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The DHHS Pandemic Influenza Preparedness Plan

ABSTRACT & COMMENTARY

Synopsis: *The Department of Health and Human Services (HHS) has placed a draft influenza preparedness and response plan on its web site. This detailed document provides useful advice about health care system guidance on staffing, infection control, and strategies to limit transmission of infection within health care institutions.*

Source: www.hhs.gov/nvpo/pandemicplan. Accessed January 18, 2005.

THE UNEXPECTED SHORTFALL IN INFLUENZA VACCINE THIS YEAR, a result of manufacturing difficulties at Chiron, may lead to a potentially significant increase in the number of influenza cases seen in the United States. Although no pandemic strain has been identified, the Influenza Preparedness and Response Plan, currently posted on the HHS web site, provides much useful information to assist with program planning within health care systems.

In the United States, annual influenza epidemics are associated with an average of 36,000 excess deaths and more than 100,000 excess hospitalizations. Given the lack of vaccine, we can expect greater numbers this year. In addition to an increased number of patients presenting with influenza, we can anticipate higher rates of work absenteeism, as health care workers either become ill themselves or need to stay home to care for ill family members. Planning at the institutional level will need to consider not only bed availability alone, but shortages in human resources as potentially limiting factors.

Influenza has a typical incubation period of 2 days with a range of 1-4 days. Viral shedding (the period in which a person may be infectious, which may begin before symptoms start) typically can last 5-7 days, longer in young children and in immunocompromised individuals. Approximately 50% of persons infected with influenza do not develop symptoms, but still may shed virus. Droplet precautions are thought to be adequate to prevent spread in a setting with an appropriate number of air exchanges.

Specific recommendations include establishing influenza triage in waiting areas for persons with respiratory illness, early discharge of patients whenever feasible, potentially canceling elective admissions and surgeries, and implementing plans to enhance hospital infection control. Other options involve converting urgent care areas into temporary triage facilities for patients with respiratory illness, or setting up alternate sites for those at high risk of complications from influenza, such as immunocompromised patients. Strategies to increase bed availability include eliminating direct admissions, requiring all patients to present to the emergency room for evaluation of need for hospitalization, increasing home health care agency support to facilitate earlier discharge, and creating a patient discharge holding area or discharge lounge to free up bed space.

Suggested mechanisms to minimize influenza transmission in health care settings include placing patients in a private room or co-boarding them with other influenza cases, use of negative pressure rooms if feasible, designation of specific wards to house influenza patients, minimization of transport of patients outside the room, limiting the number of health care workers caring for influenza patients, and limiting the number of visitors to influenza patients' rooms.

COMMENT BY JAMES E. McFEELY, MD

It behooves all of us in the critical care community to pre-plan for an increase in respiratory illness this winter. While a pandemic is unlikely, there almost certainly will be an increase in consumption of hospital resources related to the lack of influenza vaccine. The posted HHS guidelines provide a very useful start for the planning process, which will require coordination among the emergency room, intensive care units, and hospital infection control policies. Investing time now in such planning will pay dividends later, either this year if needed or in the future should another airborne infectious outbreak materialize. ■

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Should DNI Equal DN-NPPV?

ABSTRACT & COMMENTARY

Synopsis: *This prospective multicenter observational study demonstrates that patients with do-not-intubate (DNI) status who receive non-invasive positive pressure ventilation (NPPV) for respiratory failure have high hospital mortality. Presence of cough, being awake, or having a primary diagnosis of COPD or CHF, is associated with improved outcome.*

Source: Levy M, et al. *Crit Care Med*. 2004;32(10): 2002-2007.

THIS STUDY'S OBJECTIVES WERE TO DESCRIBE THE percentage of patients receiving NPPV who have DNI orders, the outcomes in such patients, and the utility of primary diagnosis and clinical observation in predicting these outcomes. All patients receiving NPPV at 4 New England hospitals were screened; patients with a written DNI order were included in the study. Those receiving continuous positive airway pressure (CPAP) alone were excluded. Patient

data were gathered by respiratory therapists, who also administered the NPPV. Recorded data included age, admitting diagnoses, patient location, timing of DNI order, arterial blood gas, mask type, NPPV settings, cough (absent, weak or strong), secretions (present or absent) and mental status (not awake, awake or agitated). Measured outcomes were duration of NPPV, survival to hospital discharge and discharge placement. Usual statistical analyses were performed with stepwise logistic regression approach to identifying predictors of outcomes.

