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INSIDE

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NPPV in Acutely Ill COPD Patients with Varying Levels of Consciousness

ABSTRACT & COMMENTARY

By Dean R. Hess, PhD, RRT

Assistant Director, Respiratory Care, Massachusetts General Hospital, Department of Anesthesiology, Harvard Medical School

Dr. Hess reports no financial relationship relating to this field of study.

Synopsis: *NPPV can be successfully applied to many patients with mild-to-moderately altered levels of consciousness during an exacerbation of COPD.*

Source: Scala R, et al. Noninvasive positive pressure ventilation in patients with acute exacerbations of COPD and varying levels of consciousness. *Chest*. 2005;128:1657-1666.

In this study, Scala and colleagues compared the clinical outcomes of patients with acute respiratory failure due to COPD exacerbations and different degrees of altered levels of consciousness. It was a 5-year case-control study with prospective data collection conducted in a respiratory monitoring unit. Of 153 consecutive COPD patients requiring noninvasive positive-pressure ventilation (NPPV) for acute respiratory failure, 80 were divided into 4 groups, which were carefully matched for the main physiologic variables according to the level of consciousness assessed with the Kelly-Matthay score, in which 1 is normal (control subjects) and 6 is severely impaired. Changes from baseline arterial blood gas levels and Kelly score, the rate and causes of NPPV failure, the rate of nosocomial pneumonia, and the 90-day mortality rate were compared.

NPPV significantly improved arterial blood gases and Kelly score in all groups after 1 to 2 hours. NPPV failure was 15% for Kelly score 1, 25% for Kelly score 2, 30% for Kelly score 3, and 45% for Kelly score > 3. Mortality at 90 days was 20% for Kelly score 1, 35% for Kelly score 2, 35% for Kelly score 3, and 50% for Kelly score > 3. Using multivariate analysis, the acute non-respiratory component of the APACHE III score and baseline pH independently predicted baseline Kelly score. After 1 to 2 h of NPPV,

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changes in the Kelly score were associated with changes in pH, but no such correlation was found with $PaCO_2$.

Scala et al concluded that NPPV may be successfully applied to patients experiencing COPD exacerbations with a milder, altered level of consciousness. The rate of failure in patients with severely altered level of consciousness (ie, Kelly score > 3) was higher, although better than expected, suggesting that an initial and cautious attempt of NPPV may be performed even in this group of patients.

COMMENTARY

Use of NPPV in patients with altered levels of consciousness is controversial. Often stated is concern related to the risk of aspiration of gastric contents should the patient vomit. Moreover, agitated patients are typically intolerant of NPPV. Most of the randomized controlled studies of NPPV have excluded a priori patients with an altered level of consciousness. Under the umbrella of "altered level of consciousness," a heterogeneous variety of different degrees of encephalopathy are typically included, ranging from coma to agitation or confusion. In patients with COPD, this is often related to the $PaCO_2$ (hypercapnic encephalopathy). A unique aspect of this study is use of the Kelly-Matthay scale to assess the level of consciousness, which has been specifically designed for critically ill patients requiring mechanical ventilation.

In this study, the application of NPPV was associated with a rapid improvement in gas exchange and neurologic status in the majority of patients, irrespective of the severity of the altered level of consciousness. In patients with mild-to-moderately altered levels of consciousness (Kelly score 3), NPPV was highly successful in terms of clinical outcomes. Patients with a severely altered level of consciousness had an increased but not a dramatically high rate of NPPV failure and 90-day mortality. In this subset of patients, cardiovascular events were more frequently the cause of NPPV failure.

Interestingly, pulmonary aspiration was not observed in any of the subjects. My observation is that aspiration is uncommon in patients receiving NPPV. It is often discussed but seldom seen—perhaps because NPPV is not offered to patients at potential risk for aspiration. Over the course of my career, I have seen many patients with pulmonary aspiration—only a few of whom were receiving NPPV at the time of aspiration. I would venture to guess that I have seen as many patients with gross aspiration past the cuff on an artificial airway as I have seen patients with gross aspiration during NPPV. It is interesting to note that the degree of respiratory acidosis did not fully explain the changes in Kelly score and that other factors, like non-pulmonary acute organ dysfunction, seemed to play an important role.

