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INSIDE

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Does Heliox Help in COPD Exacerbations?

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: *In this prospective, multicenter, randomized trial, addition of a helium-oxygen gas mixture to non-invasive positive pressure ventilation in the treatment of COPD exacerbations did not decrease the need for intubation when compared to non-invasive positive pressure ventilation alone.*

Source: Maggiore SM, et al. A multicenter randomized trial of noninvasive ventilation with helium-oxygen mixture in exacerbations of chronic obstructive lung disease. *Crit Care Med* 2010;38:145-151.

Previous studies have shown that addition of a helium-oxygen mixture (HeO_2) to non-invasive ventilation (NIV) in patients with COPD exacerbation improves dyspnea, work of breathing, and carbon dioxide elimination, but have yet to establish whether this approach is associated with improvements in other important clinical outcomes. Using a prospective, multicenter randomized study design, Maggiore and colleagues sought to address this gap in the literature and test the hypothesis that NIV combined with HeO_2 was associated with decreased need for intubation during COPD exacerbations when compared to NIV alone.

Patients were included in the study if they were between 18 and 85 years of age; had known or suspected COPD based on pulmonary function tests, blood gases, clinical history, or chest radiograph; had worsening dyspnea for 2 weeks or less; had $PaCO_2 > 45$ mm Hg; and had two or more of the following: respiratory rate > 24, pH < 7.35, and $PaO_2 < 50$ mm Hg on room air. Patients were excluded if they had respiratory arrest or need for immediate intubation, pneumothorax, a short life expectancy (< 1 month), high oxygen requirements, and a variety of other criteria.

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Enrolled patients were randomized to receive NIV plus HeO_2 or air-oxygen in addition to conventional medical treatment. All patients were treated with an FIO_2 of 0.35 and were started on an inspiratory pressure (IPAP) of 12-15 cm H_2O and an expiratory pressure (EPAP) of 5 cm H_2O with subsequent changes based on clinical status and blood gas results. NIV was not applied continuously and was, instead, applied intermittently for > 6 hours/day with clinicians free to decide how long and how often to use NIV each day. NIV was gradually discontinued when the total duration of NIV was < 6 hours/day. The decision to perform endotracheal intubation was based on pre-specified criteria that were well-defined in the study. The primary endpoint was the need for endotracheal intubation while secondary endpoints included total duration of NIV and invasive mechanical ventilation, length of ICU and hospital stay, 28-day mortality, and the incidence of adverse events.

A total of 204 patients were included in the study (102 per group). Sixty-four percent of the patients had a prior diagnosis of COPD while the remaining 36% were suspected of having the diagnosis at the time of admission. Patients in both groups received an average IPAP of 15.1 ± 4 cm H_2O and EPAP of 3.3 ± 2.0 cm H_2O. The total duration of NIV in the first 48 hours of admission did not differ between the two groups, with the HeO_2-treated patients receiving an average of 17.7 ± 9.8 hours compared to 18.8 ± 11.3 hours in the control group. A total of 56 patients in the study (27%) required intubation. The intubation rate was lower in the HeO_2 group (24.5%) compared to the control group (30.4%), but this difference was not statistically significant (P = 0.35). Statistically significant differences favoring HeO_2 were seen, however, in the subgroup of patients who required NIV for < 4 days (31% vs 53%). There were no statistically significant differences in the duration of mechanical ventilation, ICU and hospital length of stay, and mortality. Observed complications included facial skin necrosis, eye irritation, gastric distention, and nosocomial pneumonia, but there were no observed differences in the incidence of these complications between the two study groups.

■ COMMENTARY

Non-invasive positive pressure ventilation is now the standard treatment for patients who present with severe COPD exacerbations, as the treatment modality has been shown to decrease the need for intubation, shorten ICU length of stay, and improve mortality in such patients. The question is: Can we do better? The addition of HeO_2 to treatment regimens in these patients certainly makes physiologic sense — the less dense and slightly more viscous HeO_2 mixture leads to more laminar flow in obstructed airways and requires less pressure to drive ventilation — and has been shown to improve symptom-based and physiologic outcomes. Unfortunately, we still lack evidence that the therapy provides benefits over NIV alone with regard to other more important outcomes, including the need for intubation. Maggiore et al did show a trend toward improvement in this outcome measure but, as with a previous study that looked at this issue,[1] these results were not statistically significant. They did show a significant improvement in those patients who required NIV for < 4 days, but the utility of this finding is questionable, as it is very difficult to predict a priori the duration of therapy that will be required in a given patient.

