congenital systemic-to-pulmonary shunts (16%).

Contraindications

Patients with WHO Class II symptoms showed reduction in the rate of clinical deterioration and a trend for improvement in 6-minute walk distance. Physicians should consider whether these benefits are sufficient to offset the risk for liver injury in WHO Class III patients, which may exceed the risk for their disease processes.

DOSE AND ADMINISTRATION

Recombinant Epoetin

Tracleer should be initiated at a dose of 0.25 mg twice daily for 4 weeks and then increased to the maintenance dose of 120 mg twice daily. Doses above 120 mg twice daily do not appear to confer additional benefit sufficient to offset the increased risk of liver injury.

Tablets should be administered morning and evening with or without food.

Required Monitoring

Liver aminotransferase levels must be measured prior to initiation and then monthly. If elevated aminotransferase levels are seen, changes in monitoring and treatment must be initiated.

Dosage Adjustments for Developing Aminotransferase Elevations

The table below summarizes the dosage adjustment and monitoring recommendations for patients who develop aminotransferase elevations ≥ 2 ULN during therapy with Tracleer. If liver aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigues) or increases in bilirubin ≥ 2 x ULN with treatment Tracleer should be stopped. There is no experience with the re-introduction of Tracleer in these circumstances.

Table 1: Dose Adjustment and Monitoring in Patients Developing Aminotransferase Elevations ≥ 2 x ULN

<table>
<thead>
<tr>
<th>ALT/AST Level</th>
<th>Treatment and monitoring recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 2 x ULN</td>
<td>Continue Tracleer. No other action needed</td>
</tr>
<tr>
<td>2 x ULN to &lt; 5 x ULN</td>
<td>Confirm by another aminotransferase test; if confirmed, stop treatment and monitor aminotransferase levels at least every 2 weeks. If the aminotransferase levels return to pre-treatment values, consider re-introduction of the treatment (see below).</td>
</tr>
<tr>
<td>≥ 5 x ULN</td>
<td>Treatment should be stopped and re-introduction of Tracleer should not be considered. There is no experience with re-introduction of Tracleer in these circumstances.</td>
</tr>
</tbody>
</table>

If Tracleer is re-introduced it should be at the starting dose, aminotransferase levels should be checked 3 days thereafter according to the recommendations above. Use in Females of Childbearing Potential

Initial treatment in females of child-bearing potential only after a negative pregnancy test and only in females who are using two reliable methods of contraception. Females who have had a total sterilization or Copper 7380A IUD or Cu 2000 IUD inserted, in which case no other contraceptive is needed. Hormonal contraceptives, including oral, injectable, transdermal, and implantable contraceptives should not be used as the sole means of contraception because these may not be effective in patients receiving Tracleer [see Drug Interactions]. Monthly pregnancy tests should be obtained. If the drug is used during pregnancy or if a patient becomes pregnant while on the drug, the patient should be apprised of the potential hazards to the fetus [see Use in Specific Populations].

Use with Cyclosporine A

Co-administration of cyclosporine A and bosentan resulted in markedly increased plasma concentrations of bosentan. Therefore, concomitant use of Tracleer and cyclosporine A is contraindicated [see Drug Interactions].

Use with Glyceride

An increased risk of other enzyme elevations was observed in patients receiving glyceride concomitantly with bosentan. Therefore co-administration of glyceride and Tracleer is contraindicated [see Drug Interactions].

Hyposensitivity

Tracleer is contraindicated in patients who are hypersensitive to bosentan or any component of the product. Observed reactions include rash and angioedema [see Adverse Reactions].

Drug Interactions

Potential Liver Injury

Elevations in ALT ≥ 2 x ULN were observed in 11% of bosentan-treated patients (N = 990) compared to 1% of patients on TAP (N = 840). Three-fold increases in ALT/AST were observed in 2% of bosentan patients on 250 mg twice daily and 14% of bosentan patients on 200 mg twice daily. Eight-fold increases were seen in 2% of PAH patients on 250 mg twice daily and 7% of PAH patients on 200 mg twice daily. Elevations in ALT/AST ≥ 2 x ULN in placebo-CHEST_14.qxp  6/7/2011  11:06 AM  Page 1

During the course of treatment the hepatic aminotransferase concentration remained within normal limits in 88% of bosentan-treated patients compared to 36% of placebo patients. The explanation for the change in hepatic injury is not known, but it does not appear to be hemorrhagic

Pulmonary Venous-Occlusion Disease

Should signs of pulmonary edema occur when Tracleer is administered, the possibility of associated pulmonary veno-occlusive disease should be considered and Tracleer should be discontinued.

Prescribing and Distribution Program for Tracleer

Tracleer is available only through a special restricted distribution program called the Tracleer Access Program (TAP). Only prescribers and pharmacies registered with TAP may prescribe and distribute Tracleer. If Tracleer may be dispensed only to patients who are enrolled in and meet all conditions of TAP information about Tracleer may be obtained by calling 1-866-220-2546. To enroll in TAP, prescribers must complete the TAP Tracleer Enrollment and Renewal form (see TAP Enrolment and Renewal form for full prescribing physicians) and return it to Tracleer. Required information includes:

• Read and understand the communication and educational materials for prescribers regarding the risks of Tracleer.
• Review and discuss the Tracleer Medication Guide and the risks of bosentan (including the risks of anticoagulation and hepatotoxicity) with every patient prior to prescribing Tracleer.
• Review preventive liver function tests (ALT/AST/bilirubin) and, for females of childbearing potential, confirm that the patient is not pregnant.
• Agree to order and monitor monthly liver function tests and, for females of childbearing potential, pregnancy tests.
• Educate and counsel females of childbearing potential to use reliable contraception, as defined on the Tracleer Enrollment and Renewal form, during treatment with Tracleer for one month after treatment discontinuation.
• Counsel patients who fail to comply with the program requirements.
• Notify Astex Pharmaceuticals US Inc. of any adverse events, including liver injury, and report any pregnancy during Tracleer treatment.

Dosage and Administration

Tracleer is available as 62.5 mg and 125 mg film-coated, unscored tablets for oral administration. 62.5 mg tablets. film-coated, round, brown, orange-white, tablets, embossed with identification marking “62.5” 125 mg tablets. film-coated, orange-white, tablets, embossed with identification marking “125”.

CONTRAINDICATIONS

Use of Tracleer is contraindicated in females who are or may become pregnant. While there are no adequate and well controlled studies in pregnant females, animal studies show that Tracleer is likely to cause major birth defects when administered during pregnancy (see Pregnancy). Therefore, the use of Tracleer is to be avoided in females of child-bearing potential while taking bosentan, including malformations of the head, mouth, face, and large blood vessels. Therefore, pregnancy must be avoided before the start of treatment with Tracleer. Throughout treatment and for one month after stopping Tracleer, females of childbearing potential must use two reliable methods of contraception unless the patient has a total sterilization or Copper 7380A IUD or Cu 2000 IUD inserted, in which case no other contraception is needed.
Adverse Event | Bosentan No=256 | Placebo No=122
--- | --- | ---
Respiratory Tract Infection | 46 | 22 | 34 | 20 | 17
Headache | 31 | 15 | 6 | 15 | 10
Edema | 21 | 11 | 14 | 10 | 6
Connective Tissue Disease | 13 | 5 | 6 | 4 | 4
Flushing | 10 | 4 | 2 | 3 | 2
Hypersensitivity | 10 | 4 | 2 | 3 | 2
Sinusitis | 9 | 4 | 2 | 3 | 2
Arthralgia | 9 | 4 | 2 | 3 | 2
Photochemistry Function Test Abnormal | 9 | 4 | 2 | 3 | 2
Fatigue | 8 | 4 | 2 | 3 | 2
Anemia | 8 | 4 | 2 | 3 | 2

*Note: only 450 with seizure from start of treatment to 1 calendar day after end of treatment are included. All reported events (at least 3%) are included except those too general to be informative, and those not reasonably associated with the use of the drug because they were associated with the condition being treated or were very rare in the treated population.

