CRITICAL CARE ALERT®

A monthly update of developments in critical care and intensive care medicine

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INSIDE

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Selenium and Sepsis. It's Not Your Average Once-a-Day Vitamin

ABSTRACT & COMMENTARY

By Andrew M. Luks, MD

Pulmonary and Critical Care Medicine, University of Washington, Seattle

Dr. Luks reports no financial relationship to this field of study.

Synopsis: *A prospective randomized, placebo-controlled, multi-center trial demonstrates that a prolonged course of intravenous selenium improves mortality in patients with severe sepsis and septic shock and is associated with minimal to no side effects.*

Source: Angstwurm MW, et al. Selenium in Intensive Care (SIC): results of a prospective randomized, placebo-controlled, multiple-center study in patients with severe systemic inflammatory response syndrome, sepsis, and septic shock. *Crit Care Med.* 2007; 35(1):118-126.

Building on the results of previous pilot studies from their laboratory and a meta-analysis[1] that showed a tendency toward improved mortality in critically-ill patients following selenium administration, Angstwurm and colleagues used a randomized, placebo-controlled multi-center trial to determine whether intravenous administration of selenium could improve outcomes in severe sepsis and septic shock. They recruited patients from 11 centers across Germany and included those men and women above the age of 18 with Acute Physiology and Chronic Health Evaluation (APACHE) III scores > 70 and at least two other markers of sepsis, such as elevated or decreased body temperature, tachycardia, tachypnea, leukocytosis, leucopenia or thrombocytopenia. Patients were excluded if they were pregnant, or had concomitant disease with expected mortality within 2 months, hypoxic-ischemic encephalopathy, primary malignant disease or hemorrhagic pancreatitis without infection.

Subjects were randomized to receive either 1000 micrograms of selenium as an initial bolus injection followed by a 14-day continuous infusion at a rate of 1000 micrograms per 24 hours or an equal volume of normal saline. The authors did not specify whether the infusion was continued if the patients recovered prior to the end of the 14-day period. The primary end-point was 28-day mortality. Multiple secondary endpoints such as the number of days of vasopressor therapy, mechanical ventilation and hemodialysis were examined.

After excluding 60 patients due to protocol violations and other factors, the authors found that 28-day mortality among the 92 patients in the selenium group was 42.4% compared with 56.8% among the 97 patients in the placebo group. This corresponds to a number needed to treat of seven and the authors estimate that the cost per life saved is roughly 1050 Euro (about $1400 USD). Among pre-defined subgroups, mortality was improved in patients with sepsis and disseminated intravascular coagulation, patients with APACHE III scores above 102, and those patients receiving intensive insulin therapy. Mortality was inversely correlated with whole blood selenium concentrations; mortality rates as low as 23-24% were found when drug levels were among the upper two-thirds of measured concentrations in the study. There were no major differences between the selenium and placebo groups with regard to any of the secondary endpoints and there was no difference in the incidence of adverse events between the two treatment arms.

COMMENTARY

Given that the mortality from severe sepsis ranges as high as 50%, identifying a cost-effective, low risk, simple-to-use therapy that could reduce mortality would be of great benefit. On the surface, the trial presented by Angstwurm and colleagues seems to provide promise in this regard. In a clinical trial that is methodologically sound apart from a lower number of subjects than one might expect in an 11-center study, the authors demonstrate improvements in mortality using an intervention that is safe, relatively inexpensive and associated with a low number needed to treat to save one life.

While these are appealing factors, enthusiasm for the results must be tempered by a simple fact: the proposed treatment presents important logistical problems, the most important of which is the long duration over which the therapy must be administered. The selenium infusion lasted 14 days and the authors provide no information as to their protocol in the event patients improved before the two weeks had elapsed. As a result, it is not clear if the mortality benefit extends to patients who stop the infusion early and/or are converted to oral administration after their illness resolves. Given the increasing demands on hospital resources, keeping patients in the hospital for a two-week period is infeasible and exposes the patient to risks such as nosocomial infection. The fact that 49 of their original 238 patients were dropped from the study due to protocol violations involving drug administration should also serve as a warning that the protocol may, in fact, not be an easy one to follow.