During a 10-month period, 114 patients with DNI orders (2 of whom had requested comfort measures only) received NPPV. These patients represented 9.4% of all patients receiving NPPV. (Only 20.2% of these patients had DNI orders in place prior to admission.) Median age of the study patients was 78 years and 37% were male. All had hypercapnic respiratory failure: some also had a component of hypoxemia. The 3 most common primary diagnoses were chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), and pneumonia. The majority of patients (67.5%) were treated on general medical wards. Oronasal masks were used for 97.4% of patients and the mean applied airway pressures were 13 ± 3 cm H_2O during inspiration and 5.3 ± 1.2 cm H_2O during exhalation. Most patients (83.3%) were judged to tolerate NPPV and mean use was 13.2 ± 2.4 hours. No serious complications (skin ulceration, aspiration) occurred. Overall, 49 patients (43%) survived to hospital discharge: of these, 17 of these went home. A primary diagnosis of COPD or CHF was associated with the highest survival (50-70% compared to < 30% for other diagnoses) and likelihood of discharge to home. Presence of cough and being awake were associated with survival but the presence of secretions was not.

COMMENT BY SAADIA R. AKHTAR, MD, MSC

Levy and colleagues' study has several limitations, including its observational nature, the potential biases introduced by having the same respiratory therapists collect study data and administer the NPPV, absence of a specific definition of DNI (was NPPV included in the discussion?) and the lack of clear measures of NPPV tolerance, patient and family satisfaction, and quality of life (before, during and after the experience). Despite these issues, I believe this work is an important contribution to the critical care community's continuing efforts to define the most appropriate applications for NPPV. It expands the very limited literature on use of NPPV for patients with DNI status and raises a number of valuable points.

The results of this study reinforce some things that are already known, such as that NPPV is effective and indicated in respiratory failure secondary to COPD exacerbation and that it is more effective in patients who are awake.[1,2] The study adds to data suggesting that NPPV may be beneficial for CHF and that it may be more useful for hypercapnic rather than purely hypoxemic acute respiratory failure.[3,4] It reminds us of (but does not try to answer) the ethical questions surrounding NPPV use in patients with DNI status and acute respiratory failure due to irreversible conditions: does NPPV prolong suffering or offer comfort for patients who are dying?

Finally, perhaps the most interesting and important finding in Levy et al's report is the fact that only about 20% of study patients had a DNI order in place prior to the current admission for acute respiratory failure. Providing the best possible care for our patients means giving them the information necessary to understand their health status, prognosis and care options as well as offering time and opportunities for open discussion so that decisions about level of care may be made before acute crises occur. The study findings suggest that health care providers must make a much greater effort to have such conversations with patients. Furthermore, they must explicitly describe and address NPPV, with inclusion of data from studies such as this.

For patients who are willing to consider NPPV but not endotracheal intubation, I suggest using NPPV for standard indications: acute respiratory failure secondary to COPD or (as a second-line after CPAP) cardiogenic pulmonary edema. Otherwise, until there is a large, well-done, randomized, controlled trial of NPPV in patients with DNI status and acute respiratory failure which includes usual medical as well as quality of life measures, the only firm recommendation I can make is to encourage thoughtful, well-informed decision-making at all levels. ■

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Narcotics, Benzodiazepines, and Hastening Death after Withdrawal of Life Support

ABSTRACT & COMMENTARY

Synopsis: *This study found no evidence that the use of narcotics or benzodiazepines to treat discomfort after the withdrawal of life support hastens death in critically ill patients at our center. Clinicians should strive to control patient symptoms in this setting and should document the rationale for escalating drug doses.*

Source: Chan JD, et al. *Chest*. 2004;126:286-293.

A RETROSPECTIVE CHART REVIEW WAS CONDUCTED over an 8-month time period to determine whether the doses of narcotics and benzodiazepines were associated with the length of time between removal of mechanical ventilation and death among ICU patients for whom life sustaining treatments were being withdrawn. The study, conducted at a university affiliated level I trauma center on the West Coast, included 75 ICU patients with a mean age of 59 years. Patient diagnoses included intracranial hemorrhage (37%), trauma (27%), acute respiratory failure (27%), and acute renal failure (20%).