Combined data from Study 2B1, BREATHE 1 and EARLY

Postmarketing Experience

There have been several spontaneous and marketing reports of angioedema associated with the use of bosentan. The onset of the reported cases occurred within a range of 8 hours to 21 days after starting therapy. Some patients were treated with an antihistamine and their angioedema resolved without discontinuing Tracleer.

The following additional adverse reactions have been reported during the post approval use of Tracleer: Because these adverse reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to Tracleer exposure:

• Unexplained hepatic crisis [see Baxnowledged]
• Liver Failure (see Contraindications)
• Hypersensitivity (see Contraindications)
• Thrombocytopenia
• Neutropenia and leucopenia

DRUG INTERACTIONS

Cytochrome P450 Summary

Bosentan is metabolized by CYP3A and CYP3A. Inhibition of these enzymes may increase the plasma concentration of bosentan (see Contraindications). CYP3A substrates include midazolam, ranitidine (oral), lovastatin and simvastatin. Inhibition of CYP3A by bosentan over 12 weeks resulted in a 6-fold change in the AUC of midazolam and a 3-fold change in the AUC of ranitidine. The inhibition of CYP3A by bosentan was not dose related. Moreover, in a study in which bosentan at 125 mg twice daily was co-administered with midazolam, there was no prolongation of the midazolam half-life or change in the clearance of midazolam. However, during the co-administration of bosentan and ranitidine, the AUC and the half-life of ranitidine were increased 2-fold and 1.5-fold, respectively. The inhibition of CYP3A by bosentan may result in an increased plasma concentration of drugs metabolized by these enzymes.

Hemorrhage

Hemorrhagic complications, including oral, intracerebral, transfemoral, and implantable defects, may not be reliable when Tracleer is co-administered. Females should practice additional methods of contraception with bosentan. Females who have a tubal ligation or a Copper T 380A IUD or LNG 20 IUS can use these contraceptive methods. The physician should discuss with the patient possible drug interactions with contraceptives currently used. Females who are or may become pregnant must use effective contraception. Females of childbearing potential using Tracleer must use two reliable forms of contraception unless she has a hysterectomy or has a Copper T 380A IUD or LNG 20 IUS. In these cases, no additional contraception is needed. Contraception should be continued until one month after completing Tracleer therapy. Females of childbearing potential using Tracleer should seek contraception counseling from a gynecologist or other expert as needed.

Drug interaction studies show that Tracleer reduces serum levels of the estrogen and progestin in oral contraceptives. Based on these findings, hormonal contraceptives (including oral, intracutaneous, transdermal, and implantable contraceptives) may be less effective for preventing pregnancy in patients taking Tracleer and should not be used as a single contraceptive method. Women taking Tracleer should be instructed to use condoms and back-up contraception. The combination of a contraceptive method with Tracleer is not recommended.

Co-administration of bosentan decreases the plasma concentrations of drugs metabolized by CYP3A enzymes. In these cases, no additional contraception is needed. Tracleer should be used with caution in patients with impaired liver function.

Pediatric use

Safety and efficacy in pediatric patients have not been established.

Geriatric use

Clinical studies of Tracleer did not include sufficient numbers of subjects aged 65 or older to determine whether they respond differently from younger subjects.

Experience to date with bosentan did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently to bosentan than younger patients. In general, caution should be exercised in dose selection for elderly patients given the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant diseases or other drug therapy in this age group.

Hepatic Impairment

Because there is no in vitro and in vivo evidence that the main route of excretion of bosentan is liver, liver impairment could be caused by mechanisms other than reduced hepatic elimination (e.g., renal or non-renal). In normal volunteers, co-administration of Tracleer did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger patients. When bosentan was co-administered with a CYP2C9 inhibitor plus a strong or moderate CYP3A inhibitor, the trough concentrations of bosentan on Days 4 and 10 approximately 48-fold compared to placebo. Co-administration of such combinations of CYP3A inhibitors plus a strong or moderate CYP3A inhibitor with Tracleer is not recommended.

Concomitant administration of bosentan and ritonavir did not result in an increase in the plasma concentrations of bosentan, even though ritonavir is a potent inhibitor for CYP3A4. Consequently, Tracleer is not expected to increase the plasma concentrations of drugs metabolized by CYP3A enzymes.

Hormonal contraceptives, including oral, intracerebral, transfemoral, and implantable defects, may not be reliable when Tracleer is co-administered. Females should practice additional methods of contraception with bosentan. Females who have a tubal ligation or a Copper T 380A IUD or LNG 20 IUS can use these contraceptive methods. The physician should discuss with the patient possible drug interactions with contraceptives currently used. Females who are or may become pregnant must use effective contraception. Females of childbearing potential using Tracleer must use two reliable forms of contraception unless she has a hysterectomy or has a Copper T 380A IUD or LNG 20 IUS. In these cases, no additional contraception is needed. Contraception should be continued until one month after completing Tracleer therapy. Females of childbearing potential using Tracleer should seek contraception counseling from a gynecologist or other expert as needed.

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PRESIDENT'S REPORT
ACCP Activities Abound

Do you want to know what is new at the ACCP? We have just completed an extremely productive meeting of the Board of Regents of the ACCP and Board of Trustees of The CHEST Foundation. So much has happened that I thought it would be timely to provide an update on major areas of progress and accomplishments at the College.

1. Global Initiatives. One of the most exciting developments at the ACCP is the recruitment of Dr. Mark Rosen, FCCP, as Director, Global Education and Strategic Development. In this position, which begins July 1, 2011, Dr. Rosen will direct the College’s efforts in international education and staff the newly approved Global Education and Development Committee that will replace the International Strategic Committee and oversee the ACCP international strategic plan. The newly constituted committee will work with ACCP leadership to develop international programs, evaluate proposals for international projects, and assist in the session development of Global Day at the annual CHEST meeting.

2. Membership Review. After an inquiry from an interested medical student, I formed a Membership Task Force, chaired by Dr. Henri Coli, FCCP, to review our membership categories and make recommendations for simplification and inclusion. Although the task force has not completed its analysis, one recommendation passed by the Board of Regents at the June meeting was to develop a category for student membership in the ACCP. Details and implementation plans will be provided soon. The task force is also looking at all membership categories, ACCP requirements, and all dues structures. Recommendations will be designed with input from member surveys and leadership interviews.

3. Strategic Plan. Important advancements were incorporated into the ACCP Strategic Plan for 2011-2012. Based on last year’s plan, and with input from a Board strategic planning session earlier in the year, a revised Strategic Plan has been developed. This plan reflects our updated Vision statement that incorporates diversity and equity and lists six metric-driven goals that integrate all aspects of the ACCP. Kudos to Nancy MacRae—Senior Vice President for Governance and Operations, and Stacy Seiden—Special Projects Manager, for masterfully organizing this revision that was passed unanimously by the Board of Regents.

4. Finances. Our financial report, provided by Dr. Ed Diamond, FCCP, continues to reflect a positive bottom line as we expand our education efforts into new markets, grow our membership, and recruit new programs. This year, our investment income has been comparable to market increases, and revenues have exceeded expenses by more than $1 million (>$2 million if you include investment income). It is reassuring to know that in these fiscally uncertain times, the College is in an excellent financial position.

5. NetWork Organization. Last year, an ACCP task force was implemented to review and recommend enhancements to our NetWork structure, with the goal of improving efficiency and broadening participation of ACCP members. A brilliantly integrated NetWork structure was proposed in March, with a staged implementation plan. Providing momentum, three initial recommendations were approved by the Board of Regents at the June meeting. First, a motion was passed to revise the Council of NetWorks into a more nimble group of 23 members, down from the 51 current members. In addition, a new representative NetWork Executive Committee (11 members) was established to conduct the majority of business of the Council of NetWorks, including approval of NetWork projects. These changes are designed to prepare for the eventual launch of eCommunities and integration of NetWork activities throughout the College. The final action taken was the transition of the Affiliate NetWork to a Training and Transitions Committee to more effectively support the needs of subspecialty trainees and their advancement to regular membership in the College.

6. Diversity and Equity. The Board took action on a recommendation of the ACCP Presidential Task Force on Diversity established last fall. Chaired by Drs. C. Sola Olopade, MPH, FCCP and Dr. Marilyn Foreman, MS, FCCP, the task force presented a comprehensive forward-thinking report for incorporating diversity and equity within the College and its projects. The Board of Regents approved the recommendation that a Diversity Committee be established to implement the task force recommendations—stay tuned for more on this landmark development.