With these problems in mind, critical care providers would do well to avoid the quick urge to adopt interventions as standard practice after only one positive trial, as happened with activated protein C, intensive insulin therapy, and corticosteroids in refractory septic shock; and should instead wait for further trials on selenium with perhaps more feasible drug administration protocols. ■

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Reference

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Improving Staff Compliance with ICU Protocols

ABSTRACT & COMMENTARY

By Leslie A. Hoffman, PhD, RN

Department of Acute/Tertiary Care, School of Nursing, University of Pittsburgh

Leslie Hoffman reports no financial relationship to this field of study.

Synopsis: *A rewards program improved adherence to ICU protocols and produced a change in culture in the ICU that sustained protocol adherence rates at > 90% for two years.*

Source: Plost G, et al. *Am J Crit Care.* 2007;16:153-157.

In the institution in which this study took place, an audit revealed that adherence to 9 ICU protocols ranged from 62% to 77%. The protocols focused on a variety of patient care needs including sedation/analgesia, DVT prophylaxis, enteral nutrition, insulin administration, skin care, stress ulcer prophylaxis, and ventilator weaning. To effect change, the multidisciplinary ICU management team first developed a plan that encouraged nurses to recommend implementation of the protocols to physicians, a step that was unsuccessful.

The team next developed a rewards program designed to motivate change. Each staff member of any adult ICU with a 90% or greater compliance rate for the 9 selected protocols after 4 months of monitoring received a reward. The rewards were a catered dinner party, drawings at the party for individual awards (stethoscopes, personal digital assistants, gift certificates) and the grand prize which was a continuing education trip valued at $3,000.

With implementation of the rewards program, nurses became more assertive. They proactively recommended protocols to physicians or handed them directly to physicians during rounds. An audit of all ICUs found that protocol adherence ranged from 85-92% across ICUs at one month and 94-99% at four months. When the same tool was used to monitor compliance 1 and 2 years later, adherence was 91% and 95%, respectively. Initially resistant to change, physicians verbalized appreciation of the user-friendly, time-saving protocols and improved patient outcomes.

COMMENTARY

Unfortunately, adherence to guidelines is low, despite evidence that protocols developed from these guidelines can positively impact patient outcomes. A number of reasons for this have been proposed in explanation, eg, poor dissemination of guidelines, disagreement concerning content, resistance to "cookbook medicine," and a low expectancy of benefit. In the present study, the ICU multidisciplinary team began with traditional approaches to improve adherence. Classes were provided by nurse educators, protocol booklets were developed, and staff nurses were required to demonstrate knowledge by passing an examination. The ICU medical director led educational presentations for physicians, and information order sheets were developed and conveniently placed in the charting area.

When these approaches failed, the team turned to the literature. They elected to use a behavioral (motivational) approach that was prompted by the knowledge that clinicians can be grouped into four categories that characterize their willingness to change. "Seekers" (2.5%) respond by changing practice based on knowledge-oriented strategies. "Traditionalists" (12.5%) require educational and behavioral strategies. "Pragmatists" (28%) require facilitative and directive behavioral oriented strategies. The largest group, termed "receptives" (57%) require facilitative behavior-oriented strategies and directive strategies.

Their conclusion was that 97% of clinicians require an approach beyond education. Therefore, the highly successful rewards program was implemented. In this institution, rewards prompted the nursing staff to become more proactive in discussing and prompting use of the protocols. The effort had a positive impact on physicians who supported collaborative efforts to revise and develop new protocols and nurses who now volunteer for protocol development projects. ■

What Happens To Removable Vena Cava Filters?

