EVIDENCE-BASED INFORMATION FOR HOSPITALISTS, INTENSIVISTS, AND ACUTE CARE CLINICIANS

HOSPITAL MEDICINE ALERT

AHC Media LLC Home Page—www.ahcpub.com

CME for Physicians—www.cmeweb.com

AHC Media LLC

INSIDE

Can we improve our vasopressor management in patients with septic shock **page 26**

Blood clots and "the patch" **page 27**

Value of volume expansion in cardiac tamponade **page 29**

A new drug for rapid conversion of atrial fibrillation **page 30**

Survival from In-Hospital Cardiac Arrest is Worse at Night/Weekends

ABSTRACT & COMMENTARY

By David J. Pierson, MD

Professor, Pulmonary and Critical Care Medicine, Harborview Medical Center, University of Washington

Dr. Pierson reports no financial relationships relevant to this field of study. This article originally appeared in the May 2008 issue of Critical Care Alert. It was edited by David J. Pierson, MD, and peer reviewed by William Thompson, MD. Dr. Thompson is Staff Pulmonologist, VA Medical Center; Associate Professor of Medicine, University of Washington. Dr. Thompson reports no financial relationships relevant to this field of study.

Synopsis: *This study of a very large prospective series of cardiac arrests in over 500 US hospitals found that survival rates were lower during nights and weekends, differences that persisted despite adjustments for patient, resuscitation event, and hospital characteristics.*

Source: Peberdy MA, et al. Survival from in-hospital cardiac arrest during nights and weekends. *JAMA*. 2008;299:785-792.

THIS STUDY SOUGHT TO DETERMINE WHETHER THE OCCURRENCE of in-hospital cardiac arrest at night and on weekends was associated with worse outcomes compared to arrests during day/evening shifts and on weekdays. Peberdy and colleagues used data from the National Registry of Cardiopulmonary Resuscitation, a prospective registry of in-hospital resuscitation events sponsored by the American Heart Association. At each of 507 participating hospitals, specially trained quality improvement personnel prospectively recorded extensive data on each adult cardiac arrest, including the time and day of the week, as well as initial electrocardiographic rhythm, aspects of the resuscitation attempt, return of circulation, survival at 24 hours and to hospital discharge, and neurological outcome. Day/evening was defined as the interval from 7:00 am to 10:59 pm, and night from 11:00 pm to 6:59 am. Weekends were the period from 11:00pm Friday to 6:59 am Monday. In patients with more than one resuscitation event in the database, only the initial cardiac arrest was included.

Financial Disclosure

Hospital Medicine Alert's physician editor, Kenneth P. Steinberg, MD, has no relevant financial relationship related to the material presented in this issue.

Hospital Medicine Alert's physician editor, Kenneth P. Steinberg, MD, selected and reviewed the articles contained within this issue on May 15, 2008.

VOLUME 3 • NUMBER 4 • JUNE 2008 • PAGES 25-32

NOW AVAILABLE ONLINE
www.ahcmedia.com

Between January 1, 2000 and February 1, 2007, data from 86,748 consecutive cardiac arrests were included; 58,593 (68%) during day/evening hours and 28,155 (32%) at night. Patients who had cardiac arrests at night were less likely to have telemetry or other electrocardiographic monitoring, or to have their arrests witnessed, than those who arrested during day/evening hours. Asystolic arrests were substantially more common at night than during day/evening (39.6% vs 33.5%), whereas pulseless electrical activity and ventricular fibrillation/ventricular tachycardia were less common at night (34.6% vs 36.9% and 19.8% vs 22.9%, respectively; all differences $P < 0.001$).

Patients who arrested at night had poorer survival to discharge than those who arrested during day/evening hours (14.7% vs 19.8%; unadjusted odds ratio for failure to survive, 1.43, with 95% confidence interval 1.38-1.49.). Rates of initial return of spontaneous circulation, and also of survival to 24 hours, showed similar results. A favorable neurological outcome occurred in 11.0% of patients who arrested at night, as compared with 15.2% of patients who arrested on days/evenings (OR, 1.45; 95% CI, 1.39-1.52).

Among cardiac arrests occurring during day/evening hours, survival was significantly better on weekdays than on weekends (20.6% vs 17.4%), whereas this difference in survival between weekday and weekend arrests was not seen in patients whose arrests occurred at night (14.6% vs 14.8%). These survival differences between day/evening and night-time arrests, and between weekday and weekend arrests, persisted with adjustment of the data for potentially confounding patient, resuscitation event, and hospital characteristics.