Results revealed that once the process of ventilator withdrawl was initiated, patients died within a median of 35 minutes (range, 1-890 minutes). Cumulative amounts of benzodiazepines and narcotics were calculated during 3 time periods: 1) 24 hours before death, 2) time from 1 hour after ventilator withdrawl until time of death, and 3) 2-hour period prior to death (*see Table*). Morphine and lorazepam were the primary agents used and were administered by both bolus and continuous infusion during life support withdrawl. When life-sustaining therapy was anticipated, the doses of narcotics and benzodiazepines increased significantly ($P < 0.001$). Multivariate linear regression modeling demonstrated no statistically significant relationship between either benzodiazepine or narcotic dose during the time interval from 1 hour prior to ventilator withdrawl until death and the outcome of time to death from ventilator discontinuation.

Table

Morphine and Benzodiazepine use During Withdrawal of Life Support

Drug	Last 24 hours of life	1 hr after ventilator withdrawal until death	Last 2 hours of life
Morphine (equilavents)	4 mg/hr	16.2 mg/hr ($P < 0.001$)	18.1 mg/ hr ($P < 0.001$)
Benzodiazepine (equilavents)	1.6 mg/hr	7.5 mg/hr ($P < 0.001$)	9.2 mg/ hr ($P < 0.001$)

COMMENT BY KAREN L. JOHNSON, PhD, RN

Critical care physicians and nurses may withhold or limit the use of narcotics and benzodiazepines at the end of life for fear that others may perceive they are hastening death. The results of this study add to an increasing body of knowledge that this perception is not reality. This investigation found no evidence that the use of narcotics and benzodiazepines after withdrawl of life support hastened death in this sample of critically ill patients. Chan and colleagues did not find a relationship between an increased narcotic dose and time to death during the last 2 hours of life ($P = 0.11$). Chan et al did find a relationship, however, between the dose of benzodiazepines and death: increased dosages were associated with an increase in time to death! On average, every 1 mg/hour increase in benzodiazepine use corresponded to a statistically significant increase in duration of time between ventilator withdrawal and death ($P = 0.015$). Although admitting that these results need to be confirmed in a larger study, Chan et al offer 2 possible explanations: 1) patients who survive longer may have developed benzodiazepine tolerance and therefore required a larger dose, and 2) the anxiolytic effect of benzodiazepines may have achieved a calming effect in these dying patients, without the compromise of hastening death.

Another interesting (yet not surprising) finding was justifications for medication dosage increase during these times were not consistently documented in the medical record using pain or sedation scores. Chan et al (or therefore anyone else reviewing the chart) could not determine whether the levels of analgesia and sedation were appropriate. Granted, assessing pain and sedation in these patients is difficult due to impaired cognition and communication. However, doesn't the lack of documentation of the need for increasing the dose of these drugs fuel the perception that they are given to hasten death? The only way to eliminate the perception (or the fear of the perception) is for clinicians to document the rationale for escalating drug doses. The perception that narcotic and benzodiazepine use hastens death can be eliminated by a 2-pronged approach: 1) More studies, such as this one, that demonstrate there is no relationship between the use of these

drugs and time of death, and 2) thorough documentation in the medical record on the rationale for use and dose of these drugs. Only then will perception equal reality that the use of narcotics and benzodiazepines after withdrawl of life support limits discomfort during end of life care. ■

Special Feature

Cytotoxic Effects of Stress Induced Hyperglycemia

By Karen L. Johnson, PhD, RN

In 2001, the Leuven study was the first randomized control trial that demonstrated the benefit of controlling hyperglycemia in non-diabetic critically ill surgical patients.[1] Van den Berghe and colleagues demonstrated that intensive insulin therapy to maintain blood glucose at or below 110 mg/dL reduced mortality and morbidity (*see Table 1*). Krinsley compared the outcomes of 800 patients admitted consecutively to the ICU immediately before the onset of a glucose management protocol to those first 800 patients admitted after institution of the protocol.[2] This more recent study reported similar findings in a heterogeneous population of non-diabetic critically ill adults: reduced hospital mortality 29.3% (P = .002), decreased ICU length of stay 10.8% (P = .01), reduction in renal insufficiency 75% (P = .03), and reduction in use of RBC transfusions 18.7% (P = .04).