ABSTRACT & COMMENTARY

By David J. Pierson, MD, Editor

Synopsis: *Among 413 patients who underwent placement of a removable inferior vena cava filter following trauma for prophylaxis or treatment of pulmonary thromboembolism and survived to hospital discharge, subsequent removal of the filter was attempted in 116 of them and successful in only 91 (22%). Fewer patients were lost to follow-up at hospitals with policies requiring the service that placed the filters to follow them.*

Source: Karmy-Jones R, et al. *J Trauma.* 2007; 62(1):17-24.

Trauma surgeons at 21 institutions participated in this retrospective study of inferior vena cava filter (IVCF) placement and follow-up. A total of 599 IVCFs were placed at the 21 hospitals during the study year, 226 (0.8% of all admissions) at the 7 high-volume hospitals (> 2000 trauma cases admitted), and 373 (2% of all admissions, $P = 0.009$) at the 14 low-volume institutions. Of all IVCFs in the study (both permanent and removable), 74% were placed prophylactically—that is, in patients without evidence for pulmonary thromboembolism or deep-venous thrombosis.

Of the 599 IVCFs, 446 (79%) were removable filters. Ten of the 21 participating centers had policies whereby the trauma service followed up on the patients following IVCF placement, and coordinated removal. In 3 centers, these aspects were the responsibility of the service placing the filter, and in the remaining 8 centers no policies were in place. Of the 413 patients who had removable filters placed and survived to hospital discharge, filter removal was attempted in only 116 patients (28%), at 50 ± 61 (mean ± SD) days after placement. Filter removal was not actually carried out in 25 of these patients, because of technical difficulties or the presence of residual thrombus. Inability to remove the filter was more common with the Cordis Endovascular Optease filter (8/11 attempts) than with the Bard Recovery (9/50) and Cook Gunter-Tulip (8/54) filters ($P = 0.01$).

Losing the patient to follow-up was the most common reason for not attempting removal of the filter, and this was significantly more frequent in hospitals where the placing service was not required to follow up the patient (122 of 273 patients, 45%) than in the 3 institutions having this requirement (4 of 65 patients, 6%; $P = 0.001$). Among the other patients in whom filter retrieval was not attempted, the most common reasons for this were immobility (124 patients), other ongoing risk for recurrent thrombosis (12 patients), and persistence of deep venous thrombosis (11 patients).

COMMENTARY

This was not a prospective study, and the descriptions provided for case identification, patient follow-up, complication detection, and other aspects of the methods are fairly cursory. For this reason, the reported absolute complication rates and the differences between these among the various indications, institutions, and devices should be interpreted cautiously. However, despite the study's limitations, it conveys several important messages. The use of "removable" IVCFs has become widespread. Many (if not most) such devices are being placed prophylactically rather than because of the inability to adequately anticoagulate patients with known venous thromboembolism. Despite the attractiveness of the concept of removing the filter once the acute threat of thrombosis has passed, it is clear that this is not actually taking place in many (if not most) instances.

Although it may be argued that the risk of subsequent deep-venous thrombosis and other long-term vascular complications of IVCFs may be different with current devices as compared to those of a decade or two ago, the final word on this issue is certainly not in at present. The large number of patients lost to follow-up in this study is worrisome, in that these lost patients may also not be receiving therapy with anticoagulants and may be at increased risk for complications related to the filters.

Following up patients seen at major trauma centers is a difficult and complicated problem, for numerous reasons. However, this study's finding of much greater follow-up success at institutions with protocols for follow-up of patients with IVCFs by the service that placed them indicates that such continuity of care is possible, even for these challenging patients. ■

Which Mechanically Ventilated Patients Should Receive Bronchodilators?

ABSTRACT & COMMENTARY

By David J. Pierson, MD, Editor

Synopsis: *Of 206 intubated, ventilated medical ICU patients without evidence for obstructive lung disease or a known indication for bronchodilator therapy, 36% received inhaled albuterol and/or ipratropium bromide (usually every 4-6 h), at an added cost of about $450 per patient.*

Source: Chang LH, et al. Utilization of bronchodilators in ventilated patients without obstructive airways disease. *Respir Care.* 2007;52(2):154-158.