COMMENTARY

It is not possible using the findings of this study to tell whether there may be biological differences between cardiac arrests occurring during the day and evening shifts and those that happen at night. Such differences could conceivably have contributed to the results, although a more plausible explanation is that the patients who arrested at night were not found as quickly, or resuscitated as well, as their day/evening counterparts. This contention, which should not surprise anyone who works in a hospital, is supported by the greater proportion of night-arresting patients whose first-detected rhythm was asystole — typically a late manifestation in arrests that are precipitated by ventricular fibrillation or other arrhythmia. In any case, biological differences could hardly account for the worse survival on weekend days and evenings as compared to arrests during the same hours during the week.

Peberdy et al rightly conclude that "it is reasonable to focus on the potential for decreased physical and psychological performance on the part of the health care worker, different staffing patterns, and less patient surveillance during nights and weekends as possible contributing factors in poorer survival at night." Not only do these explanations provide a rational explanation for the findings, but they also point toward areas for possible intervention in efforts to decrease or eliminate the observed discrepancies. ■

Can We Improve Our Vasopressor Management in Patients with Septic Shock?

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. This article originally appeared in the May 2008 issue of Critical Care Alert. It was edited by David J. Pierson, MD, and peer reviewed by William Thompson, MD.

Synopsis: *This multi-center, randomized, double-blind clinical trial demonstrated that the addition of vasopressin to patients receiving norepinephrine for management of septic shock had no effect on mortality when compared to increasing the norepinephrine dose.*

Source: Russell JA, et al. Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med.* 2008;358:877-887.

Hospital Medicine Alert, ISSN 1931-9037, is published monthly by AHC Media LLC, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

SENIOR VICE PRESIDENT/GROUP PUBLISHER: Brenda Mooney.
ASSOCIATE PUBLISHER: Lee Landenberger.
MANAGING EDITOR: Leslie Hamlin.
MARKETING PRODUCT MANAGER: Shawn DeMario.

GST Registration Number: R128870672.

Periodicals postage paid at Atlanta, GA.

POSTMASTER: Send address changes to ***Hospital Medicine Alert***, P.O. Box 740059, Atlanta, GA 30374.

Back issues: $42. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

Subscriber Information

Customer Service: 1-800-688-2421
Customer Service E-Mail: customerservice@ahcmedia.com
Editorial E-Mail: leslie.hamlin@ahcmedia.com

Subscription Prices

United States
1 year with Free *AMA PRA Category 1 Credits™*: $249
Add $17.95 for shipping & handling.
(Student/Resident rate: $125).
Multiple Copies
Discounts are available for group subscriptions, multiple copies, site-licenses or electronic distribution. For pricing information, call Tria Kreutzer at 404-262-5482.
Canada
Add GST and $30 shipping.
Elsewhere
Add $30 shipping.

Accreditation

AHC Media LLC is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

AHC Media LLC designates this educational activity for a maximum of *20 AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

This CME activity is intended for hospitalists, intensivists and acute care clinicians. It is in effect for 36 months from the date of the publication.

Questions & Comments

Please call **Leslie Hamlin**, Managing Editor, at (404) 262-5416 or e-mail at leslie.hamlin@ahcmedia.com between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

Despite the large role that vasopressors play in the management of septic shock, an unfortunately common problem associated with high mortality, few data exist to support using one vasopressor regimen over another. Existing data focus on narrow end points such as changes in blood pressure or renal function and do not include information on broader end points such as mortality. Russell and colleagues addressed this problem by conducting a multi-center, randomized, double-blind trial to determine whether adding vasopressin in patients already receiving low doses of norepinephrine improved mortality as compared to increasing the norepinephrine dose.

Russell et al included patients over the age of 16 who had septic shock, had not responded to fluid administration, and required vasopressors including low-dose norepinephrine (> 5 µg/min). Patients were excluded if they had active myocardial ischemia or heart failure. Patients were stratified a prior as having "less severe" shock (requiring treatment with 5-14 µg/min of norepinephrine) or "more severe" shock (requiring treatment with >15 µg/min of norepinephrine). Patients were randomized to receive either vasopressin 0.03 U/min or norepinephrine at a dose of 5-15 µg/min. At the same time patients received these study drugs, nurses titrated open-label vasopressors to maintain mean arterial pressures (MAP) of 65-75 mm Hg, with up-titration of these open-label agents performed only if the target MAP was not achieved at the maximal dose of the study drugs. When the target MAP was achieved, open-label vasopressors were titrated off before tapering of the study drugs commenced. Study drug infusions were stopped if patients developed acute ST elevations, life-threatening arrhythmias, acute mesenteric or digital ischemia, or hyponatremia (sodium < 130 mmol/L). The primary end point of the trial was 28-day mortality. Russell et al also examined 90-day mortality, the incidence of adverse events, and whether outcomes varied based on the severity of illness.