Based on this emerging evidence, there are increased efforts around the world to maintain strict glycemic control in non-diabetic critically ill patients.

Table 1

Results of the Leuven Study

Normoglycemia resulted in a reduction of:

- Overall mortality
- Mortality in patients with ICU stay greater than 5 days
- Episodes of septicemia
- Polyneuropathy
- Median number of RBC transfusions
- Median TISS-28 scores
- Markers of inflammation
- Duration of mechanical ventilatory support in patients with ICU stays greater than 5 days
- Need for renal replacement therapy

Management of hyperglycemia through the use of insulin protocols is a new standard in critical care. Several protocols have been evaluated and reported in the literature.[2-5]

How could such a simple intervention, preventing hyperglycemia with insulin, prevent sepsis, MODS, and death? Why would preventing acute hyperglycemia improve mortality and morbidity in this patient population? What is the mechanism by which acute hyperglycemia causes so many complications? The answers to these questions are complex and largely speculative.

The purpose of this essay is to present some of the evidence currently available on the cytotoxic effects of stress induced hyperglycemia. Understanding the mechanisms through which stress hyperglycemia occurs and the role it plays in patient outcomes may enable clinicians to understand the importance of glycemic control in non-diabetics in the ICU. We will begin with a review of the etiology of hyperglycemia in this patient population.

Stress Induced Hypergylcemia

The initial physiologic response to acute stress (injury, illness) results in an increased availability of metabolic substrates for energy production: free fatty acids, amino acids, and glucose. This acute metabolic response is initiated by activation of the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system. Excessive counterregulatory hormone release and overproduction of cytokines are the major factors responsible for stress hyperglycemia in the non-diabetic host.[6] Epinephrine and norepinephrine via adrenergic activity directly inhibit insulin secretion. Epinephrine decreases hepatic glycogen synthesis, increases glycogenolysis, increases hepatic gluconeogenesis and increases skeletal muscle insulin resistance by altering post-receptor signals. Cortisol increases gluconeogenesis and contributes to skeletal muscle insulin resistance.

Insulin resistance is defined as the existence of metabolic characteristics of insulin deficiency (protein catabolism, hyperglycemia, lipolysis) despite adequate plasma insulin concentration.[7] The mechanism underlying the inability of hyperinsulinemia to suppress hepatic gluconeogenesis is unknown. However, skeletal muscle is the major site of reduced insulin-mediated glucose disposal and this contributes to whole body insulin resistance in critical illness.[8,9] Overall, stress hyperglycemia results from a combination of enhanced hepatic glucose production and decreased peripheral glucose utilization via insulin resistance.

Prior to the late 1990's, there was little argument for medical interference with this normal physiologic

Table 2

Stress Induced Hyperglycemia is Associated with Adverse Clinical Outcomes

Patient Population	Adverse Clinical Outcomes	Reference
Severe head injury	Diminished neurologic recovery, increased mortality	11
Acute stroke	Diminished neurologic recovery, increased mortality	12,13
Myocardial Infarction	Increased rates of heart failure, cardiogenic shock, and mortality	14,15
Trauma	Higher rates of infection and mortality (independent of severity of injury or shock)	16
Burn	Increased mortality and infection rates, reduced skin graft take	17

process during the first few hours or days of critical illness or trauma.[10] In the past several years, however, an increasing amount of evidence suggested otherwise.

Stress hyperglycemia, defined as a blood glucose greater than 200 mg/dL, is most often evident shortly after admission to the ICU.[6] It has been associated with adverse clinical outcomes in a variety of critically ill patients including those with closed head injury, stroke, myocardial infarction, trauma, and burns (*see Table 2*). As demonstrated in the Leuven[1] and Kinsley[2] studies, these complications decreased with normoglycemia induced with insulin. These results prompt the question, Are the benefits brought about directly by the infused insulin per se, or by the prevention of hyperglycemia?

In an effort to answer this question, Van den Berghe et al returned to their original data to examine the factors determining insulin requirements and the impact of insulin dose versus blood glucose control on the observed outcome benefits.[18] Mulivariate logistic regression analysis indicated that it was actually the lowering of blood glucose (rather than amount of insulin) that was associated with the reduction in mortality ($P < .001$), critical illness polyneuropathy ($P < .001$), bacteremia ($P = .02$), and inflammation ($P = .0006$).