Inhaled bronchodilators are the cornerstone of managing acute airway obstruction, and their use in intubated, mechanically ventilated patients with asthma and COPD is a standard of care. However, inhaled bronchodilators are commonly administered to mechanically ventilated patients without known obstructive lung disease, perhaps because they have a history of smoking or simply for "routine" care. Clinical evidence for benefit from these drugs administered under such circumstances is lacking. Chang and colleagues at the University of North Carolina undertook this study to determine the prevalence of inhaled bronchodilator administration to mechanically ventilated medical patients without obstructive lung disease, as well as the costs associated with this practice.

The authors prospectively determined, in the medical ICUs of 2 tertiary-care academic medical centers, how often albuterol and ipratropium bromide were administered to intubated patients without a recognized indication who were ventilated for more than 24 h during a 6-month observation period. Clinical evidence of obstructive lung disease was defined as either a documented history of asthma or COPD; the presence of wheezing noted on ICU admission; or ongoing outpatient therapy with a bronchodilator prior to admission. In these units, bronchodilators were administered by metered-dose inhaler, and the investigators determined the number of individual inhalations administered to each patient. Cost assessment was based on pharmacy acquisition costs for the drugs plus the cost of respiratory therapist or nurse administration.

Of 435 intubated, ventilated patients admitted to the 2 ICUs during the study period, 137 had clinical evidence of obstructive lung disease and were thus excluded. Another 44 were ventilated for more than a day in another location, 37 were ventilated < 24 h, and 11 were ventilated on more than 1 occasion, leaving 206 patients with no evidence of obstructive lung disease who were ventilated > 24 h. Of these 206 patients, 74 (36%) received inhaled albuterol and/or ipratropium bromide; 65 of them received both agents. Most patients were administered the bronchodilators on a scheduled basis every 4-6 h, and in 58 of 74 (78%) the drugs were started within the first 3 d on the ventilator.

Patients who received bronchodilators had worse oxygenation (measured by arterial PO_2/FIO_2 ratio: 188 vs 238 mm Hg, $P = 0.004$) than those who did not, and were more likely to have pneumonia during their ICU admission (53% vs 33%, $p = 0.007$), However, there were no differences in age, sex, race, or APACHE II score between the 2 groups. Patients receiving bronchodilators had median duration of mechanical ventilation of 8 d (interquartile range, 4-14 d), compared to 3 d (2-8 d) for those not administered bronchodilators. Patients receiving bronchodilators were not more tachycardic, had no greater incidence of tachyarrhythmias, and did not require more potassium replacement, than patients not receiving them. There were no differences in the incidence of ventilator-associated pneumonia, tracheostomy, or mortality. Total extra cost for bronchodilator administration was $449.35 per patient.

COMMENTARY

The findings of this study are consistent with what goes on in the institution in which I practice. Many ventilated patients without known asthma or COPD wind up on inhaled bronchodilators, and once they are started they are seldom stopped as long as the patient remains in the unit. In our ICUs the agents used are generic albuterol and ipratropium bromide, but I have the impression that in many institutions more expensive, brand-name drugs are commonly used. Even if inhaled bronchodilators are not "expensive" in comparison with some of the other agents we use in the ICU, the time spent in delivering them takes the respiratory therapist or nurse away from other tasks, and that time is wasted if the therapy does not help the patient.