A total of 779 patients were included in the study. The 396 patients in the vasopressin group and the 382 patients in the norepinephrine group were well-matched except for a slight difference in age between the two groups. Of note, at the time of enrollment, the mean arterial pressures in the vasopressin and norepinephrine groups were 73 ± 10 and 72 ± 9 mm Hg, respectively. There was no significant difference between the vasopressin and norepinephrine groups in 28-day mortality (35.4% vs 39.3%, $P = 0.26$), 90-day mortality (43.9% vs 49.6%, $P = 0.11$) or the rates of serious adverse events (10.3% vs 10.5%, $P = 1.0$). When outcomes were examined according to the severity of illness, mortality at 28 days in patients with less severe septic shock was lower in the vasopressin group (26.5% vs 35.7%, $P = 0.05$), but there were no significant differences between treatments for patients with more severe disease (44% vs 42.5%, $P = 0.76$).

COMMENTARY

On the surface, this study is exactly the type of trial we need more of in critical care medicine. It focuses on a common problem and on commonly used therapeutic agents for which we currently lack sufficient data regarding their optimal use. Unfortunately, however, this particular trial does nothing to clear up questions regarding optimal vasopressor management in septic shock. A critical aspect of the study was the fact that the average MAP, at the time the study drugs were initiated, was 72-73 mm Hg, a value well above the level (65 mm Hg) most practitioners would consider adequate in septic shock. As a result, the data reveal little about how to manage septic shock in patients who are refractory to catecholamines and, instead, only help us decide whether vasopressin can have a catecholamine-sparing effect in patients who have an adequate blood pressure on such agents. The fact that 28-day and 90-day mortality did not differ between the treatment groups suggests that vasopressin may, in fact, have a catecholamine-sparing effect but, given that the incidence of adverse events was equal between the two groups, it is not clear that such an effect is of any real clinical significance. In the absence of such a benefit, it is hard to justify the additional time demands on pharmacy and nursing staffs and the financial cost to the patient associated with adding the second vasopressor if they already have an adequate MAP.

In the end, this study does not do much to advance our knowledge about how to manage patients with septic shock. We are still left with the major questions regarding vasopressor management that we had before this trial: what is the best first-line vasopressor for patients with septic shock refractory to fluid administration and what is the optimal second-line vasopressor for those patients who fail to respond to first-line agents? This trial by Russell et al shows that it is possible to study these questions in a multi-center framework, but more work is necessary before we have hard evidence to guide clinical practice. ■

Blood Clots and "The Patch"

ABSTRACT & COMMENTARY

By Alison Edelman, MD, MPH

Assistant Professor, Assistant Director of the Family Planning Fellowship Department of Obstetrics & Gynecology, Oregon Health & Science University, Portland

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

This article originally appeared in the May 2008. It was edited by Leon Speroff, MD, and peer reviewed by Catherine LeClair, MD. Dr. Speroff is Professor of Obstetrics and Gynecology, Oregon Health and Science University, Portland, and Dr. LeClair is Assistant Professor, Obstetrics and Gynecology, Oregon Health and Sciences University; both report no financial relationships relevant to this field of study.

Synopsis: *The risk of venous thromboembolism was double in users of a transdermal contraceptive as compared to users of an oral contraceptive with a 35 mcg ethinyl estradiol component. Warning: no abstract skimming — it's worth your while to keep reading!*

Source: Cole JA, et al. Venous thromboembolism, myocardial infarction, and stroke among transdermal contraceptive system users. *Obstet Gynecol*. 2007;109:339-346.

Cole and colleagues used two years of insurance claims data from a large national health insurer (confirmed with medical records) to determine incidence of venous thromboembolism in women exposed to a transdermal contraception (Ortho Evra®) vs a norgestimate-containing oral contraceptive with a 35 µ ethinyl estradiol component.[1] This case-controlled study found 57 cases of venous thromboembolism (VTE; 20 cases in patch-users and 37 in pill-users) out of 340,377 women who were dispensed at least one cycle of medication (OR 2.2, 95% CI 1.3-3.8). After excluding high-risk factors (recent trauma, pregnancy, recent surgery, postoperative complications, anticoagulant, or antithrombolytic therapy), the odds ratio increased slightly to 2.4 (95% CI 1.1-5.5).

COMMENTARY

Many of you recently received a mailing regarding an update in prescribing information for Ortho Evra®.[2] This letter contained a summary of the current literature regarding venous thromboembolism (VTE) and transdermal patch use. I assume these types of mailings provide some liability safeguard for the company. However, I found the letter to be clinically unhelpful and downright scary. If I didn't know any better, my first inclination after reading the letter would be to stop prescribing the patch.