Why is acute hyperglycemia so toxic in critically ill patients when it takes years for hyperglycemia to cause disorders in diabetic patients? How is acute hyperglycemia toxic to cells? The effects of acute hyperglycemia appear to cause both intra- and extracellular pathophysiologic processes.

Intracellular Cytotoxic Effects of Stress-Induced Hyperglycemia

A recent review suggests that intracellular cytoxic effects of stress induced hyperglycemia maybe due to mitochondrial dysfunction as a result of accentuated intracellular glucose overload and more pronounced toxic side effects of glycolysis and oxidative phosphorylation.[19] A quick review of cellular glucose uptake helps to put this explanation into context.

Normal Cellular Uptake of Glucose

Skeletal muscle is the major site of peripheral insulin mediated glucose uptake in humans, accounting for 80% of whole body glucose disposal under hyperinsulinemic-euglycemic clamp conditions.[20] Stimulation of the movement of glucose into skeletal muscle is a critical component of the physiologic response to insulin. The insulin receptor is a transmembrane heterodimeric protein receptor. When insulin binds with it, insulin receptor substrate molecules phosphorylate. From there, intracellular signaling pathways culminate in the translocation of intracellular glucose transporters to the cell membrane. The GLUT transporters act as vesicles to transport glucose inside the cell. In skeletal muscle, this involves translocation of GLUT-4 and GLUT-1 vesicles. GLUT-4 transporters are insulin dependent and can become activated and increase glucose uptake several fold. GLUT-1 transporters ensure basal glucose uptake into cells. GLUT-1 transporters downregulate in normal cells when exposed to hyperglycemic conditions to protect the cell. Upon insulin removal, the transporters return to their intracellular pool.

Uptake of glucose by skeletal muscle cells is dependent on the GLUT-4 insulin-dependent transporters. Other cells take up glucose independently of insulin. Cellular compartments that take up glucose independently of insulin include the central and peripheral nervous system, hepatocytes, and endothelial, epithelial, and immune cells.[19] GLUT-1, GLUT-2, and GLUT-3 transporters facilitate insulin independent glucose transport into these tissues (*see Table 3*).

Table 3

GLUT Transporters

GLUT Transporters	Facilitate:	Cells
GLUT-1 GLUT-2 GLUT-3	Insulin independent glucose transport	Vascular smooth muscle Central nervous system Peripheral nervous system Hepatocytes Endothelial Epithelial Immune
GLUT-4	Insulin dependent glucose transport	Skeletal muscle

Once inside the cell, glucose is phosphorylated into either glycogen for storage or glycolysis, which leads to its use in the Krebs Cycle resulting in energy production via oxidative phosphorylation. In the presence of oxygen, aerobic metabolism ensues. Glucose undergoes glycolysis where pyruvate is transformed to acetyl coenzyme and oxidative phosphorylation generates adenosine triphosphate (ATP). A small amount of superoxide is produced, but it is detoxified by manganese superoxide dismutase.

Hyperglycemia Induced Mitochondrial Dysfunction

Angiogensin II, hypoxia, cytokines, and endothelin-I have been shown to upregulate expression and membrane localization of GLUT-1 and GLUT-3 transporters.[21-24] When high levels of these substances are present, as they frequently are in critically ill patients, more glucose enters cells.

As more glucose enters cells and aerobic metabolism occurs, more superoxide is produced. It reacts with nitric oxide to form peroxynitrite. Peroxynitrite breakdown intracellular proteins, most notably mitochondria. The formation of peroxynitrite is compounded in critical illness in the presence of iNOS and additional superoxide production from hypoxia/reperfusion.[25] Therefore, it appears that intracellular hyperglycemia induces mitochondrial dysfunction in those cells that take up glucose independent of insulin (*see Table 3*).

Postmortem liver biopsies performed in the Leuven study seem to support this mechanism. Hepatocytes use GLUT-1, GLUT-2, and GLUT-3 transporters facilitate insulin independent glucose uptake. Liver biopsies revealed profound abnormalities in hepatocyte mitochondria in patients who received conventional insulin therapy but no major abnormalities in patients who remained normoglycemic.