We tend to be less precise in using inhaled bronchodilators than we are in the administration of other kinds of drugs, not only in how they are ordered ("albuterol nebs q 4 h") but also in how we decide to start them and how infrequently we monitor their potential effects. Clinically important airway obstruction dur-

ing mechanical ventilation causes audible wheezing, prolongation of expiration, dynamic hyperinflation (measurable as auto-PEEP), high peak- and plateau airway pressures, increased work of breathing, and hemodynamic compromise.[1]

Studies have shown that these things can readily be monitored at the bedside,[2,3] and that whether bronchodilators are having a detectable effect can be determined objectively. As demonstrated in these and other studies, attempting to predict which ventilated patients will show measurable improvement with bronchodilators is generally unsuccessful. Thus, it is reasonable to do a therapeutic trial, and to continue bronchodilator administration if wheezing is clearly reduced, plateau pressures are decreased, auto-PEEP is diminished, or there is evidence of improvement in venous return from less hyperinflation. However, bronchodilators should not be given for days or weeks just because the patient is a smoker (only a minority of such individuals have COPD), is elderly, or has respiratory secretions.

Numerous studies have compared small-volume nebulizers and metered-dose inhalers for delivering inhaled bronchodilators—in various settings and patient populations, including with intubated, ventilated ICU patients—and their results consistently show these devices to be therapeutically equivalent.[4] Metered-dose inhalers are generally less expensive and do not require interruption of the ventilator circuit for administration, but the choice of device is not as important as assuring that it is used correctly. A common mistake is to shake the metered-dose inhaler, place it in line, and then rapidly give several puffs into the circuit; this essentially gives one puff of medication and several additional puffs of propellant. The scientific background and practical application of aerosol administration during mechanical ventilation have recently been reviewed in detail.[4] ■

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Special Feature

Clinical Research and Healthcare Insurance

By Stephen W. Crawford, MD

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Dr. Crawford reports no financial relationship to this field of study.

MANY OF THE RECENT ADVANCES IN INTENSIVE care have been the product of large clinical trials. Over the years, randomized studies have demonstrated agents and modalities that impact survival of our sickest patients. Some examples of clinical trials that have influenced our care in the ICU include the use of erythropoietin to prevent anemia, prophylaxis of gastric stress ulcers, treatment of severe sepsis with corticosteroids and drotrecogin alfa, prevention of ventilator-associated pneumonia with elevation of the head of the bed, and decreasing ventilator-associated lung injury with low-tidal-volume, lung-protective ventilation, among others.

If the past is any predictor of the future, further advances in the ICU will rely on continued performance of clinical trials. While few critics will argue the value of clinical trials in intensive care, there are important questions about how these are funded. There are many discussions occurring at the national level about increased access to health insurance. What is the role of private healthcare insurance in clinical trials in the intensive care unit?

Clinical trials in the ICU have many benefits. The goal remains the improvement in care and improved survival rates. Other end points that are important in these studies are decreasing length of stay and, possibly, decreasing costs.

This issue of cost raises the concern that clinical trials are significantly more expensive to conduct than is routine clinical care. This question has been addressed in cancer clinical trials. Most assessments conclude that cancer clinical trials are either no more expensive, or minimally so, compared to standard treatments.[1,2] This finding may be viewed as somewhat surprising. Clinical trials are associated with additional expenses. These trials require additional testing, supplies, and personnel

for data management.

Society and future patients may benefit from clinical trials. It is possible that reduced overall costs of care may result from the advances. These costs savings could result from decreased complications and length of stay. For third party payers, such as insurance companies, this should be a valid reason to consider supporting clinical trials. However, for most health plans, clinical trials in the ICU are not covered benefits.

Changing Nature of Healthcare Insurance

Many of the traditional healthcare insurance companies are increasingly less and less involved in insuring the health of the members of their plans. They are increasingly becoming providers of healthcare-related services. Many citizens continue to think of the familiar companies, like CIGNA, Aetna, United Resource Network and Blue Cross, as insurance companies. However, for some of these companies up to 70% of members are covered by self-funded employer plans. Employer groups have adopted a strategy of funding healthcare for their own employees in an effort to control costs. The traditional insurance companies provide the administrative services needed to operate these plans. These administrative services include case management, claims processing, medical director reviews, policy development, and appeal determinations, to name a few.