Both of these studies share a problem in that they were small and likely underpowered and, as a result, potentially subject to Type II errors. The study by Maggiore and colleagues likely also suffered from their overly broad inclusion criteria that might have captured patients who did not truly have COPD (e.g., prior pulmonary function testing was not required for diagnosis and relatively young patients unlikely to have COPD were eligible for inclusion) and the fact that NIV practices and other aspects of care were not standardized across study sites. It is also unclear whether the choice of HeO_2 mixture (65% helium, 35% oxygen) was

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Questions & Comments

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appropriate and, in particular, whether mixtures with a lower FIO_2 and, therefore, lower density, might have yielded more benefit. The choice of this mixture is somewhat odd in that the observed hypoxemia in COPD exacerbations is typically due to areas of low ventilation-perfusion ratios rather than shunt and usually responds to only small increases in the FIO_2 well below the 35% level used in this study.

The fact that this and the prior study showed a trend toward improvement does provide a reasonable justification for conducting a larger trial to address this question, but until the results of such a trial are available, we should not be wheeling the heliox tanks to the bedsides of our COPD patients. Although the therapy is relatively benign in terms of the side effect profile, it is not cheap. At our institution, each K-sized tank costs roughly $150 and, depending on the intensity of use in a given patient, several tanks may be required each day. Granted, this expense may be offset by savings associated with decreased hospital and ICU length of stay, but before we embark on wholesale use of the therapy we should really wait for better evidence of benefit in important clinical outcomes. ■

Reference

1. Jolliet P, et al. Helium-oxygen versus air-oxygen noninvasive pressure support in decompensated chronic obstructive disease. *Crit Care Med* 2003;31:878-884.

Prevention and Treatment Bundle Reduced Incidence of *Clostridium difficile* Infection

ABSTRACT & COMMENTARY

By Leslie A. Hoffman, RN, PhD

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

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

Synopsis: *Use of checklist-themed prevention and treatment bundles reduced the incidence of* Clostridium difficile *infection by 40% when evaluated over a 21-month observation period.*

Source: Abbett SK, et al. Proposed checklist of hospital interventions to decrease the incidence of healthcare-associated *Clostridium difficile* infection. *Infect Control Hosp Epidemiol* 2009;30:1062-1069.

THE INCIDENCE, SEVERITY, AND COSTS OF *CLOSTRIDIUM difficile* infection (CDI) are increasing, creating a substantial burden for patients and institutions. Guidelines for prevention of CDI are complex and not consistently followed. This study evaluated an intervention designed to reduce the CDI incidence that consisted of two checklists with actions grouped into prevention and treatment bundles. The prevention bundle included actions to be taken by physicians, physician assistants, nurse practitioners, nursing staff, infection control practitioners, and environmental service personnel. Prevention strategies included specific monitoring and control practices, lab notification procedures, and steps to be taken by infection control and housekeeping services aimed at decreasing CDI transmission. The treatment bundle was designed to standardize treatment of CDI based on three categories (mild, moderate, severe). The checklist defined each category using specific criteria and identified recommended medications, consultations, scans, and duration of therapy for each category.

Surveillance data encompassed 1,047,849 patient-days at one institution (Brigham and Women's Hospital in Boston), including 431,264 pre-intervention patient-days and 616,585 post-intervention patient days. The incidence of CDI deceased from an average of 1.10 cases per 1000 patient-days (95% confidence interval [CI], 1.00-1.21) during the pre-intervention period to an average of 0.66 cases per 1000 patient-days (95% CI, 0.60-0.72) during the post-intervention period. This reduction was sustained for 21 months and amounted to a 40% decrease ($P < 0.001$). Tests sent for possible CDI increased significantly ($P < 0.001$). There was an increase in medical acuity with no change in mortality.