So let's review the literature: to date, there have been three published studies specifically focusing on VTE risk and patch use. As mentioned above, Cole et al found a statistically significant increased risk of VTE in patch users, with an odds ratio of 2.4 (95% CI 1.1-5.5).[1] Jick and colleagues performed a case-control study using a database from PharMetrics, a company that collects information on claims paid by managed care plans. They also compared patch users to users of a norgestimate-containing oral contraceptive with a 35 µ ethinyl estradiol component, and found no increased risk of VTE in patch users (OR 0.9, 95% CI 0.5-1.6).[3] A follow-up study to this one was recently published which included 17 months of additional data using the same database and again, no significant increase in VTE risk for patch users was demonstrated (OR 1.1. 95% 0.6-2.1).[4] Just to muddy the waters further, a post-marketing surveillance program using the same database as Jick et al released information on the patch compared to a levonorgestrel-containing oral contraceptive with a 30 µ ethinyl estradiol component and found an increased risk of VTE in patch users (OR 2.0, 95% CI 0.9-4.1).[5]

Is it plausible that the patch has a slightly increased VTE risk compared to other estrogen containing hormonal contraception? Possibly. A small pharmacokinetic study comparing the patch, the contraceptive vaginal ring, and a combination OC with a 35 µ ethinyl estradiol component, the patch was found to have a greater area under the curve but a lower ethinyl estradiol peak level than the OC.[6] It is unknown how these pharmacokinetic differences affect VTE risk. The patch also contains a third-generation progestin. Although controversial, third-generation progestins have been linked to a slightly higher risk of VTE as compared to first- or second-generation progestins.[7-9] This would explain the difference in risk found by the post-marketing surveillance program[5] mentioned earlier, but not the findings reported in Cole's study.[1] Finally, thrombosis biomarkers are affected by estrogen-containing hormonal contraception, but differences exist between OCs vs the patch as to which markers change and by how much.[10] It is unclear how this affects VTE risk.

So what does all this mean? The increased risk of VTE with the use of an estrogen-containing contraceptive is not a surprise. We already knew that OC users have a slightly increased risk of VTE as compared to non-users (4-5 cases vs 12-20 cases per 100,000 women per year).[11] However, VTE risk in OC users is still signif-

icantly lower than compared to pregnancy (48-60 cases per 100,000 women per year). Using the most conservative estimate that the patch "doubles the risk" of VTE, the risk is still lower in patch users than in pregnancy. Thus, even with this conflicting data, the patch remains a safe and effective method of contraception — one that I will continue to prescribe until further evidence to the contrary emerges.

Finally, avoid the trap of using language that can inflate a patient's perception of risk. Although "double the risk" is easy to remember and statistically correct when comparing an odds ratio that increases from 1 to 2, it does not accurately reflect what the VTE risk is for an individual patient. "Double the risk" of a rare event is still a rare event when looking at actual case numbers.

Clinical Tips:

- Estrogen contraception (patch, ring, OCs) should be avoided in women with VTE risk.
- VTE risk should always be discussed and documented with any woman starting an estrogen-containing hormonal contraceptive.
- VTE risk is slightly increased with any use of an estrogen-containing hormonal contraceptive but this is significantly less then the risk of VTE in pregnancy.
- The VTE risk with the contraceptive patch vs OCs may be similar or slightly increased but overall is still low.
- VTE risk in nonusers 4-5 cases per 100,000 women per year
- VTE risk in OC users 12-20 cases per 100,000 women per year
- VTE risk in patch users 12-20 vs 24-40 cases per 100,000 women per year
- VTE risk in pregnancy 48-60 cases per 100,000 women per year. ■

References

1. Cole JA, et al. Venous thromboembolism, myocardial infarction, and stroke among transdermal contraceptive system users. *Obstet Gynecol*. 2007;109:339-346.
2. Ortho Women's Health & Urology. Letter: Ortho Evra Important Prescribing Information. Feb 2008.
3. Jick SS, et al. Risk of nonfatal venous thromboembolism in women using a contraceptive transdermal patch and oral contraceptives containing norgestimate and 35 µg of ethinyl estradiol. *Contraception*. 2006;73:223-228.
4. Jick S, et al. Further results on the risk of nonfatal venous thromboembolism in users of the contraceptive transdermal patch compared to users of oral contraceptives containing norgestimate and 35 µg of ethinyl estradiol. *Contraception*. 2007;76:4-7.
5. Boston Collaborative Drug Surveillance Program. Postmarketing study of ORTHO EVRA and levonorgestrel oral contraceptives containing hormonal contraceptives with 30 µg of EE in relation to nonfatal venous thromboembolism, ischemic stroke, and myocardial infarction. Accessed March 27, 2008 http://www.clinicaltrials.gov/ct2/show/NCT00511784.
6. van den Heuvel MW, et al. Comparison of ethinylestradiol pharmacokinetics in three hormonal contraceptive formulations: the vaginal ring, the transdermal patch and an oral contraceptive. *Contraception*. 2005;72:168-174.
7. Spitzer WO. The aftermath of a pill scare: regression to reassurance. *Hum Reprod Update*. 1999;5:736-745.
8. Lidegaard O. Thrombotic diseases in young women and the influence of oral contraceptives. *Am J Obstet Gynecol.* 1998;179:S62-67.
9. Lidegaard O, et al. Oral contraceptives and venous thromboembolism: a case-control study. *Contraception*. 1998;57:291-301.
10. Kluft C, et al. Comparison of a transdermal contraceptive patch vs. oral contraceptives on hemostasis variables. *Contraception*. 2007;77:77-83.
11. Speroff and Darney. A clinical guide for contraception. 4th Edition. Lippincott, Williams & Wilkins 2005. Philadelphia, PA.