For these self-funded plans, although the member identifies the large healthcare insurance company as their insurer, in fact, the financial risk of the costs of care are retained by their employer. In an effort to control potential expenses, the employer groups are often actively involved in dictating the specific details of the benefit plan. It is this plan language that determines what medical procedures, supplies and services are benefits covered under the plan.

In many cases, clinical trial participation of any kind is excluded from coverage. It is considered to represent experimental, investigational or unproven care and not a benefit of a plan designed to provide for the standard healthcare needs of the employees. When clinical trials are covered, invariably these are limited to trials of cancer treatments, and only those performed according to specific rigorous safeguards and oversight.

Impact of Re-Insurance

Most of the self-funded employer groups have limited financial reserves to back the healthcare costs of the employees. In order to minimize the financial risk of a catastrophic case that could bankrupt the plan, they purchase insurance against such events. This re-insurance acts as a stop-loss against costs above a predetermined fixed cost.

For obvious financial reasons, the carriers that provide this re-insurance exert tight controls over the administration of this stop-loss coverage. Failure of the benefit coverage being provided strictly according to the language of the benefit plan results in a denial of coverage by the re-insurer for outlier costs above the stop-loss mark. In such cases, the catastrophic costs are borne by the employer group, or depending on the contractual arrangements, by the healthcare company administering the plan.

In either case, there is strong incentive on the part of everyone involved to be certain that procedures not covered in the plan are not authorized. Healthcare insurance company medical directors and administrators have limited latitude in the interpretation of benefit plan language as a result.

Is It Right?

Clinical trials benefit society and lead to advances in healthcare. Is it ethical to have participation in clinical trials limited by third-party payers? One question is: right for whom?

For the groups who are actually financing the healthcare services, they have an interest in seeing that their monies are spent for the healthcare needs of their employers. It can be argued that they do not have a financial obligation to fund research that does not directly benefit their company. These companies have financial and moral obligations to limit coverage to essential, basic healthcare needs of their beneficiaries.

As a result of the changes in the costs and funding mechanisms for healthcare in this country, to an increasing degree, the employers are dictating what medical care is paid for. As a result, clinical research funding in the private sector is being impacted by a form of rationing. Interestingly, this rationing is not being driven by the government or by large insurance companies. It is not the product of coordinated, thoughtfully considered, national policy. Rather, it is driven by employer groups, and driven by the "bottom-line," by money considerations.

Summary

The ICU represents a microcosm of the financial impact of changes in private healthcare insurance, in general. A shift to self-funded healthcare plans probably

makes it increasingly unlikely that clinical trials will be considered benefits covered by insurance. This leaves private industry and government funding as the major sources of support for clinical trials in the ICU. Perhaps it is time for a national discussion about the value and need for clinical trials in medicine. ■

NOTE: The views expressed are those of the author and do not necessarily reflect the views of CIGNA Healthcare.

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2. Fireman BH, et al. Cost of Care for Patients in Cancer Clinical Trials. *J Clin Oncol.* 2001;19:105-110.

CME / CNE Questions

5. **In the study by Angstwurm and colleagues, intravenous administration of selenium led to improvement in which of the following endpoints:**
   a. number of days on the ventilator
   b. number of days on dialysis
   c. 28 day mortality
   d. 60 day mortality
   e. incidence of nosocomial pneumonia

6. **The most successful method of motivating protocol compliance was a rewards program focused on:**
   a. house staff
   b. attending physicians
   c. ICU nurses
   d. nurses, physicians and respiratory therapists
   e. none of the approaches were successful

7. **In the study of trauma patients who had removable vena cava filters placed, what proportion of surviving patients had a subsequent attempt to remove the filter?**
   a. 12%
   b. 28%
   c. 42%
   d. 67%
   e. 85%

8. **Which of the following was/were associated with the use of inhaled bronchodilators in mechanically ventilated patients with no evidence of airway obstruction?**
   a. reduced total duration of mechanical ventilation
   b. decreased incidence of ventilator-associated pneumonia
   c. increased incidence of tachyarrhythmias
   d. better oxygenation as measured by PO_2/FIO_2 ratio
   e. none of the above