These data suggest that, during an exacerbation of COPD, NPPV can be successfully applied to many patients with mild-to-moderately altered levels of consciousness. Patients with severely altered levels of consciousness may also benefit from NPPV. However, close monitoring is needed in these patients and prompt intubation should be available if the patient does not

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respond rapidly. The changes in mental status after a brief trial of NPPV are not exclusively associated with changes in $PaCO_2$, but rather with acute non-respiratory organ impairment. This suggests that level of consciousness may be a more important monitor of success that changes in arterial blood gases.

It should be noted that this study was limited to patients with COPD exacerbation and hypercapnia. Caution is urged when extrapolating these results to the application of NPPV in other patient populations with altered levels of consciousness. ■

Is ICU Care Appropriate for the Very Elderly?

ABSTRACT & COMMENTARY

By David J. Pierson, MD, Editor

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

Synopsis: *Very elderly patients survive critical illness less often than younger patients and have worse functional outcomes, although the findings of existing studies are inadequate for specific predictions and some patients do have good outcomes. Prognostic models such as APACHE are poorly suited for use in very elderly patients.*

Source: de Rooij SE, et al. Factors that predict outcome of intensive care treatment in very elderly patients: a review. *Crit Care*. 2005;4:R307-R314.

INVESTIGATORS AT THE UNIVERSITY OF AMSTERDAM performed an extensive review of articles, retrieved via Medline, that reported ICU outcomes in very elderly patients. Their goals were to examine the predictors of mortality, to evaluate the appropriateness of existing models such as the APACHE scores in predicting outcomes, and to assess existing data relating to patient preferences for ICU care among such patients. They considered patients aged 80 years and older to be "very elderly," although studies in the literature varied as to how this was defined.

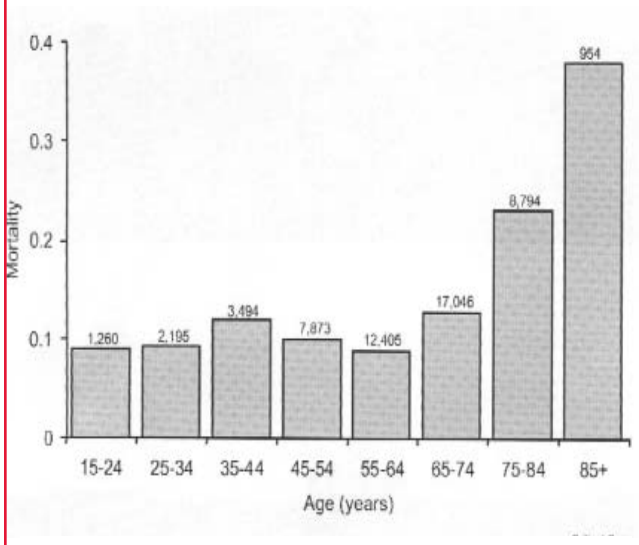
Twelve studies (9 prospective and 3 retrospective) were identified that were based on large databases and deemed appropriate for inclusion in the review, although these were so sufficiently heterogeneous that formal meta-analysis could not be performed. In consequence, the authors discussed the findings in narrative form under several categories. That mortality increases with increasing age was a consistent finding, although the rates and magnitude of age association varied among studies. It was clear that the reason for ICU admission exerts a strong influence on outcome, although an effect of age per se could not be consistently determined.

Although very elderly patients commonly have more comorbidities than younger patients, the influence of comorbidities has not been specifically studied and no fixed conclusions could be drawn. Functional and cognitive status, while seemingly very important as determinants of overall outcomes in very elderly patients, similarly could not be quantitated as specific predictors. The reviewed studies shed little light on patient preferences in the very elderly in contrast to those in younger patients. However, in the SUPPORT Study,[1] physicians were more likely to believe incorrectly that older patients did not want life-sustaining treatments: 79% for patients over 80 years, as compared to 36% for patients younger than 50 years.

While, in general, ICU patient population prognostic models such as SAPS II, MPM II, APACHE II, and APACHE III are predictive of survival, these models are not calibrated for use in very elderly patients, and they do not take into consideration a number of factors that are major determinants of outcome in such individuals. The authors conclude that a new model is needed for predicting outcome in very elderly ICU patients.

Figure

In hospital mortality of 54,021 ICU patients by age group



Data obtained from: Coakley JH, et al. Intensive Care Med. 1998;24:801-807.