Value of Volume Expansion in Cardiac Tamponade

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Professor of medicine, Chief of Clinical Cardiology, University of California, San Francisco

Dr. Crawford is on the speaker's bureau for Pfizer.

This article originally appeared in the May 2008 issue of Clinical Cardiology Alert. It was peer reviewed by Rakesh Mishra, MD, FACC. Dr. Mishra is Assistant Professor of Medicine, Weill Medical College, Cornell University; Assistant Attending Physician, NewYork-Presbyterian Hospital. Dr. Crawford serves on the speaker's bureau for Pfizer; he reports no financial relationships relevant to this field of study.

Source: Sagristà-Sauleda J, et al. Hemodynamic effects of volume expansion in patients with cardiac tamponade. *Circulation*. 2008;117:1545-1549.

INTRAVASCULAR VOLUME EXPANSION HAS LONG been advised as an effective temporizing technique for patients with cardiac tamponade prior to

drainage of the fluid, but there is little data supporting this practice. Thus, Sagrista-Sauleda and colleagues from Spain studied 49 patients with large pericardial effusions who were referred to the catheterization laboratory for drainage and who met hemodynamic criteria for cardiac tamponade (equalization of pericardial and right atrial pressure ± 2mmHg). Patients were excluded who were on hemodialysis, had significant valve disease, evidence of pericardial constriction, left ventricular dysfunction, pulmonary hypertension, or hyperacute cardiac tamponade due to aortic dissection or cardiac rupture. The patients ranged in age from 23-83 years, and 57% had physical signs of tamponade. Hypotension (systolic BP < 100) was noted in 20%. All were given 500 mL of normal saline over 10 minutes. Hemodynamics were repeated then and after pericardiocentesis. Volume expansion increased mean arterial pressure (from 88 to 94 mmHg, P < .003) and mean cardiac index (from 2.46 to 2.64, P = 0.13); however, cardiac index increased by 10% in 47%, was unchanged in 22%, and decreased in 31%. An increase in cardiac index was predicted by a low cardiac index and hypotension, but not with any other physical, hemodynamic, or echocardiographic findings. Also, volume expansion increased right atrial pressure (from 10-13 mmHg) and left ventricular end-diastolic pressure (from 14-19 mmHg) both P < .001. No clinical adverse effects of volume expansion were noted. Sagrista-Sauleda et al concluded that about half of patients with cardiac tamponade given volume expansion will increase their cardiac output, and this response is predicted by hypotension and a low cardiac index.

COMMENTARY

In many ways, these results make sense. With the heart tamponaded, how could much more volume get into it? Probably only if part of the patients problem is hypovolemia. Those in this study, with low cardiac indices and hypotension, were probably hypovolemic. In the rest of the patients, volume did little except raise intracardiac pressures. With normovolemia, what little fluid gets into the cardiac chambers significantly increases diastolic pressures because the chambers are on the steep portion of a pressure volume curve due to the resistive force of the increased pericardial pressure. In this study, only 500 mL of saline was administered, and no adverse effects were noted, except that cardiac index fell in 31%. However, one can imagine a situation where more fluid is given and pulmonary edema ensues. Thus, fluids should only be given to hypotensive cardiac tamponade patients who cannot be rapidly drained.

So another medical myth bites the dust. Most critical care physicians believe fluids are indicated as a first step in almost all cases of hypotension. This would apply to cardiac tamponade, but not hypotension, due to right ventricular infarction. In this situation, the RV is on a steep pressure volume curve due to the infarction, and fluids do little unless hypovolemia is present. These patients usually require pressors to increase RV output. So the common denominator of a beneficial response to fluids is the presence of hypovolemia. Low blood pressure may be a sign of hypovolemia, but not always. Elevated jugular veins are usually a sign of adequate or high filling pressures and might be a double check in hypotensive patients. Most patients with hemodynamically significant RV infarct have elevated jugular venous pressure and don't respond to fluids. Whether this rule would apply in cardiac tamponade is unknown. In this study, only 43% had elevated jugular veins on physical examinations, but we don't know if the others were among the 47% of patients who responded to fluids. Right atrial pressure was lower in those who responded to fluids, but this was not statistically significant.