■ COMMENTARY

Findings of this study are notable for several reasons. The intervention resulted in a statistically significant, hospital-wide reduction in the incidence of CDI when evaluated over a 21-month period. The decrease was substantial (40%) and occurred despite an increase in patient acuity. The checklist developed for the project was concise (< 1 page) but comprehensive as it involved multiple levels of providers, e.g., the medical team, bedside nursing staff, infection control, and environmental services. Actions identified in the prevention and treatment bundles were designed to prevent transmission of CDI in an effective and timely manner. Checklist statements were written in an action-oriented format, e.g., "order stool for *C. difficile* toxin testing" (medical

team), "place dedicated stethoscope in patient room" (bedside nurse), "provide daily list of positive test results" (infection control), and "clean the room with a bleach-based agent" (housekeeping). The treatment bundle included recommended medications for each level of severity, suggested actions if there was no clinical improvement, and indications for infectious disease and general surgery consultations.

The checklist did not restrict the use of high-risk antibiotics because this was judged to require a high intensity of resources, making the intervention less cost-effective. This approach contrasts with prevention efforts that seek to employ antibiotic restriction. The intervention did attempt to increase medical team suspicion regarding CDI and resulted in a significant increase in CDI testing. The authors noted that, while testing has inherent costs, there is a cost to be paid in lives lost and money wasted, in decreased documentation and, hence, spread of CDI. The strategy seemed highly effective, judged by the reduction in incidence of CDI at this hospital and ability to sustain this reduction over time. ■

Do Antipsychotics Help with ICU Delirium?

ABSTRACT & COMMENTARY

By Andrew M. Luks, MD

Synopsis: *This small, randomized, placebo-controlled trial demonstrated that use of haloperidol or ziprasidone in mechanically ventilated medical and surgical ICU patients was not associated with adverse outcomes, but did not improve the number of days alive without delirium or coma.*

Source: Girard TD, et al. Feasibility, efficacy, and safety of antipsychotics for intensive care unit delirium. *Crit Care Med* 2010;38:428-437.

Although delirium is a common complication of critical illness associated with considerable morbidity and mortality and haloperidol is widely used for treatment of the problem, there are no controlled studies examining whether this or other medications are effective therapeutic modalities in ICU patients. Girard and colleagues conducted a randomized, controlled trial to determine if antipsychotic agents were safe and effective at treating delirium in mechanically ventilated patients with the larger goal of assessing whether a larger, multicenter trial is warranted to address these issues.

They enrolled mechanically ventilated adults (> 18 years) on sedative and/or analgesic medications in medical or surgical ICUs at six tertiary medical centers. Patients were excluded if they were pregnant, had been on mechanical ventilation > 60 hours, had no plan for gastric access within 48 hours, took antipsychotics as an outpatient, or had underlying neurologic diseases (ongoing seizures, recent stroke, dementia, or anoxic brain injury), or other problems such as severe heart failure, predisposition to tachyarrhythmia, or severe electrolyte abnormalities. Enrolled patients were then randomized to one of three treatments (haloperidol 5 mg, ziprasidone 40 mg, or placebo) every 6 hours for up to 14 days, after which time all study drugs were discontinued. Short-term use of IV formulations was permitted if gastric access had not been established but study drugs were otherwise administered orally or via nasogastric tube.

Patients were evaluated twice daily for the presence of delirium and their level of sedation using the Confusion Assessment Method for the ICU (CAM-ICU) and Richmond Agitation-Sedation Scale (RASS), respectively. Dosing frequency was reduced or the study drug was discontinued according to a pre-specified protocol if patients were CAM-ICU negative on consecutive assessments or had evidence of over-sedation. Study drug could be restarted or the dosing frequency increased if patients developed recurrent delirium following such changes. The managing ICU teams determined all other treatments, including the approach to sedation, and could use open-label antipsychotic medications for severe agitation or delirium. The primary endpoint was the number of days alive without delirium or coma during the 21-day study period, while secondary endpoints included the duration of coma or delirium, ventilator-free days, time to ICU and hospital discharge, and all-cause 21-day survival.

Of 3297 patients screened over a 2-year period, a total of 101 (35 haloperidol, 30 ziprasidone, 36 placebo) were enrolled in the study and included in the final analysis, with adequate matching between the three groups. Over the 21-day study period, patients treated with haloperidol spent a similar number of days in delirium or coma (14.0; interquartile range, 6.0-18.0), as patients in the ziprasidone (15; interquartile rate, 9.1-18.0) and placebo (12.5; interquartile range, 1.2-17.2) groups. Daily sedation goals were also similar in the three groups throughout the entire study period. There were no statistically significant differences in secondary outcomes or the use of additional open-label antipsychotics, while the numbers of patients developing akathisia or extrapyramidal symptoms were similar

between the two groups. No patients developed neuroleptic malignant syndrome or ventricular arrhythmias following initiation of the study drugs.