COMMENTARY

Outcomes of critical illness are not as good in elderly patients as in those who are younger.[2] In the SUPPORT study,[1] the risk of death increased by 1% per year of age among patients 18 to 70 years old, and by 2% per year for patients older than 70. The likelihood of dying appears to go up the older the patient is, as shown in the Figure (*below*), taken from the Dutch National Intensive Care Evaluation (NICE) database.[3] Patients aged 85 and older had substantially higher in-hospital mortality than those aged 75-84, who in turn survived less well than patients younger than 75. In a study of more than 40,000 ICU patients requiring mechanical ventilation in one state,[4] 70% of patients aged 85 or older died, as compared to 32% of patients younger than age 30.

These things are understood by everyone who works in an ICU. Even within a particular diagnostic category or for a given set of comorbidities, very old patients are more likely to do poorly than those who are younger. However, currently available studies are insufficient to provide clinicians with specific guidance as to which elderly patients do or do not stand to benefit from ICU care. Most studies that report what happened to a particular group of ICU patients suffer from unknown selection bias: how was the decision made to admit a particular individual to the ICU in the first place? The importance of this is borne out by the Dutch NICE database,[3] as discussed by de Rooij et al. In the population of ICU patients older than age 80, mortality was 16.5% among those who had undergone cardiac surgery as compared to 46% in the others. Clearly, patients more likely to survive were somehow being selected for cardiac surgery.

The bottom line appears to be that age by itself is a general predictor of a poor outcome from critical illness, but probably not as important a predictor as other factors that are similar to those in other patients. The appropriateness of ICU care needs to be determined in the context of the cause of critical illness, the nature and severity of coexisting conditions, baseline functional status, and patient preferences—in very elderly patients just as for everyone else. ■

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Special Feature

Critical Illness Polyneuromyopathy: Risk Factors and Clinical Consequences

By Karen L. Johnson PhD, RN, CCRN

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Dr. Johnson reports no financial relationship to this filed of study.

MORE THAN 20 YEARS AGO, CASE REPORTS APPEARED in the literature describing a neuromuscular abnormality that developed as a consequence of critical illness.[1] Despite its slow acceptance, the description of a neuromuscular abnormality secondary to critical illness is now reasonably rooted in the literature, although its explanation remains unclear. This is a highly unrecognized complication of critical illness that is associated with prolonged mechanical ventilation, prolonged ICU stays, and increased hospital mortality. The potential economic impact of this complication has been estimated to cost more than $66,000 per patient (1996 dollars) in excess of hospital charges.[2] At present, there is no treatment. A clearer understanding and appreciation of the risk factors may help to prevent and therefore treat this complication of critical illness.

Definition

Critical illness can be complicated by extreme neuromuscular weakness associated with a delay in weaning from mechanical ventilation, prolonged hospitalization and rehabilitation. Neuromuscular abnormalities have been found in a majority of patients within a week of admission to the ICU.[3-6] These neuromuscular disorders develop in patients without previously known neuro-

Table 1

Terms used to describe ICU-acquired neuromuscular weakness

- ICU-acquired paresis
- Floppy person syndrome
- Acute quadriplegic myopathy
- Necrotizing myopathy of the ICU
- Critical illness neuropathy
- Thick filament myopathy
- Critical illness myopathy
- Steroid-induced tetraplegia
- Critical illness neuropathy and myopathy
- Acute respiratory failure neuropathy

muscular disorders. A clear classification of ICU acquired neuromuscular disorders is difficult because of inconsistent terminology in the literature. Terms used to describe this ICU-acquired neuromuscular disorder are listed in Table 1.

Two main clinical, pathological, and electrophysiological types of acquired neuromuscular involvement in critically ill patients have been described: critical illness polyneuropathy[1,7] and critical illness myopathy.[8] The differentiation between them is based on the assumption that most cases can be categorized as one or the other.[9] However, there is evidence that these conditions coexist.[8] Therefore, until more data on the different pathogenesis of various pathological subtypes are available, the use of the term "critical illness polyneuromyopathy" (CIPNM) has been suggested.[6]