9. **To an increasing extent, the health care services and procedures that will be paid for by a patient's insurance coverage are being determined mainly by:**
   a. the Federal Government
   b. large insurance companies
   c. state regulations
   d. employers
   e. health care providers

10. **Which of the following advances in critical care practice have resulted from large clinical trials?**
    a. decreasing ventilator-associated lung injury with low-tidal-volume, lung-protective ventilation
    b. the use of erythropoietin to prevent anemia
    c. treatment of severe sepsis with corticosteroids and drotrecogin alfa
    d. all of the above
    e. none of the above

Answers: 5 (c); 6 (c); 7 (b); 8 (e); 9 (d); 10 (d)

CME / CE Objectives

After reading each issue of *Critical Care Alert*, readers will be able to do the following:

- Identify the particular clinical, legal, or scientific issues related to critical care.
- Describe how those issues affect nurses, health care workers, hospitals, or the health care industry in general.
- Cite solutions to the problems associated with those issues.

In Future Issues:

Prognosis in Family Conferences

PHARMACOLOGY WATCH

Supplement to Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.

Long-Awaited Torcetrapib Will Not Be Released, Too Risky

Torcetrapib, a cholesteryl ester transfer protein (CETP) inhibitor, has been in development by Pfizer for nearly 15 years. The drug has been shown to elevate HDL levels while reducing LDL levels, prompting hopes that torcetrapib would be the first in a new class of important cholesterol medications. In December, Pfizer abruptly pulled the plug on further development of torcetrapib when the Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events trial showed an increase in death from all causes associated with the drug, including an increased rate of cardiovascular events and hypertension. A new study points out a possible mechanism for the lack of cardiovascular benefit. In the international study, 1,188 patients with cardiovascular disease underwent intravascular ultrasonography. They then received atorvastatin and were randomized to receive 60 mg of torcetrapib daily or placebo along with atorvastatin for 24 months. Atorva/torcetrapib resulted in a 61% relative increase in HDL and a 20% further reduction in LDL, resulting in an average HDL higher than LDL. But the drug combination was also associated with an increase in systolic hypertension of 4.6mm Hg, and more importantly an increase in atheroma volume of 0.12%, compared to an increase of 0.19% in the atorvastatin alone group (P = 0.72). The authors conclude that treatment with the CETP torcetrapib was associated with improved lipid endpoints, but was also associated with an increase in blood pressure and no significant decline in coronary atherosclerosis (*N Engl J Med.* 2007;356:1304-1316.). In an accompanying editorial, Dr Alan Tall holds out hope that other CETP inhibitors may not show the same adverse effects but suggests that further development of this class of drugs needs to proceed with caution (*N Engl J Med*. 2007;356:1364-1366). ■

IBS-Drug Treatment Pulled, CV Side Effects

Tegaserod (Zelnorm), Novartis Pharmaceutical's drug for irritable bowel syndrome has been removed from the market by the FDA based on recent findings of increased risk of serious cardiovascular events associated with use of the drug. Tegaserod was approved in 2002 for women with irritable bowel syndrome whose primary symptom was constipation. It was given the additional indication in August 2004 for chronic constipation in men and women under the age of 65. Withdrawal was based on analysis of 29 studies involving more than 18,000 patients that showed a small, but statistically significant increase in the risk of cardiovascular side effects (0.1% serious adverse effects with tegaserod vs 0.01% with placebo). The FDA may allow continued use of the drug in a limited number patients for whom no other treatment options are available and the benefits of tegaserod outweigh the chance of serious side effects. The FDA may consider limited reintroduction of the drug at a later date if the population patients can be identified in whom the benefit of the drug outweighs the risk. ■

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5431. E-mail: jennifer.corbett@ahcmedia.com.