■ **COMMENTARY**

On the surface, this study appears to call into question a long-standing, but poorly supported practice, the use of haloperidol and other antipsychotics for the management of delirium in the ICU, as there were no differences in the number of delirium-free days between the various treatment groups. It is important to remember, however, that the primary goal of this study was to demonstrate the feasibility and safety of conducting a larger multicenter trial on this question rather than show a clear difference between these treatment options for delirium itself. In fact, with only 36 or fewer patients in each treatment group, the likelihood of a Type II error for the primary hypothesis is reasonably high.

Beyond the issue of the study size, there are some other important methodological issues that warrant attention when considering these results. First, although the study design included a mechanism for decreasing the frequency of the study drug, there was no protocolized mechanism for dose increases. Second, all other decisions regarding management of the study patients were made at the discretion of the primary treating teams. To the extent that inter-physician and inter-institutional differences affect choice of sedative medications, and that the various sedative medications (e.g., dexmedetomidine vs midazolam) differentially affect the likelihood of developing delirium, the lack of protocolized sedation practices across study sites may have affected the results.

If the authors are able to proceed with a larger trial building on these results, these issues will need to be incorporated into study design. If this study is completed and shows similar results to those seen in this pilot study, intensivists will be left with the challenging question of how best to treat a vexing problem when non-pharmacologic measures are not sufficient. Recent work has suggested that dexmedetomidine may be associated with less delirium than benzodiazepines,[1,2] but the evidence on that question is still inconclusive and no other good pharmacologic options appear to be on the horizon. ■

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Special Feature

Brain Attack

By Saadia R. Akhtar, MD, MSc

Idaho Pulmonary Associates, Boise

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

EACH YEAR, ABOUT 795,000 STROKES OCCUR IN THE United States; 85% of these are acute ischemic strokes. Acute stroke remains the third leading cause of death in the United States (137,000 persons yearly) and accounts for significant morbidity and disability in survivors. Risk factors for acute stroke include race (incidence is higher in African-American and Hispanic patients, compared to Caucasians), age (75% of patients are > 65 years), obesity, hypertension, atrial fibrillation, diabetes, hyperlipidemia, and tobacco use.[1]

The underlying pathophysiology of acute ischemic stroke generally involves acute intracranial arterial occlusion (thrombotic or embolic). Neurons in the area of the brain being primarily supplied by the occluded vessel die within minutes. Adjacent to and surrounding the immediate area of ischemia and infarct are further at-risk areas of diminished blood flow, the ischemic penumbra. Without rapid revascularization, these areas may infarct as well, greatly extending the injury.[2]

In the past, clinical observation and supportive care were all that could be offered for acute ischemic stroke. More recently, thrombolysis in the early hours has been shown to significantly improve outcomes. To convey the importance of early detection and intervention for stroke, the term "brain attack" (analogous to heart attack) has been advocated by some experts. This review will discuss diagnosis and initial evaluation of acute ischemic stroke, the evidence and indications for thrombolysis, and some key issues in subsequent ICU management.

Diagnosis

Acute ischemic stroke typically presents as acute onset of focal neurological deficits with or without higher cerebral dysfunction. As the term brain attack implies, these patients should be triaged with no less urgency than those with acute myocardial infarction. After assessing and stabilizing airway, breathing, and circulation, a focused history (including risk factors for ischemic stroke and potential contraindications for thrombolytics, discussed below) and examination

should be performed. Determination of the exact time of symptom onset is essential for making treatment decisions.[3] It is important to consider and rule out conditions that may mimic stroke, such as severe hypoglycemia, seizure, migraine, or conversion disorder.[4] Use of a formal stroke scale is recommended by expert guidelines. There are a variety of validated assessment and scoring systems for initial diagnosis, grading of severity and subsequent monitoring of patients with acute stroke. The National Institutes of Health Stroke Scale (NIHSS) is perhaps the most commonly endorsed and utilized. It is a simple series of tests evaluating level of consciousness, comprehension, and visual, motor, sensory, and language responses, taking about 5 minutes to administer.[5]