Diagnosis

Clinically, CIPNM manifests as sensory deficits and general weakness. These symptoms are usually not detected because ICU patients are intubated and sedated. The first sign of CIPNM may become apparent as a failure to wean from mechanical ventilation. Cranial nerves may be intact on clinical—but not electromyographic (EMG)—examination, an important clinical finding distinguishing this disorder from Guillain-Barré syndrome and other myopathies. Limbs have varying degrees of flaccid weakness and atrophy. Distal atrophy may be obscured by limb edema. The majority of patients have loss of previously normal deep tendon reflexes. Disappearance of these reflexes is an important sign that neuropathy has developed. Unfortunately, this simple neurologic test is routinely omitted in daily physical examinations. While loss of reflexes is commonly blamed on sedatives and analgesics, there is little evidence that these drugs eliminate them. Propofol may cloud the bedside neurologic examination by rendering flaccid areflexic paralysis. Sensory examination is often unreliable and may only become apparent if the patient has a clear sensorium.

Recently, the Medical Research Council (MRC) score,[10] has been validated in the ICU patient population to evaluate muscle strength.[11] Each muscle group score ranges from 0 (paralysis) to 5 (normal muscle strength), and the overall score from 0 to 60. In a recent study,[11] patients with an MRC score less than 48 were diagnosed as having CIPNM, whereas those with a MRC score of 48 or higher, which indicated muscle strength of 5 (normal) or 4 (subnormal) in each limb segment were considered normal. The most important factor that limits a reliable clinical examination with the MRC is the alteration of consciousness frequently present in the ICU patient.

Electrophysiologic studies are the diagnostic standard for identifying CIPNM. Nerve conduction studies reveal declines of the amplitudes of compound muscle action potentials with relatively preserved motor conduction velocities, distal motor latencies, and F-wave latencies. There is variable loss of sensory nerve action potential amplitudes with preserved sensory nerve conduction velocities. One problem complicating interpretation of high-gain surface electrode recordings of sensory potentials is edema. Near-nerve needle recordings have been used to help with this problem. Needle EMG has identified fibrillation potentials and positive sharp waves.

Muscle biopsy may show loss of myosin documented by decreased or absent myosin ATP staining of atrophic fibers or selective loss of myosin filaments with relative sparing of actin filaments and Z discs on ultrastructural examination, degenerative-necrotic changes, and type II fiber atrophy detected by quantitative automatic morphometrical analysis of the mean cross sectional area of both types of muscle fibers.

Incidence

The incidence of CIPNM is larger than generally recognized: 33-80% depending on the group of critically ill patients evaluated and the timing of electrophysiologic and histologic study.[7,12] In prospective, observational studies, electrophysiologic abnormalities ranged from 47% to 90% of patients[7,13] and histologic abnormalities range from 71% to 96%.[3,14]

Risk Factors

While there is considerable debate as to the precise etiology of this neuromuscular disorder, multiple risk factors have been implicated (*see Table 2*).

Table 2

Risk Factors for Critical Illness Polyneuromyopathy

Cytokines (TNF-alpha; Interleukin-1)
Drugs:
Neuromuscular blocking agents
Aminoglycosides
Muscle relaxants
Furosemide
Corticosteroids
Metabolic abnormalities:
Hyperglycemia
Hyperglycemia
Hyperosmolarity
Hyponatremia
Azotemia
Hypoalbuminemia
Prolonged duration of mechanical ventilation
Chronic renal failure
Continuous renal replacement therapy
Prolonged ICU length of stay
Parenteral nutrition
Malnutrition
Age (older)
Sex (female)
Immobility
Neurologic failure
Severity of illness
SIRS
Sepsis
MODS (> organs)
Underlying disease:
cancer
alcohol abuse
diabetes mellitus
chronic renal failure

MODS, multiple organ dysfunction syndrome
SIRS, systemic inflammatory response syndrome
TNF, tumor necrosis factor

SIRS and MODS

Several prospective studies have confirmed the association between the systemic inflammatory response syndrome (SIRS), multiple organ dysfunction syndrome (MODS), and CIPNM.[4,6,11,15] When both factors are present, the risk is as high as 70%.[15] As early as 1892, Osler described a condition of muscle wasting as a complication of prolonged sepsis.[16] However, the association between sepsis and CIPNM in modern medicine did not become apparent until almost a hundred years later when Bolton and colleagues through a series of papers, hypothesized that a systemic inflammatory response/sepsis contributed to neuronal damage in critically ill patients.[1,7,17,18] More recent studies offer experimental evidence that CIPNM is characterized by generalized axonal motor and/or sensory denervation.[4,6,19] There is a significant association between the development of CIPNM and respiratory failure,[20] neurologic failure, and renal failure.[6] These associations raise questions as to whether neuromuscular involvement is a consequence of these organ failures, or whether it represents another organ failure.