Controlling hyperglycemia may prevent mitochondrial dysfunction in cells that allow glucose to enter passively and may explain some of the results of reported in the Leuven study.[1] (*see Table 4*). Further investigation of the mitochondrial abnormalities in tissues that take up glucose passively should be investigated in greater detail.

Extracellular Cytoxic Effects of Stress Hyperglycemia

Intracellular hyperglycemia induced mitochondrial dysfunction only explains some of the pathophysiology of stress induced hyperglycemia. While increased intracellular glucose occurs in some cells, there appears to be decreased glucose uptake by other cells, particularly in skeletal muscle cells. This results in extracellular hyperglycemia.

Hyperglycemia, commonly associated with septic shock, may be the result of insulin resistance in skeletal muscle cells. Experimental data from rats indicate that LPS alters multiple steps in the insulin signal transduction pathway.[26] Glucocorticoids impair insulin mediated glucose uptake in skeletal muscle likely by inhibiting translocation of the GLUT-4 transporter.[27] Defects of GLUT-4 may be the underlying mechanism of peripheral insulin resistance in critical illness.[28] TNF-a produces insulin resistance in both liver and skeletal muscle through modification of signaling properties of insulin receptor substrates.[29] Interestingly, prolonged bedrest (seven days) produced insulin resistance in skeletal muscle in healthy subjects.[30] Catecholamines may also play a role in insulin resistance. Blockade of beta-2 adrenergic receptors prevents the decline in insulin-mediated glucose uptake in septic rats.[31]

Overall the mechanisms by which insulin signal transduction pathways and/or GLUT4 expression and function may be altered leading to reduced insulin-stimulated glucose disposal in critical illness are far from established. But the net result is increased extracellular glucose.

Many theories have been postulated and there is extensive research in an effort to explain the pathogenesis of prolonged hyperglycemia and its effect on biochemical changes in cells, but less is known about the effects of short term acute hyperglycemia. Short term hyperglycemia increases apoptosis in cultured endothelial cells.[32,33] After several days of exposure to hyperglycemic conditions, endothelial cells have increased oxidative stress, increased intracellular calcium, loss of mitochondrial polarization, and decreased

Table 4

Correction of Hyperglycemia in Cells that Allow Passive Glucose Transport May Explain Leuven Study Results

Cells that allow passive glucose transport	Effect of hyperglycemia on the cells	Leuven results with normoglycemia
Immune cells	↓macrophage function ↓neutrophil function	↓sepsis ↓nosocomial infections
Renal tubular cells	↓erythropoesis	↓# transfusions
Peripheral nervous system	Polyneuropathy (axonal dysfunction and degeneration)	↓rate of polyneuropathies(↓need for mechanical ventilation)
Central nervous system	↑ICP	↓ICP, ↓seizures, ↓DI

intracellular ATP content.[34] Acute hyperglycemia decreases respiratory burst of alveolar macrophages and influences phagocytic cells,[35] impairs immune function by altering cytokine production from macrophages and decreases lymphocyte proliferation.[36] Acute hyperglycemia increases release of IL-6 and TNF—which suggests a pivotal role of hyperglycemia in the inflammatory responses in sepsis.[37]

Summary

Stress-induced hyperglycemia, associated with adverse clinical outcomes, is present within hours of ICU admission and results from a combination of enhanced glucose production, increased glucose uptake by some cells, and decreased peripheral glucose uptake by skeletal muscle cells (via insulin resistance). Increased glucose uptake produces mitochondrial dysfunction as a result of accentuated intracellular glucose overload and more pronounced toxic side effects of glycolysis and oxidative phosphorylation. Peroxynitrite forms and breaks down intracellular proteins, most notably the mitochondria. The net result is mitochondrial dysfunction. Insulin resistance results in decreased glucose uptake by skeletal muscle cells with the net result of increased extracellular glucose concentrations. Exposure to hyperglycemic conditions has negative effects on cells particularly endothelial cells and immune cells and also potentates cytokine release.