7. OneBreath®. You do not need to hold your breath any longer! The OneBreath campaign of The CHEST Foundation is about to move into high gear. The College is in the midst of hiring a dynamic leader for the OneBreath campaign to coordinate efforts for The Foundation and across the College.

8. Leadership Development. An integrated program for leadership development in the College is being spearheaded by Dr. Suha AlJafari, FCCP, President-Elect of the College. This plan will assist those interested in moving through leadership tracks in the College, both domestically and internationally, and will serve to support and educate those already involved in leadership positions. As NetWorks restructure to involve more members, and as our international efforts grow, this program will become increasingly more important. As part of the leadership development plans, the Board is undergoing periodic self-assessment to help identify opportunities for leadership education. The first of these assessments was conducted this spring— I hope you are as excited about all these activities as I am!

ACCP Delegation Visits China

By Dr. David D. Guterman, FCCP; and Dr. Darcy Marciniuk, FCCP

An ACCP delegation, led by President Dr. David Guterman, embarked on a professional learning exchange with colleagues from China on April 8, 2011, visiting Beijing, Shanghai, and Hangzhou. Joining Dr. Guterman was ACCP President—Designate Dr. Darcy Marciniuk, and ACCP members, Drs. Robert Baughman, FCCP; Kevin Brown, FCCP; Teofillo Lee-Chiong, FCCP; Bruce Davidson, FCCP; Renli Qiao, FCCP; Curtis Sessler, FCCP; and Momen Wahid, FCCP. Marisa McCarren accompanied the team in her role as ACCP Global Education and Development Manager.

Our ACCP team, the largest ever to visit China, met with International Regent Dr. Chunxue Bai, FCCP, as well as ACCP Governors Dr. BoQiang Cai, FCCP, and Dr. Guangfa Wang, FCCP. We also met with Dr. Chen Wang, FCCP, President of the Chinese Thoracic Society, and Dr. Yang Ke, Vice-President of Peking University. We were most honored to meet with Dr. Qian Liu, Deputy Minister of Health in China, for what was a very productive gathering, addressing a number of important issues affecting respiratory health.

Our fellow ACCP delegation members shared the podium with distinguished Chinese lecturers at a number of outstanding and well-attended conferences, including the ACCP and Peking Union Medical College conference in Beijing, the ACCP and Shanghai Respiratory Society conference in Shanghai, and the Chinese Medical Association Respiratory Branch and Chinese Journal of Respiratory Diseases and Tuberculosis conference held in Hangzhou. We were also privileged to accept an official invitation to visit Peking University. In addition, we had the opportunity to meet with Mark Danderson, Vice-President of the China Medical Tribune (CMT), the broadest medical news publisher in China. The CMT publishes a monthly abstract selection from the journal CHEST, translated into Chinese. We were also honored to speak at Anzhem Hospital for a conference under the leadership of Dr. Shuang Liu and the Department of Pulmonary Diseases and Respiratory Critical Care Medicine; and, before

Continued on following page
TEFLARO™ (ceftaroline fosamil) injection for intravenous (IV) use
Rx Only
Brief Summary of Full Prescribing Information
Initial U.S. Approval: 2011
INDICATIONS AND USAGE: Teflaro™ (ceftaroline fosamil) is indicated for the treatment of patients 18 years of age and older who are suspected to be infected with susceptible isolates of the designated microorganisms. Acute Bacterial Skin and Skin Structure Infections - Teflaro is indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of the following Gram-positive and Gram-negative microorganisms: Staphylococcus aureus (including methicillin-susceptible and -resistant isolates), Staphylococcus pyogenes, Streptococcus agalactiae, Escherichia coli, Klebsiella pneumoniae, and Pseudomonas aeruginosa. Community Acquired Bacterial Pneumonia - Teflaro is indicated for the treatment of community acquired pneumonia caused by susceptible isolates of the following Gram-positive and Gram-negative microorganisms: Streptococcus pneumoniae (including penicillin-susceptible isolates only), Haemophilus influenzae, Klebsiella pneumoniae, Staphylococcus aureus, Escherichia coli, and Pseudomonas aeruginosa. Upper Respiratory Tract Infections - The efficacy and effectiveness of Teflaro and other antibacterial drugs should be tested to identify the characteristic pathogens and to determine their susceptibility to Teflaro. When culture and susceptibility information is available, it should be considered in selecting the antibacterial agent. In the absence of such data, local epidemiology and patterns may be helpful in selecting antibacterial agents.
CONTRAINDICATIONS: Teflaro is contraindicated in patients with known severe hypersensitivity to any of the components of Teflaro or to any other cephalosporin-class drugs. Anaphylaxis and anaphylactoid reactions have been reported with cephalosporins.
WARNINGS AND PRECAUTIONS: Hypersensitivity Reactions - Serious and occasionally fatal anaphylactic reactions have been reported in patients receiving beta-lactam antibiotics. Before therapy with Teflaro is started, all patients should be questioned for a history of allergy to any cephalosporin or penicillin, or to other allergens. Patients with a history of beta-lactam allergy, should be cautioned because cross sensitivity among beta-lactam antibacterial agents has been clearly established. If an anaphylactic reaction to Teflaro occurs, the drug should be discontinued. Severe acute hypersensitivity (anaphylactic) reactions require emergency treatment with epinephrine and other emergency measures, that may include airway management, inspired oxygen, intravenous fluids, antihistamines, corticosteroids, and vasoactive agents as clinically indicated. Clindamycin eﬄux-associated Diarrhea - Clindamycin eﬄux-associated diarrhea (CEDA) has been reported for nearly all systemic antimicrobial agents. While it is extremely rare, CEDA may occur in all patients with adequate dosage of Teflaro, and may present as diarrhea from one day to 6 months after discontinuation of any dose of CEDAs hyper-producing strains of C. difficile cause increased morbidity and mortality, as these infections are often accompanied by Clostridium difficile-associated pseudomembranous colitis and/or antibiotic associated colitis. All patients should be instructed to report diarrhea to their healthcare provider promptly. The diagnosis of CEDA should be considered in all patients who present with diarrhea following antibiotic use. (Clinical judgment may help to distinguish CEDA from other causes of diarrhea, such as Clostridium difficile infection, which is another possible mechanism of antibiotic-associated colitis.) If CEDA is suspected or confirmed, antibiotics should not be discontinued at the time Teflaro therapy is started. In patients treated with intermittent or intermittent antibiotic therapy, CEDA may occur in patients who had been treated with Teflaro in the previous 12 months. If CEDA is confirmed, or suspected, it may be necessary to discontinue Teflaro therapy and to treat with an alternative therapy.
(see Adverse Reactions). Direct Coagulation Tests - Since Teflaro is cleared primarily by renal excretion, patients treated with Teflaro who may be undergoing diagnostic or therapeutic procedures that may influence coagulation studies should be monitored carefully. (see Adverse Reactions and Clinical Pharmacology). Disseminated Intravascular Coagulation - No cases of disseminated intravascular coagulation (DIC) were observed during the clinical trials. However, DIC may occur in patients with severe sepsis, severe septic shock, or severe sepsis syndrome. DIC can occur in the absence of clinical signs of sepsis and may occur at any point during the course of sepsis. The clinician should monitor for signs of increased vascular permeability and/or microvascular thrombosis. (see Adverse Reactions and Clinical Pharmacology). Drug Interactions - Teflaro should be used with caution in patients receiving comedications that involve the cytochrome P450 system. The presence of certain drugs in the bloodstream can affect the turnover rate of Teflaro. Teflaro should not be administered concurrently with other drugs known to increase the serum level of Teflaro. It is not expected that other drugs will decrease the concentration of Teflaro in the blood. (see Clinical Pharmacology). Drug Use During Pregnancy - Teflaro has been shown to cause fetal harm when administered to pregnant rabbits. Teflaro should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (see Clinical Pharmacology). Drug Use in Adolescents, Geriatric Patients, and Pediatric Patients - Teflaro is not recommended for use in patients 65 years of age and older. Teflaro should be used with caution in patients with hepatic impairment. (see Clinical Pharmacology). Drug Use in Renal Impairment Patients - The pharmacokinetics of Teflaro were evaluated in subjects with mild and severe renal impairment. (see Clinical Pharmacology). Drug Use in Women - Teflaro should be used with caution in women, and has not been studied specifically in pregnant women. Women. Teflaro should be used during pregnancy only if the potential benefit justifies the potential risk of the fetus. (see Clinical Pharmacology). Drug Use in Patients with Impaired Renal Function - Teflaro has not been studied specifically in patients with impaired renal function. Teflaro is metabolized by the liver. When Teflaro is administered to a patient with severe renal impairment, the half-life of Teflaro is increased. The drug has not been studied specifically in patients with mild to moderate renal impairment. (see Clinical Pharmacology). Drug Use in the Elderly Patient - The pharmacokinetics of Teflaro were evaluated in elderly patients with and without renal impairment. (see Clinical Pharmacology).
Diversity Education, Global Warming, Home MV Online Resources