Prolonged Mechanical Ventilation

Another risk factor associated with the development of CIPNM is prolonged mechanical ventilation. Duration of mechanical ventilation is significantly longer in patients with CIPNM.[5,6,11,20] One recent study reported that CIPNM increased length of mechanical ventilation 11.6 days.[5] Others postulate that readmission to the ICU for respiratory failure may be due to undetected CIPMN prior to discharge from the ICU.[21]

Drugs

Critical illness myopathy was originally reported as a complication of corticosteroid administration, either alone or in association with non-depolarizing neuromuscular blocking agents (NMBA).[22,23] Prospective studies however, report conflicting data on the significant independent influence of corticosteroids or NMBA on development of CIPNM.[11,15,20,24] There is evidence that ICU patients who receive corticosteroids are susceptible to developing histologic features of myopathy that include type 2 fiber atrophy and myosinolysis.[11] It has been postulated that these lesions are the consequence of corticosteroid muscle receptor stimulation by exogenous corticosteroids[25] that maybe enhanced by muscle denervation.[26] However, in a recent prospective multi-center cohort study, De Jonghe and colleagues reported no significant difference in the duration or cumulative dose of corticosteroids in patients with and without CIPNM.[11] They suggested 2 explanations: 1) the medical condition that prompts corticosteroid administration is responsible for the neuromuscular dysfunction, or 2) corticosteroids may act as a trigger for neuromuscular dysfunction.

Aminoglycosides have been linked to presynaptic neuromuscular transmission defects, implying that these agents may be toxic to distal motor terminals.[27] However, recent prospective studies have not found electrophysiologic evidence of a neurotoxic effect of aminoglycosides on the neuromuscular junction.[5,15]

Hyperglycemia

Hyperglycemia has been associated with an increased risk of CIPNM.[5,11,20] Van den Berghe demonstrated that tight glycemic control led to a reduction in the incidence of CIPNM.[28] Possible explanations include the direct cytotoxic effects of hyperglycemia or the neuroprotective effects of insulin.[28]

Prevention and Treatment

At present, there are no definitive therapies to prevent or treat CIPNM. Current therapy is directed at supportive care. An understanding and appreciation of the risk factors identified here are essential in order to prevent this complication of critical illness.

Patients with initial high APACHE III score and development of SIRS should have regular assessments of muscle strength. As soon as CIPNM is suspected, an electromyogram should be done to confirm findings. Although evidence does not support the direct deleterious effects of NMBA and corticosteroids on development of CIPNM, their use should be restricted. De Jonghe suggests that until more evidence is available, clinicians should weigh the indications of corticosteroids in ICU patients and restrict their use to conditions, such as septic shock, unresolved acute respiratory distress syndrome, status asthmaticus, in which corticosteroids have been shown to have a significant impact on mortality and morbidity.[11] Van den Berghe et al have shown that tight glycemic control reduces the incidence of CIPNM by half.[28]

The risk factor of prolonged mechanical ventilation on the development of CIPNM may likely represent another example of the deleterious effects of immobilization which raises the question of whether ICU patients are getting adequate range of motion exercises and/or physical therapy. In my own experience, bedside nurses say they are too busy to perform range-of-motion exercises and physical therapists say the patient is too sick to participate in physical therapy. Teaching family members to perform range-of-motion exercises has been successful in my experience. The patients get the therapy and the family members feel as though they are contributing to the patient's recovery. Certainly, studies are needed to evaluate the effects of an aggressive range-of-motion exercise program on reducing CIPNM. ■

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CME Questions

8. NPPV can be successfully applied to a many patients with mild-to-moderately altered levels of consciousness associated with:
a. acute respiratory distress syndrome.
b. COPD exacerbation.
c. asthma flare.
d. acute cardiogenic pulmonary edema.
e. None of the above

9. The primary concern when patients receiving NPPV have altered level of consciousness is for which of the following?
a. Vomiting and aspiration
b. Inability to correct hypoxemia
c. Ineffective CO2 removal
d. All of the above
e. None of the above