Drug Combo Better for Migraine Treatment

Naprosyn plus sumatriptan is better than either drug alone for the treatment of acute migraine according to a new report. In 2 studies, nearly 3,000 patients with a history of migraine were randomized to sumatriptan 85 mg plus naproxen sodium 500 mg, both drugs alone, or placebo to be used after the onset of a migraine with moderate to severe pain. The primary outcome was headache relief at 2 hours, absence of photophobia, absence of phonophobia, absence of nausea, and sustained pain-free response. Sumatriptan plus naproxen was superior to placebo in all measures and was superior to either drug alone in sustained pain-free response. The incidence of adverse effects was the same for the combination as for the individual medications. The authors conclude that sumatriptan 85 mg plus naproxen 500 mg as a single pill for acute treatment of migraine is more effective than either drug as monotherapy (*JAMA*.2007; 297:1443-1454.). Pozen Pharmaceuticals/ GlaxoSmithKline is developing the combination pill, which is expected to be approved later this year under the trade name Trexima. ■

Pergolide Off the Market, Heart Disease Risk

Pergolide (Permax) is being withdrawn from the market after reports of serious valvular heart disease associated with the drug. Pergolide is a dopamine agonist used for the treatment of Parkinson's disease, hyperprolactinemia and pituitary tumor (?). The action was prompted by 2 reports in the January 4, 2007, *New England Journal of Medicine* that showed increased rates of valvular dysfunction in Parkinson's patients who were taking the drug. These findings coupled with the availability of other dopamine agonists prompted the FDA's action. Valeant Pharmaceuticals is removing Permax brand pergolide as are all generic manufacturers. ■

Hormone Treatment, Does Timing Matter?

Further analysis of the Women's Health Initiative suggests that the timing of the initiation of hormone therapy may have an effect on the risk of cardiovascular disease. The analysis looked at postmenopausal women who had undergone a hysterectomy and were randomized to conjugated estrogen or placebo and women who had not had a hysterectomy who were randomized to conjugated estrogen plus medroxyprogesterone or placebo. The main outcomes were coronary heart disease (CHD) and stroke. Women who initiated hormone therapy within 10 years of menopause had a lower incidence of CHD (HR 0.76 [95% CI, 0.50-1.16]), which equates to 6 fewer events per 10,000 person-years. For women who initiated therapy 10-19 years after menopause the hazard ratio was 1.10 (95% CI, 0.84-1.45), and for women who initiated therapy 20 years after menopause the hazard ration was 1.28 (95% CI, 1.03-1.58) or 12 excess events per 10,000 person years. CHD risk increased when patients were stratified by age as well. Hormone therapy increased the risk of stroke with no significant difference based on time since menopause or age. There was a non-significant trend for improved overall mortality in younger women. The authors conclude that women who initiated hormone therapy closer to menopause had a reduced risk of CHD, with an increase risk among women more distant from menopause although the trends did not meet their criteria for statistical significance (*JAMA*. 2007:297;1465-1477.). ■

FDA Actions

The FDA has approved Cangene's immune globulin to prevent reinfection with the hepatitis B virus in certain liver transplant patients. The product was previously approved for preventing hepatitis B infection after exposure in 2006. It is marketed as HepaGam B.

The FDA has banned rectal suppositories that contain trimethobenzamide due to lack of efficacy in preventing nausea and vomiting. The popular suppositories have been marketed under various trade names including Tigan, Tebamide, T-Gen and others. The drug will still be available as oral and injectable preparations. The evaluation which eventually led to the withdrawal is part of the FDA's ongoing Drug Efficacy Study Implementation (DESI) which evaluates older drugs previously approved based on safety data to make sure that they are also effective.

The FDA has approved Merck's combination diabetes drug Janumet, which combines sitagliptin with metformin. Sitagliptin, which is a dipeptidyl peptidase-4 inhibitor, has been marketed by Merck since last October under the trade name "Januvia." The combination is approved for the treatment of patients with type 2 diabetes; it should be dosed twice daily with meals with gradual dose escalation. ■