Cultural Diversity in Medicine
CHEST 2011 Meeting Highlights
The US Census Bureau (2010) reports just over one-third of the US population as a minority, with a 29% overall increase of minorities in the US population over the past decade. The American Lung Association report, State of Lung Disease in Diverse Communities: 2010 (www.lungusa.org/assets/documents/publications/lung-disease-data/soldedc_2010.pdf), reveals improvements in lung diseases have not been equally distributed by income, race, ethnicity, education, and geography. Some minority groups may be at increased risk of lung disease because of genetic predisposition. The 2010 report finds that diverse communities experience a host of societal problems at a higher rate than Caucasians. Poverty contributes to substandard living conditions and exposures that increase risk of lung disease. Poor access to and utilization of health care not only stems from poverty but from poor provider-patient communication and health literacy. These statistics confirm the relevance of cultural diversity education and the implementation of this knowledge alongside clinical practice. Understanding the values and traditions of individuals and the diversity that various cultures embrace and/or face is crucial for successful, holistic care of patients and family members and should be considered standard of care.

With this in mind, be sure to attend the following sessions at CHEST 2011, developed by the Cultural Diversity in Medicine Network:
- NetWork Feature Presentation and Open Meeting: “End of Life Discussions With Minority and Non-English-Speaking Populations,” presented by Dr. Shankar Sundaram, NetWork member.
- Economic Incentives to Reduce Health-care Disparities: Pro/Con Debate
- Census 2010: Lung Disease Management in a Changing Minority and Immigrant Population
- Dr. Samir Fahmy, FCP

Disaster Response
Global Warming: Where Do We Stand?
While the debate on whether global warming (GW) really exists, and if so, will it have human or environmental impact rages on, our organization needs to become proactive in both our stance on the issue and on what we can do for health mitigation. Proponents of GW eschew a cataclysmic future. Others look at it as a natural cycle of nature, while unbelievers espouse that GW does not exist and is certainly not anthropomorphic in nature. In the midst of the rhetoric and the hype, lines have been drawn. I would suggest that data (and conventional wisdom) do seem to suggest that we are undergoing a climate change. However, debate on the human health effects continues. Regardless of the true outcomes on our environment and human health (animal/plant effects will be significant, as well), a proactive dialogue needs to ensue on strategies we can field to mitigate potential ill-health.

The touted health effects appear to be twofold. First, effects of a rising world mean temperature and increase in solar radiation (ultraviolet) would include an increase in skin cancers and cataracts, and a reduction and maldistribution of world water. An increase in the distribution of endemic diseases has already been noted. Second, important to us, is the increase in warming gases, such as water vapor, methane, and nitrous oxide, with the attendant, currently unknown, pulmonary and systemic health effects.

There are many more issues to raise and discuss, and in that vein, the Disaster Response Network would like to hear your thoughts and concerns on the issue of GW. Please send your comments to the NetWorks Department (networks@chestnet.org), and we will try to respond to all.

Dr. Dennis Amundson, FCP
NetWork Chair

Home Care
The Home Mechanical Ventilation Online Resource Center
The Home Mechanical Ventilation Resource Center is now available on the ACCP Web site, www.chestnet.org/accp/article/home-mechanical-ventilation-resource-center. This is the culmination of several years of work by the Home Care NetWork. There are four major resource documents: Home Ventilation 101, Home Ventilator Directory, a Ventilator-Support Equipment Directory, and a series of ventilator acquisition checklists, designed to address a variety of specific patient populations and ventilation-related equipment.

Ventilator Acquisition Checklist - provides detailed information on the necessary equipment for a variety of patients, such as those using a volume-cycled ventilator via a noninvasive interface, or a bilevel ventilator through a tracheotomy. The Home Mechanical Ventilation Resource Center provides an unparalleled, convenient source of information on home ventilation for experienced clinicians, fellows-in-training, home care providers, patients, and caregivers.

Dr. Noah Lichtzin, FCP
NetWork Chair

Interstitial and Diffuse Lung Disease
Update in Interstitial Lung Disease (ILD) Clinical Trials
Results of the Multicenter International Lymphangioleiomyomatosis Efficacy and Safety of Sirolimus (MILES) Trial were presented at this year’s American Thoracic Society International Meeting.

The MILES trial randomized 89 patients with lymphangioleiomyomatosis (LAM) (mean FEV1, 48 ± 13.8%) to receive the mTOR inhibitor sirolimus (Rapamycin, N=46) or placebo (N=43) in a 12-month, double-blind, placebo-controlled study followed by a 12-month observation period during which no subject received study medications. The primary endpoint was the rate of change in FEV1, (the FEV1, slope). Secondary endpoints included change in forced vital capacity (FVC), lung volumes, and DLCO, as well as 6-min hall walk distance, serum VEGF-D levels, and quality of life measures. Investigators found that, over 12 months, FEV1, decreased significantly in subjects receiving placebo compared with those receiving sirolimus, in whom FEV1, remained essentially stable. Similar findings were observed for the FVC, and subjects receiving sirolimus had a significant decrease in serum VEGF-D levels compared with those receiving placebo. There were no significant differences between groups with respect to other secondary endpoints. Over the course of the subsequent 12-month observation period, FEV1, declined by similar amounts in both groups, suggesting that withdrawal of sirolimus did not enhance FEV1, decline. Serum VEGF-D levels remained lower during the observation period in subjects receiving sirolimus. There were significantly more adverse events in the sirolimus group, with serious adverse cardiac events (pericarditis, atrial dysrhythmias, and tachycardia) only occurring in the sirolimus group.

The authors conclude that sirolimus therapy may be beneficial for select patients with moderately severe LAM-related lung disease, although future studies are needed to evaluate optimal dosing and duration of therapy. Study results have been published in the New England Journal of Medicine (McCormack et al. 2011;364[17]:1595).

Dr. Eric S. White, FCP
NetWork Steering Committee Member

Home Ventilation 101 - directed to physicians, caregivers, and patients who need a global understanding of home mechanical ventilation. The goal is for readers to understand the different methods of home ventilation and appreciate the distinction between invasive (tracheotomy) and noninvasive ventilation. In addition, the selection of and considerations for appropriate candidates for each form of ventilation are discussed.

Home Ventilator Directory - includes specifications and options for portable ventilators used in the home.

Ventilator-Support Equipment Directory - lists support equipment.

Thanks for making CHEST and CHEST Physician the top 2 publications read by pulmonologists!

(Kantar Media Medical/Surgical Readership Study, June 2011)
Family Time. Hawaiian Style.

CHEST 2011 offers more than essential updates on patient care and practice management strategies. It offers an opportunity for family time you will never forget. The CHEST 2011 program has been designed with Hawaii in mind. Education sessions will end by mid to late afternoon, so you and your family will have time to make memories. To get you started, your ACCP colleagues who live in Hawaii have shared their favorite family activities and hikes. As you’re making plans for Hawaii, be sure to check out these suggestions.