10. Which of the following statements is true about very elderly patients admitted to the ICU?
a. Their rate of survival is the same as for younger patients
b. They have the same number of comorbidities as younger patients
c. They have outcomes after mechanical ventilation as good as younger patients
d. Because of their age, they should not be admitted to the ICU
e. None of the above

11. Which of the following ICU prognostic models has been validated for use in patients older than age 80?
a. APACHE II
b. APACHE III
c. SAPS II
d. All of the above
e. None of the above

12. Which of the following are signs of critical illness polyneuromyopathy?
a. Loss of cranial nerves
b. Loss of previously normal deep tendon reflexes
c. Failure to wean
d. Seizures
e. Leukocytosis

13. Which of the following drug is a risk factor for critical illness polyneuromyopathy?
a. Aminoglycosides
b. Cephalosporins
c. Corticosteroids
d. Dobutamine
e. Propofol

Answers: 8 (b); 9 (a); 10 (e); 11 (e); 12 (b); 13 (c)

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PHARMACOLOGY WATCH

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Beta-Blockers Therapy for the Treatment of Hypertension

Beta-blockers should not be recommended as first-line therapy for hypertension in patients without heart disease, according to a new study. Researchers from Sweden performed a meta-analysis on 13 randomized controlled trials comparing treatment with beta-blockers with other antihypertensive drugs. Seven other studies were reviewed in which beta-blockers were compared with placebo or no treatment. The relative risk of stroke was 16% higher for patients who were treated with beta-blockers (95% CI, 4-30%) compared to other drugs. Beta-blockers reduced the relative risk of stroke by 19% compared to no treatment or placebo; however, this was about half the reduction expected from previous hypertension trials. There was no difference seen in the rates of myocardial infarction or overall mortality. A possible mechanism for these findings is that beta-blockers reduce brachial blood pressure out of proportion to central blood pressure compared with other antihypertensives.

The authors suggest that beta-blockers are less effective than other antihypertensive drugs in preventing stroke, and should not be a first choice in the treatment of primary hypertension (Lindholm LH, et al. Should Beta Blockers Remain First Choice in the Treatment of Primary Hypertension? A Meta-Analysis. *Lancet*. 2005;366:1545-1553). This same group published a study in 2004, suggesting that atenalol was a poor choice for treatment of hypertension (Carlberg B, et al. Atenolol in Hypertension: Is It Wise?*Lancet*. 2004;364:1684-1689). An accompanying editorial states "Surely, therefore, the era of beta-blockers for hypertension is over," but suggests that these drugs should not be discontinued abruptly, and should be discontinued with extreme caution in patients with coronary artery disease (Beever DG, et al. The End of Beta Blockers for Uncomplicated Hypertension? *Lancet*. 2005;366:1510-1512).

Treatments for Acute Migraine

Two studies in the September issue of the Journal of Headache find that sumatriptan alone is inferior to other treatments for acute migraine. In the first study, 972 migraine patients were randomized to treatment with sumatriptan 50 mg, naproxen sodium 500 mg, sumatriptan 50 mg plus naproxen 500 mg, or placebo at the onset of headache symptoms. The sumatriptan plus naproxen group fared the best, with 46% of subjects achieving a 24-hour pain relief response. Sumatriptan alone resulted in 29% of patients achieving the same result, while naproxen alone resulted in the 25% response, and placebo resulted in a 17% response ($P < .001$). Relief of pain at 2 hours was achieved in 65% of the combination group, 49% of the sumatriptan patients, 46% of naproxen patients, and 27% of placebo patients ($P < .001$). The incidence of recurrent headache 24 hours later was also lowest in the sumatriptan plus naproxen group. Other migraine symptoms, includ-

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ing nausea, photophobia, and phonophobia were also most effectively treated with sumatriptan plus naproxen. Adverse effects were similar in all the treatment groups (Smith TR, et al. Sumatriptan and Naproxen Sodium for the Acute Treatment of Migraine. *Headache*. 2005;45:983-991). In the second study, sumatriptan was compared with acetaminophen-aspirin-caffeine (AAC) in the early treatment of migraine. In a randomized, controlled clinical trial, 171 patients took either sumatriptan 50 mg or AAC (acetaminophen 500 mg, aspirin 500 mg, and caffeine 130 mg [Excedrin Extract Strength 2 tabs], or Excedrin Migraine 2 tabs at the first sign of a migraine attack. AAC was significantly more effective ($P > .05$) than sumatriptan in the early treatment of migraine, as shown by superiority and summed pain intensity difference, pain relief, pain intensity difference, response, sustained response, relief of assisted symptoms, use of rescue medications, disability relief, and global assessments of effectiveness (Goldstein J, et al. Acetaminophen, Aspirin, and Caffeine Versus Sumatriptan Succinate in the Early Treatment of Migraine: Results From the ASSET Trial. *Headache*. 2005;45:973-982).