The initial imaging study should be a noncontrast head CT scan. This will generally rule out hemorrhagic stroke, as well as mass lesions, and may give clues about the vascular distribution of an ischemic stroke. A standard brain MRI is equally useful but generally not as readily available in many centers.[6]

Additional imaging may be obtained but is not usually necessary in the initial evaluation and decision-making process about thrombolytic therapy. CT-angiography or contrast-enhanced MR-angiography can define vascular anatomy and directly identify vascular occlusions or stenoses. Diffusion-weighted MRI will demonstrate infarct within minutes of vascular occlusion and perfusion CT or perfusion-weighted MRI may help to delineate the ischemic penumbra.[6]

Thrombolysis

Stroke management changed dramatically in 1995. The National Institute of Neurological Disorders and Stroke (NINDS) undertook a randomized, double-blind, placebo-controlled clinical trial of the use of intravenous (IV) recombinant tissue plasminogen activator (tPA; 0.9 mg/kg with maximum dose of 90 mg) within 3 hours of stroke onset on neurological outcome at 3 months. Several important exclusion criteria were used: history of intracranial hemorrhage, stroke or head trauma in the past 3 months, major surgery in the past 2 weeks, GI or GU hemorrhage in the past 3 weeks, arterial puncture at noncompressible site within the past week, current use of anticoagulants or evidence of coagulopathy, BP > 185/110 mm Hg, minor or rapidly improving symptoms, symptoms strongly suggestive of subarachnoid hemorrhage, or seizure at onset of stroke. The study found that, compared with placebo, patients receiving tPA had an increase in favorable outcome; they were at least 30% more likely to have minimal or no disability at 3 months following their strokes (this benefit was later shown to extend to 1 year following treatment). This was despite an increase in symptomatic intracerebral hemorrhage in the first 36 hours following tPA administration (6.4% vs 0.6% in the placebo group). There were no differences in serious systemic hemorrhage or in 3-month mortality between the placebo and treatment groups.[7]

The findings of the NINDS trial have subsequently been replicated in large prospective observational studies of tPA.[6] More recent, robust data by Hacke et al support extension of tPA use to 4.5 hours after stroke onset, although there is a clear direct relationship between earlier time of treatment and likelihood of favorable outcome.[8] Systemic tPA is now the standard of care for acute ischemic stroke and it is suggested that institutions develop their own protocol for this with inclusion and exclusion criteria based on those used in the above hallmark studies *(see Table, page 95)*.[4]

There is no place in acute stroke management for other thrombolytic agents at this time: Considerably higher incidence of intracerebral hemorrhage has been seen with streptokinase and data for other agents (urokinase, desmoteplase) are insufficient.[4]

The role of intra-arterial thrombolysis directly at the occlusion site remains unclear. There is limited evidence to suggest benefit in patients with middle cerebral artery occlusions presenting within 6 hours of stroke onset, but no studies directly compare systemic IV tPA to intra-arterial thrombolysis.[9] There are some pilot studies looking at intra-arterial thrombolysis as an early "rescue" therapy if response to systemic IV tPA is limited.[6]

Finally, at this time, there is no defined role for mechanical thrombectomy/embolectomy in management of acute ischemic stroke. Small studies of endovascular devices have shown reasonable rates of vascular recanalization, but neurologic outcome has not been evaluated as a primary endpoint and there have been no head-to-head comparisons with IV tPA.[10]

ICU Care

Airway, ventilation, and oxygenation must continue to be monitored closely once a patient is admitted to an ICU. Depressed level of consciousness and brainstem dysfunction from stroke may lead to hypoventilation, hypoxia, airway compromise, or aspiration; a low threshold must be maintained for intubation in such patients. Untreated hypoxia may worsen cerebral ischemic injury. Aspiration and other pneumonia may adversely impact outcomes. If intubation and mechanical ventilatory support are required, prognosis is guarded; half or more of patients requiring intubation in the setting of acute stroke may not survive beyond 30 days.[11]

Table

Criteria for use of tPA for acute ischemic stroke[4]

Inclusion

- Clinical diagnosis of acute ischemic stroke with more than minor deficits
- Within 4.5 hours of onset
- No hemorrhage on CT scan