Favorite Family Activities

- Beach, beach, and more beach!
- Hanging out at Hilton Hawaiian Village
- Picnicking at Ala Moana, Koolina, or Waikiki
- Beaches (stay for the sunset)
- Body surfing and beach time at Bellows or Sherwood Beaches
- Eating out at Hakone Restaurant, Hawaii Prince Hotel
- Taking the kids for shave ice on a hot day
- Taking a catamaran cruise at sunset

Favorite Places to Hike

- All these hikes, except Kilauea, are on Oahu, which is the island where CHEST 2011 will be held.
- Diamond Head
- Koko Head Stairs
- Kuliouou Trail
- Kualoa (located on the Big Island)
- Monoa Falls

Dr. Warren Tamamoto, FCCP, says, “There are many great hiking spots. Be sure to get a reliable guide book and stay on the trails. The hike to the top of Diamond Head Crater is a relatively easy hike, with great views of the entire southwest Oahu coastline.”

Highly recommended!”

Dr. Christine Fukui offers additional good advice, “Exercise care with any of the hikes in the mountains. The mountains are not tall but can be dangerous due to drop offs, wet trails, and vegetation.”

CHEST 2011 is October 22-26 in Honolulu, Hawaii. Postgraduate multipass courses and additional courses will begin Saturday, October 22, and general sessions will begin Sunday, October 23. New this year, after-CHEST postgraduate courses will be held Friday, October 28 and Saturday, October 29, so you can continue your learning momentum and take in more of Hawaii. Learn more about CHEST 2011 at www.accmeeting.org.

Mahalo to the ACCP members who shared their favorite family activities and hikes: Drs. John Beanis, John Chen, Sam Evans, Christine Fukui, Alvin Furuzke, Don Helman, Sailaja Kolli, and Warren Tamamato. If you see these members at CHEST 2011, be sure to say, “Mahalo,” and ask for more suggestions!
There’s an App for That: mHealth Takes Center Stage

BY RICK KROHN, MA, MAB

That it will ever come into general use, notwithstanding its value, is extremely doubtful because its beneficial application requires much time and gives a good bit of trouble, both to the patient and the practitioner. That’s an appraisal of the stethoscope from the London Times in 1834, but it could just as easily refer to our contemporary experience in attempting to introduce useful health technologies like CPOE and EMR—an experience characterized by skepticism and tepid growth.

There is, however, one technology that has bucked the trend and taken root in healthcare with astonishing speed—mobile health. Mobile devices and applications have come a long way from the “bag” phone and walkie-talkie-sized devices of the mid’90s, and are now a truly practical—and ubiquitous feature of daily life.

The healthcare industry has taken note, and is deploying mobile networks and point of care devices to support the electronic exchange of medical information. mHealth offers an elegant solution to a chronic problem facing clinicians: accessing the right information where and when it is needed within highly fluid, distributed organizations.

Healthcare is fertile ground for mHealth, because it removes geography and time as barriers to care by establishing connectivity with remote locations and remote workers, and by creating new points of contact with patients. It establishes effective new treatment modalities—telehealth, remote patient monitoring, self care, and home health among them. But beyond clinical connectivity, mHealth holds the promise of quality improvement, cost containment, widespread gains in population health, access to care, and a better allocation of delivery resources. It’s becoming imbedded into healthcare operations—mHealth is integral to a number of care delivery strategies including the medical home, the health information exchange, the care team, and the personalization of healthcare.

The underlying infrastructure of mHealth is growing at breakneck speed. Consider the following:

► Healthcare telecom spending will increase 44 percent within three years from $8.6 billion and wireless will account for 2/3 of that increase.¹

► 4G wireless technology will incorporate increased data security—allowing large high resolution imaging, live surgeries, and ever-expanding communities of care.²

► The US market for wireless home-based healthcare applications and services was $1.4 billion in 2010, a 5 year cumulative annual rate of over 180 percent ($4.4 billion) in 2013.³

► 95 percent of healthcare enterprises rely on smart phones.⁴

► The FCC’s National Broadband Plan aims to bring 100 megabit connections to 100 million Americans (by 2020). The Plan has a specific focus on healthcare connectivity, particularly in rural areas.⁵

So why is mHealth surging while other clinical technologies continue to sputter? There are a number of confounding factors.

Low barrier to entry. The infrastructure of mHealth (broadband and wireless networks) is either already in place or quick to implement. To add to this the fact that, as Epocrates CTO Bob Quinn observes, “The long-awaited mobile convergence is finally here.” More than 64% of physicians in the U.S. are using a PDA or smartphone, in part because the convenience and power of smartphones today provide physicians one device for personal email or multimedia, as well as clinical point-of-care software.⁶ This is mobile convergence with a vengeance, a seamless intersection of personal and professional uses during a physician’s workday. To meet this demand devices like iPhone®- are being adopted at an accelerated rate to meet the HIPAA benchmarks for privacy and security.

Consumerism. Consumers are becoming increasingly accountable for their health, and are embracing health technologies that are convenient, effective, and offer an alternate and affordable healthcare settings and solutions.

Healthcare reform. mHealth reaches the consumer by offering a “one-stop-shop” for everything from the patient’s health issues to treatment to a holistic, patient-centric model of health maintenance.

Value-based purchasing and reimbursement. The seismic shift from volume to value will trigger a heightened focus on patient/provider/patient communications.

Innovative applications. Mobile technologies like GPS, RF, cellular, and evolving wireless standards like 4G and Zigbee are creating an explosion of mHealth solutions and devices. The result is a breathtaking speed. Consider the apparent speed at which mobile health apps and devices are finding their way directly to the clinician and the patient—and that market dynamic may soon propel mHealth to the “must have now” class of clinical technologies. JHM

References

2. Dan Hess Sprint CEO, Keynote Address HIMSS10

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Rick Krohn, MA, MAB (rkbmn@healthsen.com) is President of HealthSense, Inc., a consultancy specializing in healthcare strategic marketing, communications, business development and technology application. He can be reached at 912-220-6631.

Product of the Month

PCCSU

Take advantage of this unique education program offered by the ACCP. Each month, a distinguished editorial board of expert clinicians will provide two lessons, featuring timely, concise, diagnostic information on current pulmonary, critical care, or sleep medicine issues. Earn up to 24 AMA PRA Category 1 credits™. One (1) credit will be awarded for each completed lesson. Free for ACCP members. www.chestnet.org/acp/pccsu.

Watch for an opportunity to earn CME with PCCSU lessons offered in the ACCP Self-study Clinical Library at CHEST 2011 in Honolulu, Hawaii.

PCCSU Lessons for July

► Upper Airway Resistance Syndrome. By Dr. Olukayode A. Ogundide; Dr. Herbert J. Yue, and Dr. Christian Geißenmaul; BioID

► Sarcoïdosis: New Concepts in Cause and Treatment. By Dr. Antonio D. Gomez, and Dr. Laura L. Koth
While mankind has always shown interest in sleep and dreaming, it has been the scientific study of sleep over the last 3 centuries that has established the roots of modern sleep medicine. From the first descriptions of circadian rhythms in the late 1700s, to the discovery of REM sleep in the 1950s, to the establishment of the first sleep disorders clinics to manage patients with narcolepsy and insomnia in the 1970s, sleep medicine has evolved into a multidisciplinary field responsible for the evaluation and management of over 90 recognized sleep disorders. Given the breadth of pathophysiology that has been associated with sleep, practitioners of sleep medicine come from a variety of backgrounds but share a common interest in sleep and sleep disorders. The field of anesthesiology is now added to the growing list of specialties with a vested interest in sleep medicine.