Another consideration is low pressure cardiac tamponade where the pericardial pressure is < 7mmHg with near equal right atrial pressures. In this study, these patients did not consistently respond to fluids. Thus, hypotension appears to be the best guide to which cardiac tamponade patients would benefit from a modest fluid bolus if pericardial drainage is delayed. ■

A New Drug for Rapid Conversion of AF

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, PhD

Professor of Medicine, Division of Cardiology, University of Virginia, Charlottesville

Dr. DiMarco is a consultant for Novartis, and does research for Medtronic and Guidant. This article originally appeared in the May 2008 issue of Clinical Cardiology Alert. It was edited by Michael H. Crawford, MD, and peer reviewed by Rakesh Mishra, MD.

Source: Roy D, et al. Vernakalant hydrochloride for rapid conversion of atrial fibrillation: a phase 3, randomized, placebo-controlled trial. *Circulation*. 2008;117:1518-1525.

Vernakalant is a new investigational antiarrhythmic drug. The compound is relatively selective, blocking the early-activating potassium channel and the frequency-dependent sodium channel; it has a half-life of two to three hours. This study evaluates the ability of intravenous vernakalant to terminate acute onset atrial fibrillation (AF). Patients with sustained atrial fibrillation, with a duration from three hours to 45 days, were eligible for inclusion. Patients were hemodynamically stable, and had no history of sick sinus syndrome, marked QRS, or QT prolongation, or recent acute coronary syndrome, myocardial infarction, or cardiac surgery. Rate control therapy with AV nodal blocking agents was permitted prior to study drug infusion. Other antiarrhythmic drugs as background therapy were permitted. Patients received a ten-minute infusion of either vernakalant (3 mg/kg) or placebo, followed by a 15-minute observation period. Patients who did not convert received an additional 2 mg/kg dose of vernakalant or matching placebo. A Holter monitor continuously monitored the cardiac rhythm from screening to 24 hours after the last dose of study drug. Electrical cardioversion was permitted in nonresponders after two hours. The primary efficacy end point was the proportion of patients who had conversion to sinus rhythm, for at least one minute, within 90 minutes of drug administration. Patients were stratified by the duration of AF into two groups: short duration AF (3 hours to 7 days) and longer duration AF (8-45 days).

A total of 356 patients were randomized to either vernakalant or placebo. Twenty patients were withdrawn after randomization for various reasons. The mean age was approximately 62 years. Two hundred and twenty patients were in the short duration AF group and 116 patients were in the long duration AF group. Hypertension and ischemic heart disease were the most common cardiac diagnoses. Most patients were on some form of AV nodal blocking agent, and approximately 10% were receiving a class I or class III antiarrhythmic drug. In the short duration AF group, 75 of 145 vernakalant patients (51.7%) converted to sinus rhythm within 90 minutes, compared with three of the 75 placebo patients (4%; $P < 0.001$); patients with AF lasting 3-48 hours had a higher success rate (62.1%). Of the 75 patients who demonstrated conversion, 57 (76%) did so with the initial 3 mg/kg dose. The median time to conversion was 11 minutes, and only 75 of the vernakalant-treated patients who initially converted relapsed to atrial fibrillation within 24 hours. In contrast, only six of the 76 vernakalant patients in the longer duration AF group had termination of atrial fibrillation, compared with zero of the 40 placebo patients. Nineteen vernakalant patients (8.6%) converted to atrial flutter in the first 90 minutes; five patients subsequently converted to sinus rhythm. None of the episodes of atrial flutter were associated with 1:1 AV conduction. During 30-day follow-up, there were three deaths, all in the vernakalant group; however, none of the deaths were considered to be related to study drug. Adverse events were uncommon. There were four serious adverse events that were considered to be possibly or probably related to vernakalant. Two patients developed significant hypotension and one 90-year-old woman had complete heart block after electrical cardioversion 2.5 hours after completion of the second vernakalant infusion. There were no significant increases in ventricular arrhythmias associated with vernakalant, as well as no episodes of torsades de pointe or ventricular fibrillation in either group in the first 24 hours after drug administration. Notable adverse events in the vernakalant group included dysgeusia, sneezing, and nausea. The median duration for all of these adverse events was less than 15 minutes. Vernakalant had no significant effect on heart rate in patients who remained in atrial fibrillation. Vernakalant produced moderate increases in the QRS interval and in the QTc intervals.

Roy and colleagues concluded that vernakalant is an effective agent for rapid conversion of short duration atrial fibrillation. Serious adverse events were uncommon and minor adverse events were of short duration.