Exclusion

- History of intracranial hemorrhage
- Stroke or head trauma in the past 3 months
- Major surgery in the past 2 weeks
- GI or GU hemorrhage in the past 3 weeks
- Acute myocardial infarction in the past 3 months
- Arterial puncture at noncompressible site within the past week
- Current use of anticoagulants or evidence of coagulopathy (INR > 1.7, elevated aPTT, platelets < 100,000)
- BP > 185/110 mm Hg
- Minor or rapidly improving symptoms
- Symptoms strongly suggestive of subarachnoid hemorrhage
- Seizure at onset of stroke (if unclear whether residual neurological deficits are post-ictal effect or stroke)
- Multilobar infarct (involving > 1/3 cerebral hemisphere) on CT

Blood pressure management is one of the key aspects of acute stroke care in the ICU. Hypertension is common after acute stroke, and may reflect underlying chronic hypertension or acute pain or anxiety. It may also be an appropriate physiological response to maintain cerebral perfusion in the setting of loss of normal autoregulation at the area of ischemia. There is a clear U-shaped relationship between initial blood pressure and mortality from acute stroke, with adverse outcomes associated with very low and very high systolic blood pressures.[12] Very severe hypertension may increase risk of cerebral edema, hemorrhagic transformation of the ischemic stroke, or other end-organ complications (myocardial ischemia, pulmonary edema, acute renal failure); overly aggressive lowering of blood pressure may worsen cerebral perfusion and risk extension of an ischemic stroke.[6]

Therefore, current guidelines suggest not treating blood pressure in the setting of acute ischemic stroke until it exceeds 220/120 mm Hg; if patients have received thrombolytics, this parameter is lowered to 180/105 mm Hg. Beyond this, blood pressure should not be lowered more than about 15% in the first day.[4] The antihypertensive agents of choice include nonselective beta-blockers, such as labetolol, and calcium channel blockers, such as nicardipine and ACE-inhibitors; nitroprusside and hydralazine should be avoided as they may be more likely to cause cerebral vasodilation and elevation of intracranial pressure.[6]

Hypotension is uncommon in the setting of acute ischemic stroke and is a poor prognostic indicator. Intravascular volume should be maintained in these patients, using isotonic IV fluids. Clinical trials are ongoing to assess whether inducing hypertension may have benefit in patients with acute ischemic stroke and initial hypotension.[6]

It remains unclear how to best manage body temperature in patients with acute ischemic stroke. Hyperthermia (fever) is associated with worse neurological outcomes, but it has been difficult to demonstrate improvement in outcomes with treatment (or prophylaxis) with antipyretics.[13,14] Thus, the only recommendation that can be made is to consider antipyretics if fever occurs and treat the source of fever whenever possible. Similarly, although hypothermia is neuroprotective in animal models of stroke and has been shown to improve neurological outcomes after out-of-hospital cardiac arrest, further clinical trials are needed to determine whether it may benefit patients with acute ischemic stroke.[15,16]

Hyperglycemia is associated with poorer outcomes after acute ischemic stroke. It is clearly a marker of stroke severity. It worsens ischemic damage in animal models of acute stroke and is associated with increased risk of hemorrhagic transformation of acute stroke, greater infarct size on MRI, and, in some reports, less favorable neurological outcome and increased mortality. The mechanism is unclear; anaerobic glycolysis, increased free-radical formation, and disruption of the blood-brain barrier may occur. Despite these observations, there is a paucity of data to guide how best to manage glucose and whether any approach alters outcomes in patients with acute ischemic stroke. Until further evidence is obtained, guidelines recommend targeting glucose < 140-180 mg/dL.[4]

Early antiplatelet therapy with aspirin is indicated for all patients with acute ischemic stroke. Two very large randomized, placebo-controlled clinical trials (about 20,000 patients each) have shown that aspirin given within 48 hours of acute ischemic stroke reduces risk of recurrent stroke, death, and dependence.[17,18] It is recommended that aspirin be started immediately if thrombolytics are not given; if IV tPA is given, aspirin should be started 24 hours later.[19]