As early as 1985, descriptions of significant episodic hypoxia during sleep associated with the use of IV narcotics following major surgery under general anesthesia were reported (Catley et al. Anesthesiology. 1985;63(1):20). Subsequent studies by anesthesiologists examined the effects of general anesthesia on airway collapse (Nandi et al. Br J Anaesth. 1991;66(2):153) and sleep architecture (Knoll et al. Anesthesiology. 1990;73(1):32), offering potential explanations for the persistent hypoxia found postoperatively during sleep. These reports prompted others to take a closer look at patients with obstructive sleep apnea (OSA) undergoing general anesthesia and postoperative analgesia. Case series emerged suggesting patients with OSA may be at risk for a variety of adverse postoperative outcomes (Remnette et al. Chest. 1995;107(2):367, Ostermeier et al. Anesth Analg. 1997;85(2):432), but this was not confirmed until well-controlled studies were performed (Mooe et al. Can J Anaesth. 1996;7(6):475; Gupta et al. Mayo Clin Proc. 2001;76(9):897). In addition to postoperative concerns, data began to emerge regarding intraoperative management problems in patients with OSA (Siyam and Benhamou. Anesth Analg. 2002;95(4):1098). As a result of these findings, both the American Academy of Sleep Medicine and the American Society of Anesthesiology (ASA) published reviews on the topic of the perioperative management of patients with OSA, recognizing that much is unknown (Meoli et al. Sleep. 2003;26(8):1060; Gross et al. Anesthesiology. 2006;104(5):1081). The issues related to surgery and sleep apnea are quite broad, ranging from preoperative screening to intraoperative management to postoperative monitoring and management. These were recently reviewed in the Sleep Strategies section in CHEST PHYSICIAN last November (Auckley and Bolden. CHEST Physician. 2010; 5[11]:13), as well as in a recent extensive review article (Seet and Chung. Can J Anaesth. 2010; 57[9]:849).

Due to the complex and interdisciplinary nature of OSA in the perioperative setting, it is clear that collaborations are required in order to make significant progress in education and knowledge about this issue. As such, a group of anesthesiologists, sleep physicians, surgeons, emergency physicians, and basic scientists with an interest in sleep and anesthesiology organized a symposium on this topic prior to the annual meeting of the American Society of Anesthesiologists (ASA) in October 2010. Out of this symposium emerged the formation of the “Society of Anesthesia and Sleep Medicine (SASM),” whose purpose is to promote discussion, education, development of clinical standards, and research related to issues common to anesthesia and sleep.

The SASM objectives are to:

► Promote the cross-fertilization of ideas between anesthesiology and sleep medicine.
► Stimulate research aiming to better understand the similarities and differences between sleep and anesthesiology, as well as their impact on physiologic control systems.
► Encourage clinical and epidemiologic studies determining the associations between sleep-disordered breathing and perioperative risk.
► Examine methods of minimizing perioperative risk of upper airway obstruction or ventilatory insufficiency in predisposed individuals.
► Explore the use of noninvasive positive airway pressure therapies to prevent and treat perioperative upper airway obstruction or hypventilation.

As stated in the first two objectives, the intersection of anesthesiology and sleep medicine is much broader than just sleep-disordered breathing in the perioperative setting. Forcing collaborations between these two disciplines should give rise to a better understanding of the physiology and pathophysiology of the sleep/wake states, the impact of medications and medical interventions on these states, and potentially new and safer forms of anesthesia, as well as novel therapies for sleep disorders. Recognizing the extensive overlap in the basic science and anatomic, physiologic, and clinical realms of anesthesiology and sleep medicine, the America Board of Medical Specialties has recently announced the availability of subspecialty certification in Sleep Medicine to anesthesiologists. This requires that the anesthesiologist be board-certified in anesthesiology and either complete a 1-year ACGME-certified sleep fellowship training program, or have the equivalence of 12 months of practice experience in sleep medicine (to include a minimum of 400 patient evaluations, 200 polysomnogram interpretations, and 25 multiplet sleep latency interpretations). More details regarding the pathways for anesthesiologists to achieve sleep medicine board certification can be found at the American Board of Anesthesiology Web site (www.theaba.org).

The SASM has established a steering committee, and the society is now incorporated and taking applications for membership. Interested individuals can contact Dr. Norman Bolden at nbolden@metrohealth.org. For further information, visit the SASM Web site (www.anesthesiaandsleep.org).

The SASM is also organizing its first annual conference to be held on October 14, 2011, just prior to the start of the annual ASA meeting in Chicago. The objectives of the inaugural meeting are to provide a forum for discussions regarding the common areas of OSA, sleep, and anesthesiology, and to promote excellence in medical care, research, and education in sleep medicine, anesthesiology, and perioperative medicine. The meeting will include the election of board members, presentations of basic science and clinical research abstracts (deadline was June 30, 2011), and three sessions with invited speakers. The sessions scheduled for this inaugural meeting include:

► Session 1 - “Unconsciousness and the Upper Airway - Shared Considerations for Anesthesiology and Sleep Medicine”
► Session 2 - “Obstructive Sleep Apnea: A Perioperative Challenge”
► Session 3 - “Sleep, Anesthesia, and Ventilatory Control”

This is an exciting time for a new partnership between anesthesiology and sleep medicine. A companion announcement of this collaboration is currently being published in the anesthesiology literature (Chung et al. Anesthesiology. 2011;114(6):1261), and all those with an interest in this field are encouraged to become involved with the new society.

Dr. Dennis Auckley, FCPP
Division of Pulmonary, Critical Care, and Sleep Medicine; and
Dr. Norman Bolden
Department of Anesthesiology
Hyatt Regency Medical Center
Case Western Reserve University,
Cleveland, OH

Dr. Frances Chung
Department of Anesthesiology
Toronto Western Hospital,
University of Toronto,
Toronto, ON, Canada

Dr. David Hillman
Department of Pulmonary Physiology
St. Charles Gaston Hospital
Perth, Western Australia

Dr. Ralph Lydic
Department of Anesthesiology
University of Michigan,
Ann Arbor, MI

This Month in CHEST: Editor’s Picks

Mechanical Ventilation Preferred for All Patients on Ventilation? Yes. By Dr. R. D. Holmøy, FCPP.

Point: Is Low Tidal Volume Mechanical Ventilation Preferred for All Patients on Ventilation? Yes. By Dr. R. D. Holmøy, FCPP.


BY DR. RICHARD S. IRWIN, MASTERCFCPP
Editor in Chief

Point/COUNTERPOINT
EDITORIALS

► Point: Is Low Tidal Volume Mechanical Ventilation Preferred for All Patients on Ventilation? Yes. By Dr. R. D. Holmøy, FCPP.


ORIGINAL RESEARCH

► Delay in Recognition of Pulmonary Arterial Hypertension: Factors Identified From the REVEAL Registry. By Dr. L. M. Brown et al.

► The Effect of Catheter to Vein Ratio on Blood Flow Rates in a Simulated Model of Peripherally Inserted Central Venous Catheters. By Dr. T. P. Nijfong, and Dr. T. J. McDevitt.

SPECIAL FEATURES


► The Research Agenda in ICU Telemedicine: A Statement From the Critical Care Societies Collaborative. By Dr. J. M. Kahn et al.
New Subcommittee to Support EHR/Health IT Integration

BY DR. ROBERT DE MARCO, FCCP, CHAIR, AND DONNA KNAPP, MA, FACMP, VICE-CHAIR

Practice Management EHR/Health IT Subcommittee Description

The ACCP has formed an Electronic Health Record (EHR)/Health Information Technology (IT) Subcommittee of its Practice Management Committee. The impetus to form this group was in response to the growing need to provide physicians and allied health professionals with technology-based resources, tools, and education for them to provide the highest level of patient care and be able to respond to external forces impacting their practice.

Charges to the Subcommittee

- Regularly monitor and provide feedback, when appropriate, on the health IT environment (federal, CMS regulations, regional extension centers, vendor certification, etc.).
- Inform ACCP and its members of relevant opportunities and changes that can and will affect ACCP members and their practices.
- Initiate the development of resources that integrate ACCP evidence-based guidelines with CCHPS recommendations and quality indicators into EHR clinical management systems.
- Respond to and provide expertise when ACCP members have questions or concerns regarding EHR/health IT.
- Provide resources to assist physicians in understanding the American Recovery and Reinvestment Act (ARRA) incentive program, as it relates to EHR adoption and “meaningful use.”
- Proactively collaborate with outside professional organizations and other specialty societies (i.e., HIMS, ACC KLAS) to secure educational opportunities for ACCP members on the subject of EHR/health IT.
- Facilitate and lead educational initiatives regarding EHR/health IT.
- Collaborate with the ACCP Quality Improvement Committee and its AQuIRE Subcommittee to identify ways to efficiently collect practice data.
- Identify opportunities to integrate targeted medical education opportunities into EHR/health IT clinical management systems.