COMMENTARY

New or recent onset atrial fibrillation is a common problem in emergency rooms and among hospitalized patients. Although transthoracic cardioversion is highly effective, cardioversion requires anesthesia or sedation and may be complicated by immediate or early recurrence of AF. Current pharmacologic options for acute conversion are limited. Oral flecainide or propafenone may be used in patients with little or no structural heart disease. Intravenous ibutilide is more effective than procainamide, but ibutilide may cause torsades de pointes, and requires careful monitoring. Amiodarone and dofetilide may convert AF; usually, multiple doses are required. In this paper, Roy et al show that vernakalant, a multichannel blocker, is moderately effective and fairly safe when used to convert AF episodes of recent onset. As with other drugs, the efficacy rate is greatest in those with very recent onset, but these patients are frequently seen by physicians

since they can become very symptomatic at the start of the episode. Based on the data in this paper, the FDA Cardio-Renal Advisory Committee recently voted in support of the market release of vernakalant for patients with AF. It's likely that it will largely replace ibutilide as the intravenous drug of choice for atrial fibrillation. However, ibutilide may remain the first option for patients with atrial flutter. ■

CME Questions

10. In the study by Peberdy et al, the following observations about in-hospital cardiac arrest were made *except*:

a. patients who arrested at night had poorer survival to discharge than those who arrested during the daytime.
b. patients who arrested at night had poorer rates of return of spontaneous circulation than those who arrested during the daytime.
c. patients who arrested at night had more favorable neurological outcomes than those who arrested during the daytime.
d. Asystolic arrests were more common at night than during the daytime or evening.

11. According to the study by Sagrista-Sauleda et al, in patients with cardiac tamponade by hemodynamic criteria, a 500 mL saline infusion resulted in:

a. development of pulmonary edema in one-third of patients.
b. an improvement in mean arterial pressure and cardiac output in patients who were hypotensive.
c. an improvement in mean arterial pressure and cardiac output in all patients.
d. an improvement in mortality.

12. In the randomized, controlled trial by Russell et al, the addition of vasopressin in patients with septic shock on norepinephrine was associated with:

a. an overall improved rate of survival.
b. an increased risk of acute renal failure.
c. an improvement in survival for those patients with severe septic shock.
d. an important in survival for those patients with mild septic shock.

Answers: 10. (c); 11. (b); 12. (d)

CME Objectives

The objectives of *Hospital Medicine Alert* are to:

• review pertinent safety, infection control, and quality improvement practices;

• discuss diagnosis and treatment of acute illness in the hospital setting; and

• review current data on diagnostic and therapeutic modalities for common inpatient problems. ■

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.

New Study on Thiazolidinediones May Show Benefits

In this Issue: Pioglitazone and heart disease; ARBs manufacturers spend millions to show the non-inferiority of their products compared to less expensive, generic ACE inhibitors; some athletes turn to growth hormone because it is difficult to detect; FDA Actions

The thiazolidinediones rosiglitazone (Avandia) and pioglitazone (Actos) have taken their lumps in the last year, with evidence associating drugs with increased risks of heart failure. Rosiglitazone has also been associated with increased cardiovascular mortality, while evidence suggests that pioglitazone may actually improve cardiovascular outcomes. Now a new study compares pioglitazone with the sulfonylurea glimepiride measuring the progression of coronary atherosclerosis in patients with type 2 diabetes. A total of 543 patients with type 2 diabetes and coronary disease underwent coronary intravascular ultrasonography and were then randomized to receive glimepiride 1 to 4 mg daily or pioglitazone 15 to 45 mg daily for 18 months with titration to a maximum tolerated dosage. Intravascular ultrasonography was repeated in 360 patients at completion of the study. The primary endpoint was percent change in atheroma volume (PAV). Patients were also treated with standard therapy (statins, renin-angiotensin blockers, and aspirin). Glimepiride resulted in an increase in PAV of 0.73% (95% CI, 0.33%-1.12%) while pioglitazone decreased PAV by 0.16% (95% CI, -0.57% to 0.25%) (*P*=.002). Blood sugar control as measured by HbA1c was similar in both groups. Pioglitazone also resulted in increase in HDL cholesterol of 5.7 mg/dL compared to 0.9 mg/dL for glimepiride (P<.001), and pioglitazone lowered triglyceride levels an average of 16.3 mg/dL compared to an increase of 3.3 mg/dL with glimepiride (*P* <.001). Hypoglycemia was more common in the glimepiride group while edema, fractures, and decreased hemoglobin levels were more frequent in the pioglitazone group. The authors conclude that in patients with type 2 diabetes and coronary artery disease, pioglitazone slows progression of coronary atherosclerosis compared to glimepiride (*JAMA* 2008; 299: 1561-1573). An accompanying editorial points out that outcomes such as those found in the study may not translate to improving cardiovascular outcomes, however the results are consistent with a modest clinical benefit demonstrated in the PROACTIVE trial (*JAMA* 2008; 299:1603-1604).