Finally, ICU caregivers must be vigilant for neuro-

logical complications of acute ischemic stroke: cerebral edema, hemorrhagic transformation, and seizure. Frequent examinations and monitoring with a validated stroke scale are essential for identifying neurological changes early. Cerebral edema is most common following large middle cerebral artery distribution or cerebellar strokes. Although it can progress rapidly with severe clinical deterioration within the first 24 hours, it presents most typically at about day 4. Usual treatment for elevated intracranial pressure is recommended (elevation of head of bed, hyperosmolar therapy, short-term moderate hyperventilation, CSF drainage) along with early consideration of decompressive craniotomy. Hemorrhage at the area of stroke is often limited, of little clinical consequence, and managed supportively. For more significant, symptomatic intracranial hemorrhage, particularly after tPA, fresh frozen plasma and cryoprecipitate should be administered emergently.[4,6]

Conclusion

Acute ischemic stroke is a common problem resulting in considerable morbidity and mortality. Rapid, coordinated triage/evaluation, early treatment with thrombolytics, and subsequent aggressive supportive ICU care have the potential to vastly improve outcomes. ■

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CME / CNE Questions

45. Addition of a mixture of helium and oxygen to non-invasive ventilation is associated with which of the following benefits in patients presenting with COPD exacerbation?

a. Decreased hospital mortality
b. Decreased need for intubation in patients receiving non-invasive ventilation for < 4 days
c. Decreased need for reintubation with extubation failure
d. Decreased duration of non-invasive ventilation
e. Decreased carbon dioxide elimination

46. Conditions that may commonly mimic acute ischemic stroke include all *except*:

a. hypoglycemia.
b. hyperthyroidism.
c. migraine.
d. intracranial hemorrhage.
e. seizure.

Answers: 45. b, 46. b.

CME / CNE 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.

PHARMACOLOGY WATCH

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

Oral Treatments for Relapsing-remitting MS

In this issue: Two oral medications for relapsing-remitting MS in phase III development; antihypertensives find new uses; *Ginkgo biloba* does not prevent cognitive decline in elderly; and FDA Actions.

Oral medications for relapsing-remitting MS

Two new oral medications are effective treatments for relapsing-remitting multiple sclerosis (MS) according to three studies published on-line in the *New England Journal of Medicine*. Fingolimod and cladribine differ in the mechanism of action but both reduce the number of potentially auto-aggressive lymphocytes that are available to enter the central nervous system. In the Cladribine Tablets Treating Multiple Sclerosis Orally (CLARITY) trial, two different doses of cladribine were compared to placebo with the endpoint being relapse at 96 weeks. Both doses were more effective than placebo at preventing relapses and reducing brain lesion count on MRI ($P < 0.001$ for all comparisons). The drug was associated with lymphocytopenia and a higher risk of herpes zoster.

Fingolimod was compared to placebo in the FREEDOMS trial and compared to injectable interferon in the TRANSFORMS trial. The 24-month FREEDOMS trial compared two doses of fingolimod to placebo and similarly found a lower rate of relapse ($P < 0.001$ for both doses) and disability progression ($P = 0.02$ for both doses). The drug also reduced the number of new lesions found on MRI. Significant side effects included bradycardia, AV block, macular edema, elevated LFTs, and mild hypertension. When compared to interferon, fingolimod was associated with significantly lower annualized relapse rates at both doses tested ($P < 0.001$ for both comparisons), although there was no significant difference with respect to progression of disability. Two fatal infections occurred with the higher dose of fingolimod (disseminated primary varicella zoster and herpes simplex encephalitis). (All three studies published on-line at www.NEJM.org, Jan. 20, 2010).

An accompanying editorial calls the arrival of oral formulations of MS drugs "welcome news for the estimated 2.5 million people worldwide with this chronic, disabling disease." While suggesting these drugs "support a change in treatment approach to directly prevent immune-related injury," the editorial also suggests that long-term goals of MS therapy are currently lacking (published online at www.NEJM.org, Jan. 20, 2010). Both drugs are in phase III trials for treatment of MS; cladribine is currently approved in parenteral form for treatment of hairy cell leukemia. ■

Antihypertension drugs for AF and dementia?