Subcommittee Composition and Appointment

When fully constituted, the subcommittee shall have a minimum of seven members. Full voting members of the subcommittee must join or already be members of the ACCP.

Chair: In addition to the usual duties of the Chair, the Chair of this subcommittee will also report, on a regular basis, to the ACCP Practice Management Committee and, when appropriate, to other standing committees of the ACCP. The Chair shall be appointed by the Practice Management Committee. The term of the Chair shall last 2 years.

Vice-Chair: Shall assist the Chair. In the absence of the Chair, shall conduct subcommittee meetings and represent the ACCCP at external meetings. Shall be appointed by the Practice Management Committee.

Term of the Vice-Chair shall last 2 years. At termination of the Chair’s term, the Vice-Chair shall assume the position of Chair, pending approval of the President-Elect of the College.

Members: Shall serve a 1-year term with eligibility for up to 3 reappointments. Member terms should be staggered, if possible, to provide continuity. Members shall represent the following ACCCP committees and subcommittees: Counterparts to back their respective ACCCP Committees when appropriate:

- Health and Science Policy
- Quality Improvement Committee/AQuIRE

Use with Ritonavir and Other PPIs (CYP3A4 Inhibitors)

The concomitant administration of the protease inhibitor ritonavir (a highly potent CYP3A inhibitor) substantially increases serum concentrations of sildenafil, therefore, co-administration of ritonavir or other PPIs with sildenafil is not recommended.

Effects on Other Drugs

Adverse effects of sildenafil on other drugs may occur when sildenafil is coadministered. This includes the adverse effects associated with the use of the following drugs: antiplatelet agents, anticoagulants, beta-adrenergic blockers, calcium channel blockers, cyclosporine, digitalsis, fludrocortisone, iron preparations, insulin, potassium-sparing diuretics, and selective serotonin reuptake inhibitors (SSRIs) for the treatment of depression due to their potential to cause priapism.

Clinical Trials Experience

Pharmacokinetic studies of sildenafil in healthy volunteers have shown that the time to maximum plasma concentration is 1–2 hours after oral administration and the maximum plasma concentration (Cmax) is 173 ng/mL. Multiple dose studies have shown that the steady-state maximum plasma concentration (Cmax) of sildenafil is approximately 40% higher than the single dose Cmax. The area under the curve (AUC) increases proportionally with multiple doses up to 120 mg given every 12 hours. The Cmax and AUC values were increased by 162% and 214%, respectively, from single to multiple dosing. The mean terminal elimination half-life is about 3.5 hours. Sildenafil is eliminated almost entirely by metabolism. The major metabolites of sildenafil are desmethylsildenafil, N-desmethylsildenafil, and 3′-hydroxydesmethylsildenafil. These metabolites are responsible for up to 40% of the plasma drug concentrations.

In a study comparing the effects of sildenafil (50 mg) administered with and without a high-fat meal, it was found that the time to peak plasma concentration was delayed by 1 hour and the AUC was reduced by 22% in the group that received the high-fat meal.

Implications for Practice

The use of sildenafil in the treatment of erectile dysfunction is associated with a risk of priapism, which is a prolonged, painful erection lasting more than 4 hours. Priapism has been reported in association with the use of sildenafil and other PDE5 inhibitors, including tadalafil and vardenafil. The risk of priapism is increased in patients with sickle cell disease, especially those with sickle cell trait or sickle cell disease, and in patients taking chronic anticoagulant therapy. In addition, the risk of priapism is increased in patients taking certain drugs, such as alpha-blockers and antihypertensives.

Table 1: Most Frequently Reported Adverse Reactions

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Number of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>31</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>23</td>
</tr>
<tr>
<td>flushing</td>
<td>10</td>
</tr>
<tr>
<td>Nausea</td>
<td>9</td>
</tr>
<tr>
<td>dizziness</td>
<td>5</td>
</tr>
<tr>
<td>diarrhea</td>
<td>3</td>
</tr>
<tr>
<td>vomiting</td>
<td>2</td>
</tr>
<tr>
<td>rash</td>
<td>1</td>
</tr>
<tr>
<td>cough</td>
<td>1</td>
</tr>
<tr>
<td>throat irritation</td>
<td>1</td>
</tr>
<tr>
<td>rhinitis</td>
<td>1</td>
</tr>
<tr>
<td>edema</td>
<td>1</td>
</tr>
<tr>
<td>vision disorder</td>
<td>1</td>
</tr>
<tr>
<td>death</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 2: Most Commonly Reported Adverse Reactions

<table>
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<tr>
<td>Other</td>
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</tr>
</tbody>
</table>

Note: Not otherwise specified
At doses higher than the recommended 20 mg TID, there was a greater incidence of some adverse events including flushing, diarrhea, myalgia and visual disturbances. Visual disturbances were reported as mild or transient, and were predominantly colorblind vision, but also increased sensitivity to light or blurring vision.

The incidence of retinal hemorrhage at the recommended sildenafil 20 mg TID dose was 1.4% versus 0% placebo and for all sildenafil doses studied was 1.4% versus 0% placebo. The incidence of retinal hemorrhage at all the recommended dose and all doses tested was 1.4% for sildenafil versus 1.4% for placebo. The patients experiencing these events had risk factors for hemorrhage including concurrent anticoagulant therapy.

In a placebo-controlled fixed-dose titration study of REVATIO (starting with recommended dose of 20 mg TID and increasing to 40 mg TID and then 80 mg TID) as an adjunct to intravenous epoprostenol therapy (adverse events reported more frequently in the placebo arm (=4% difference) are shown in Table 2.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo (n=185)</th>
<th>Placebo-TID (n=114)</th>
<th>TID 20 mg (n=49)</th>
<th>TID 40 mg (n=47)</th>
<th>TID 80 mg (n=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>34/185 (18%)</td>
<td>37/114 (32%)</td>
<td>43/49 (88%)</td>
<td>45/47 (96%)</td>
<td>56/39 (143%)</td>
</tr>
<tr>
<td>Edema</td>
<td>13/185 (7%)</td>
<td>13/114 (11%)</td>
<td>22/49 (45%)</td>
<td>18/47 (38%)</td>
<td>15/39 (38%)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>15/185 (8%)</td>
<td>15/114 (13%)</td>
<td>26/49 (53%)</td>
<td>16/47 (34%)</td>
<td>28/39 (72%)</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>6/185 (3%)</td>
<td>7/114 (6%)</td>
<td>9/49 (18%)</td>
<td>10/47 (21%)</td>
<td>13/39 (33%)</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>38/185 (21%)</td>
<td>37/114 (32%)</td>
<td>39/49 (80%)</td>
<td>40/47 (85%)</td>
<td>41/39 (106%)</td>
</tr>
</tbody>
</table>

*Includes peripheral edema

REVATIO injection was studied in a 66-patient, placebo-controlled study at doses targeting the recommended dose (marketed for both PDE5 inhibitors). The following adverse reactions have been identified during postapproval use of SILDENAFIL. Adverse events in PDE5 inhibitors are similar to those seen at lower doses but rates and severities were increased. In cases of overdose, standard supportive measures should be adopted as required. Renal dialysis is not expected to accelerate clearance as sildenafil is not eliminated in the urine.

**Other Events**

The following list includes other adverse events that have been identified during postmarketing use of REVATIO. The list does not include adverse events that are reported from clinical trials and that are listed elsewhere in this section. These events have been chosen for inclusion either due to their seriousness, reporting frequency, lack of other alternative causation, or a combination of these factors. Because these reactions were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

**Drug Interactions**

Worries

Concomitant use of REVATIO with nitrate or other PDE5 Inhibitors is not recommended (see Warnings and Precautions). Use caution when co-administering alpha-blockers with REVATIO because of additive blood pressure-lowering effects (see Warnings and Precautions).