ARBS effective as ACE?

Are angiotensin-receptor blockers (ARBs) as effective as angiotensin-converting-enzyme (ACE) inhibitors in reducing vascular events in high-risk patients? Manufacturers of ARBs have spend millions trying to show the non-inferiority of their products compared to the less expensive, generic ACE inhibitors. The current entry funded by Boehringer Ingelheim, the ONTARGET trial, com-

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) 262-5413. E-mail: iris.young@ahcmedia.com.

pares their product telmisartan (Micardis) with the ACE inhibitor ramipril. In this large double-blind randomized trial of 25,000 patients with vascular disease or high risk diabetes, over 8500 patients received ramipril 10 mg per day, telmisartan 80 mg per day, or the combination of both drugs. The primary outcome was death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure. Mean blood pressure was slightly lower in the telmisartan and combination therapy group than in the ramipril group. After a median follow-up of 56 months, the primary outcome occurred in 16.5% of the ramipril group, 16.7% of the telmisartan group, and 16.3% of the combination group. The ramipril group had a higher incidence of cough and angioedema, while the telmisartan group had a higher rate of hypotensive episodes. The combination group had a higher risk of hypotensive episodes, syncope and renal dysfunction compared to the ramipril group. The authors conclude that valsartan was equivalent to ramipril in patients with vascular disease or high risk diabetes, and was associated with less angioedema. There was no benefit in the combination of the two drugs (*NEJM* 2008; 358: 1547-1559). An accompanying editorial points out the difficulty in interpreting non-inferiority trials. In this study telmisartan preserved 94% of the benefit of 10 mg of ramipril (95% CI, 85 to 105). It is also the fourth trial showing that combinations of ACE inhibitors and ARBs are of no value in reducing cardiovascular events compared to ACE inhibitors alone. The author concludes that the ARBs provide a similar benefit to prevent ACE inhibitor therapy; however "because ARBs are more costly than ACE inhibitors and have more side effects, their primary value is as an alternative for patients who cannot tolerate ACE inhibitors because of cough." (*NEJM.* 2008; 358:1615-1616).

Athletes and Growth Hormone

As testing for performance-enhancing drugs becomes more prevalent in sports, some athletes have turned to growth hormone because it is difficult to detect. Touted as an anabolic agent that improves athletic performance, the drug is also associated with significance side effects including diabetes, hepatitis, and acute renal failure. Recently a group from Stanford performed a meta-analysis of 44 articles describing 27 study samples in which 303 participants received growth hormone representing 13.3 person-years of treatment. Participants were average 27 years old with lean body mass and physically fit. Lean body mass increased with growth hormone compared to participants who did not receive it (increase 2.1 kg 20.1 kg [95% CI, 1.3 to 2.9 kg]), however strength and exercise capacity did not improve. Lactate levels during exercise were statistically significantly higher in two of three studies, and growth hormone treated participants experienced soft tissue edema and fatigue more often than those who did not receive it. The authors conclude that claims that growth hormones enhance physical performance are not supported by the scientific literature. The drug may increase body mass but it is does not improve strength, and it may worsen exercise capacity and adverse events (*Ann Int Med,* early online release 18 March 2008, print date 20 May 2000).

FDA Actions

Cefixime (Suprax), the only CDC recommended oral treatment for gonorrhea, is now available for the first time since 2002 in a 400 mg tablet. Wyeth Pharmaceuticals discontinued production of the drug when its patent expired. Now Lupin Pharmaceuticals has received FDA approval to market the 400 mg tablets. The company has been marketing the oral suspension since 2004. Cefixime 400 mg as a single dose is recommended treatment for all types of gonorrhea infections (urogenital, rectal, and pharyngeal).

The FDA has approved methylnaltrexone bromide (Relistor) for the treatment of opioid-induced constipation in patients with late stage, advanced illness who are receiving opiates on a continuous basis. The injectable medication is started on an every-other-day basis, then increased to once a day as needed.

The FDA has approved a new biologic, certolizumab (Cimzia) for the treatment of Crohn's disease. Certolizumab is a TNF blocker similar to other drugs used for this indication. The initial dose is one injection every two weeks for the first three injections, then decreasing to once every four weeks. Like other TNF blockers, certolizumab is associated with increased risk of serious infections, lymphomas, and other malignancies.

The FDA has investigated reports of increased depression in patients switched from Wellbutrin XL 300 mg to Teva's generic bupropion XL 300 mg (Budeprion). Nearly 80 patients of the thousands who were changed to the generic noted loss of antidepressant effect following the switch. The agency reevaluated bioequivalency studies and concluded that, although there are small differences in the kinetic profiles the two formulations they were within the establish boundaries of equivalents. They conclude that the generic is bioequivalent and therapeutically equivalent to the branded product. ■