Different classes of blood pressure (BP) medications may have different benefits according to two new studies. In the first study, researchers from the United Kingdom performed a nested

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) 262-5468. E-mail: paula.cousins@ahcmedia.com.

case-control analysis to evaluate whether different antihypertensive drug classes may alter the risk for atrial fibrillation. The researchers reviewed records from a large patient population, specifically patients who were on a single agent for lowering BP. A lower odds ratio (OR) for atrial fibrillation was noted with ACE inhibitors (OR, 0.75; 95% confidence interval [CI], 0.65-0.87), angiotensin receptor blockers (ARBs) (OR, 0.71; 95% CI, 0.57-0.89), and beta-blockers (OR, 0.78; 95% CI, 0.67-0.92) compared with current exclusive therapy with calcium channel blockers. Although the researchers were unable to assess why patients were receiving one class of blood pressure medicine over another, they concluded that long-term therapy with ACE inhibitors, ARBs, or beta-blockers reduces the risk for atrial fibrillation compared with calcium channel blockers. These findings generally relate to patients with mild hypertension, since patients on multiple drugs were excluded from the study (*Ann Intern Med* 2010;152:78-84).

In the second study, researchers from Boston set out to investigate whether ARBs reduce the risk of Alzheimer's disease and dementia or reduce the progression of both diseases. More than 800,000 predominately male participants, age 65 or older with cardiovascular disease, were studied. Patients were divided into three cohorts (ARBs, lisinopril, and other cardiovascular drugs as a comparator) and followed over 4 years, with adjustments for age, diabetes, stroke, and cardiovascular disease. Hazard rates for dementia in the ARB group were 0.76 (95% CI, 0.69-0.84) compared to the cardiovascular comparator, and 0.81 (95% CI, 0.73-0.90) compared to the lisinopril group. In patients with pre-existing Alzheimer's disease, ARBs were associated with significantly lower risk of admission to a nursing home. The combination of the ARB and ACE inhibitor was better than ACE inhibitor alone in preventing dementia and reducing admission to nursing home. The authors conclude that ARBs are associated with a significant reduction in the incidence and progression of Alzheimer's disease and dementia compared to ACE inhibitors or other cardiovascular drugs (BMJ 2010;340:b5465, doi: 10.1136/bmj.b5465, published on-line Jan. 12, 2010). An accompanying editorial points out that several studies have shown that treatment with any antihypertensive is associated with a lower risk of cognitive decline or incident dementia in older adults. What is not clear is whether some antihypertensives also have other biological mechanisms that help prevent dementia. It is plausible that ARBs are more neuroprotective than other drugs because of their effect on type 2 angiotensin receptors in the brain (*BMJ* 2010:340;b5409, doi: 10.1136/bmj.b5409, published on-line Jan. 12, 2010). ■

Ginkgo does not prevent cognitive decline

The National Center for Complementary and Alternative Medicine (NCCAM) was founded during the Clinton administration as part of the National Institutes of Health to investigate complementary and alternative medicines. Many of the NCCAM-funded studies, however, have shown no benefit from complementary or alternative treatments, and that is the case with a new study looking at *Ginkgo biloba* and cognitive function in older adults. *Ginkgo biloba*, which is widely marketed as an aid to preventing cognitive decline and dementia, was previously found to have no benefit in reducing the incidence of Alzheimer's disease or dementia overall (*JAMA* 2008;300:2253-2262).

In a new study sponsored by NCCAM, researchers set out to determine whether *Ginkgo biloba* slows the rate of global or domain-specific cognitive decline in older adults. More than 3000 participants age 72-96 years were enrolled and randomized to *G. biloba* 120 mg or placebo twice daily. Rates of change over time in two different objectives cognitive tests, as well as neuropsychological tests, were the primary endpoints. There was no difference in the decline in cognitive scores between *Ginkgo biloba* and placebo in any of the domains including memory, attention, and visuospatial abilities, language, or executive functions. There was also no difference in the rate of change in the standardized cognitive exams. The authors conclude that compared to placebo, *Ginkgo biloba* did not result in less cognitive decline in older adults (*JAMA* 2009;302: 2663-2670). ■

FDA Actions

Novo Nordisk has received approval to market liraglutide, a once-daily injection for the treatment of type 2 diabetes in adults. The drug is a glucagon-like peptide-1 receptor agonist similar to exanatide (Byetta®). The company is required to perform additional post-marketing cardiovascular studies as well as a 5-year epidemiological study to evaluate the risk of thyroid cancer. Liraglutide will be marketed under the trade name Victoza®. ■

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CUMULATIVE INDEX

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