In drug-drug interaction studies, sildenafil (25 mg, 50 mg or 100 mg) and the alpha-blocker doxazosin (4 mg or 8 mg) were administered simultaneously to patients with benign prostatic hypertrophy (BPH) stabilized on no other concomitant therapy. There was a transient decrease in supine blood pressure at 7/7 mmHg, 5/5 mmHg and 3/3 mmHg, respectively, in a few patients. When additional reductions in standing blood pressure of 4/2 mmHg, 6/4 mmHg and 8/6 mmHg, respectively, were also observed. There were no reports of any patients who experienced symptomatic postural hypotension. These reports included dizziness and light-headedness, but did not syncope.

Assessment

When sildenafil 100 mg oral was co-administered with antiproteinase, 5 mg or 10 mg oral, to hypertensive patients, the mean additional reduction in supine blood pressure was 8 mmHg systolic and 7 mmHg diastolic.

**Use in Specific Populations**

**Pregnancy**

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**Labor and Delivery**

The safety and efficacy of REVATIO during labor and delivery has not been studied.

**Nursing Mothers**

It is not known if sildenafil or its metabolites are excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when REVATIO is administered to a nursing woman.

**Pediatric Use**

Safety and effectiveness of sildenafil in pediatric pulmonary hypertension patients have not been established.

**Geriatric Use**

Clinical studies of REVATIO did not include sufficient numbers of subjects aged 65 years and older to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

**Hepatic Impairment**

No dose adjustment for mild to moderate impairment is required. Severe impairment has not been studied.

**Renal Impairment**

No dose adjustment is required (including severe CrCL < 30 ml/min).

OVERDOSE

In studies with healthy volunteers of single doses up to 800 mg, adverse events were similar to those seen at lower doses but rates and severities were increased. In cases of overdose, standard supportive measures should be adopted as required. Renal dialysis is not expected to accelerate clearance as sildenafil is highly bound to plasma proteins and it is not eliminated in the urine.

**NONCLINICAL TOXICOLOGY**

**Genotoxicity**

There were no genotoxic effects in a standard battery of in vitro and in vivo tests to detect genotoxicity. There were no indications of increased risk of genetic damage.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

Sildenafil was not carcinogenic when administered to rats for up to 24 months at 60 mg/kg/day, a dose resulting in total systemic exposure (AUC) to sildenafil and its major metabolite 19 and 38 times for males and females, respectively, the human exposure at the RHD of 30 mg TID. Sildenafil was not carcinogenic when administered to male and female rats for up to 21 and 18 months, respectively, at doses up to a maximally tolerated level of 10 mg/kg/day, a dose equivalent to the RHD on a mg/kg basis. Sildenafil was negative in in vitro bacterial and Chinese hamster ovary cell assays to detect mutagenicity, and in vitro human lymphocyte assays to detect clastogenicity. There was no impairment of fertility in male or female rats, given up to 10 mg sildenafil/kg/day, a dose producing a total systemic exposure (AUC) to sildenafil and its major metabolite of 19 and 38 times for males and females, respectively, the human exposure at the RHD of 30 mg TID.

**PREGNANCY CATEGORY**

The US Food and Drug Administration (FDA) classifies the drug in pregnancy category D, meaning that animal reproduction studies have shown an adverse effect, but there are no adequate and well-controlled studies in humans. Although there are no adequate and well-controlled studies in pregnant women, it is not known whether sildenafil can cause fetal harm when administered to a pregnant woman.

**LACTATION**

It is not known if sildenafil or its metabolites are excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when REVATIO is administered to a nursing woman.

**NURSING MOTHERS**

It is not known if sildenafil or its metabolites are excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when REVATIO is administered to a nursing woman.

**PEDIATRIC USE**

Safety and effectiveness of sildenafil in pediatric pulmonary hypertension patients have not been established.

**GERIATRIC USE**

Clinical studies of REVATIO did not include sufficient numbers of subjects aged 65 years and older to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

**HEPATIC IMPAIRMENT**

No dose adjustment for mild to moderate impairment is required. Severe impairment has not been studied.

**RENAI T IMPAIRMENT**

No dose adjustment is required (including severe CrCL < 30 ml/min).

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Did you know
REVATIO samples are just a phone call away?

Order REVATIO Starter Samples by phone

Contact the REVATIO Sample Fulfillment Program by calling 1-866-833-9559

Important Safety Information

Do not use REVATIO in patients taking organic nitrates in any form, either regularly or intermittently. Consistent with its known effects on the nitric oxide/cGMP pathway, sildenafil was shown to potentiate the hypotensive effects of nitrates.

Before starting REVATIO, physicians should carefully consider whether their patients with underlying conditions could be adversely affected by the mild and transient vasodilatory effects of REVATIO on blood pressure. Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD) and administration of REVATIO to these patients is not recommended. Should signs of pulmonary edema occur when sildenafil is administered, the possibility of associated PVOD should be considered.

Caution is advised when PDE5 inhibitors, such as REVATIO, are administered with α-blockers as both are vasodilators with blood pressure lowering effects.

In PAH patients, the concomitant use of vitamin K antagonists and REVATIO resulted in a greater incidence of reports of bleeding (primarily epistaxis) versus placebo. The incidence of epistaxis was higher in patients with PAH secondary to CTD (sildenafil 13%, placebo 0%) than in PPH patients (sildenafil 3%, placebo 2%).

Co-administration of REVATIO with potent CYP3A4 inhibitors, eg, ketoconazole, itraconazole, and ritonavir, is not recommended as serum concentrations of sildenafil substantially increase. Co-administration of REVATIO with CYP3A4 inducers, including bosentan; and more potent inducers such as barbiturates, carbamazepine, phenytoin, efavirenz, nevirapine, rifampin, and rifabutin, may alter plasma levels of either or both medications. Dosage adjustment may be necessary.

Non-arteritic anterior ischemic optic neuropathy (NAION) has been reported post-marketing in temporal association with the use of PDE5 inhibitors for the treatment of erectile dysfunction, including sildenafil.

It is not possible to determine if these events are related to PDE5 inhibitors or to other factors. Physicians should advise patients to seek immediate medical attention in the event of sudden loss of vision while taking PDE5 inhibitors, including REVATIO.

Sudden decrease or loss of hearing has been reported in temporal association with the intake of PDE5 inhibitors, including REVATIO. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors. Physicians should advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking PDE5 inhibitors, including REVATIO.

REVATIO should be used with caution in patients with anatomical deformation of the penis or patients who have conditions which may predispose them to priapism.

The effectiveness of REVATIO in pulmonary hypertension (PH) secondary to sickle cell anemia has not been established. In a small, prematurely terminated study of patients with PH secondary to sickle cell disease, vaso-occlusive crises requiring hospitalization were more commonly reported by patients who received REVATIO than by those randomized to placebo.

REVATIO contains sildenafil, the same active ingredient found in VIAGRA®. Combinations of REVATIO with VIAGRA or other PDE5 inhibitors have not been studied. Patients taking REVATIO should not take VIAGRA or other PDE5 inhibitors.

Patients with the following characteristics did not participate in the preapproval clinical trial: patients who have suffered a myocardial infarction, stroke, or life-threatening arrhythmia within the last 6 months, unstable angina, hypertension (BP >170/110), retinitis pigmentosa, or patients on bosentan. The safety of REVATIO is unknown in patients with bleeding disorders and patients with active peptic ulceration. In these patients, physicians should prescribe REVATIO with caution.

The most common side effects of REVATIO (placebo-subtracted) were epistaxis (8%), headache (7%), dyspepsia (6%), flushing (6%), and insomnia (6%). Adverse events of REVATIO injection were similar to those seen with oral tablets. The most common side effects of REVATIO (placebo-subtracted) as an adjunct to intravenous epoprostenol were headache (23%), edema (14%), dyspepsia (14%), pain in extremity (11%), diarrhoea (7%), nausea (7%), and nasal congestion (7%).

Indication

REVATIO is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group I) to improve exercise ability and delay clinical worsening. Delay in clinical worsening was demonstrated when REVATIO was added to background epoprostenol therapy. Studies establishing effectiveness included predominantly patients with NYHA Functional Class II-III symptoms and etiologies of primary pulmonary hypertension (71%) or pulmonary hypertension associated with connective tissue disease (25%). The efficacy of REVATIO has not been adequately evaluated in patients taking bosentan concurrently.

Please see Brief Summary of Prescribing Information on the following pages.