Statin Therapy for ACS Patients

Early aggressive statin therapy is beneficial for patients with acute coronary syndrome (ACS), according to a new study. In a continuation of the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22 (PROVE IT -TIMI 22) trial, the timing of intensive statin therapy was evaluated in patients with acute coronary syndrome. A total of 4162 patients with ACS were randomized to intensive statin therapy with atorvastatin 80 mg or standard therapy with pravastatin 40 mg. The composite end points of death, MI, or rehospitalization for recurrent ACS were determined for each group at 30 days. ACS patients who were started in the hospital on intensive statin therapy fared better than those with standard therapy (composite end point at 30 days 3% intensive therapy vs 4.2% standard therapy [HR = 0 .72; 95% CI, 0.52 to 0.99; $P = .046$]). The authors conclude that ACS patients should be started on aggressive statin therapy in the hospital and continued long-term (Ray KK, et al. Early and Late Benefits of High-Dose Atorvastatin in Patients With Acute Coronary Syndromes: Results from the PROVE IT-TIMI 22 Trial. *J Am Coll Cardiol*. 2005;46:1405-1410). In another follow-up from the PROVE IT-TIMI 22 study in the same Journal, researchers looked at whether very low LDL levels from aggressive statin therapy are associated with adverse effects. Thirty-one percent of patients treated with atorvastatin achieved LDL levels between 80 and 60mg/dL, with another 34% between 60 and 40 mg/dL, and 11% less than 40 mg/dL. There were no significant differences in safety parameters, including muscle, liver, or retinal abnormalities, intracranial hemorrhage, or death in the very low LDL groups. Patients with LDL levels less than 60 had fewer major cardiac events, including death MI and stroke. The authors conclude that very low LDL levels are not associated with adverse effects, and appear to be associated with fewer adverse cardiovascular outcomes (Wiviott SD, et al. Can Low-Density Lipoprotein Be Too Low? The Safety and Efficacy of Achieving Very Low Low-Density Lipoprotein With Intensive Statin Therapy: A PROVE IT-TIMI 22 Substudy. *J Am Coll Cardiol*. 2005;46:1411-1416).

The Correct Dosing for Onychomycosis

Many physicians have prescribed terbinafine in a pulse-dosing regimen of 2 pills per day for one week, one week a month, for 3 to 4 months for the treatment of onychomycosis. The regimen is thought to increase compliance, as well as reduce cost. Pulse dosing however is not an approved therapy, and now a new study suggests that it is not as effective as once daily dosing.

The study recruited 306 volunteers with onychomycosis, involving at least 25% of the toenail. Patients were randomized to terbinafine 250 mg daily for 3 months or terbinafine 500 mg daily for one week per month for 3 months. Mycological cures were higher with once-a-day dosing (71% vs 58.7%; $P = .03$). Clinical cures were also higher with once-a-day dosing (44.6% vs 29.4%; $P = .007$), as were complete cures of target toenail (40.5% vs 28.0%; $P = .02$), and complete cure of all 10 toenails (25.2% vs 14.7%; $P = .03$). Tolerability of the regimens did not differ significantly between groups.

The authors conclude that once daily dosing appears to be superior to pulse dosing, however, they also found "this expensive therapy to me much less effective than previously believed, particular for achieving complete cure of all 10 toenails" (Warshaw EM, et al. Pulse Versus Continuous Terbinafine for Onychomycosis: A Randomized, Double-Blind, Controlled Trial. *J Am Acad Dermatol*. 2005;53:578-584).

FDA Actions

The FDA has approved the once-a-day oral iron chelator for the treatment of chronic iron overload due to blood transfusions. Novartis will market deferasirox (Exjade) as an oral alternative to intravenous chelating agents. ■