Controlling stress-induced hyperglycemia with insulin in non-diabetic critically ill patients decreases morbidity and mortality. The intracellular and extracelluar effects of stress-induced hyperglycemia have been elucidated in an effort to help clinicians better understand why prevention of stress induced hyperglycemia via insulin protocols is so important in decreasing the morbidity and mortality of critical illness. ■

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CME / CE Question

27. The number of deaths in the United States each year related to influenza is estimated to be:

a. 10,000.
b. 36,000
c. 60,000
d. 100,000

Answer: 27 (b)

In Future Issues: Troubleshooting the Ventilated Patient in Distress

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.*

Statins and the Incidence of Rhabdomyolysis

The most commonly prescribed statins have a low incidence of rhabdomyolysis, according to the results a new study of more than 250,000 patients. Atorvastatin, pravastatin, and simvastatin were found have very low and virtually indistinguishable rates of rhabdomyolysis of 0.44 per 10,000 person-years (95% CI, 0.20-0.84). The data were obtained from 11 managed care health plans across United States from January 1, 1998, through June 30, 2001. Cerivastatin (Baycol-Bayer), which was withdrawn from the market in 2001, was found have a much of a higher rate of rhabdomyolysis, 5.34 cases per 10,000 person-years (95% CI, 1.46-13.68). The concomitant use of a fibrate with atorvastatin, pravastatin, or simvastatin was found to have increased the rate to 5.98 (95% CI, 0.72-216.0), while use of a fibrate with cerivastatin dramatically increased the rate to 1035 cases per 10,000 person-years of treatment (95% CI, 389-2117), or nearly 1 in 10. Older patients, especially those with diabetes, were found to have higher rates of rhabdomyolysis. The authors conclude that the most commonly prescribed statins have a low incidence of rhabdomyolysis, which is increased with the addition of a fibrate (*JAMA.* 2004;292:2585-2590).

The study confirms the safety of the most commonly used statins, but raises issues regarding the post marketing surveillance of cerivastatin. These concerns were addressed in a review in the same issue of *JAMA* regarding the potential conflict of interest once initial reports of rhabdomyolysis were reported to the company, and the delay in the availability of this information to consumers. The critique is accompanied by Bayer's rebuttal (*JAMA.* 2004;292:2622-2631, 2643-2646, 2655-2657, 2658-2659), which makes fascinating reading given the recent criticisms of the FDA and post marketing surveillance regarding coxibs.

A Crackdown on Importation of Drugs

Officials in both the United States and Canada are taking steps to crack down on the importation of prescription medications across the border. A New York District Court issued an injunction in December against Canada Care Drugs Inc., which gave the FDA authority to inspect the company to assure that they no longer import drugs to American consumers. The FDA had petitioned the court to take this action based on a sting operation run by the agency. FDA investigators purchased Neurontin and Sporanox through Canada

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Care. Instead of Neurontin, investigators received APO-gabapentin and NOVO-gabapentin, formulations of the drug that are not subject to FDA scrutiny in this country. The Sporanox shipment included 84 tablets of the correct drug, but investigators felt that the amount was excessive, determining that patients should not take Sporanox continuously without checking with their physician. The court is scheduling a trial date for Canada Care, an action that is sure to put other Canadian importation companies on alert. Meanwhile, the Canadian government is also cracking down on Internet pharmacies that export drugs to the United States without evaluation by Canadian doctors. The government is considering making it illegal for Canadian doctors to countersign prescriptions from other countries. This move in Canada is prompted by concern over shortages of drugs for Canadian citizens, especially given threats by American drug companies to withhold additional shipments of drugs to Cananda, where they have strict price controls, knowing that many of these drugs may come back to the US market were there are no price controls. These moves are strongly supported by PhRMA, the powerful pharmaceutical advocacy group.

FDA Actions

The FDA has approved a new non-benzodiazepine hypnotic for the treatment of insomnia. Sepracor, a company that specializes in marketing active isomers of currently approved drugs, has received approval to market eszopiclone, the active (S)-isomer of zoplicone, which is available outside the United States. The drug is similar to zopidem (Ambien) and zaleplon (Sonata) in that it has a lower incidence of tolerance, dependence, and withdrawal symptoms than benzodiazepines. Based on a 6-month, double-blind, placebo-controlled safety and efficacy trial, the FDA decided not to limit eszoplicone's indication to short-term use. Eszoplicone will be available in 1mg, 2mg, and 3mg tablets, and will be marketed in United States under the trade name Lunesta. Sepracor is also studying the drug for treatment of insomnia in patients with depression or pain, and in peri-menopausal women.

Novartis has received approval to market darifenacin extended release tablets for the treatment of overactive bladder with symptoms of urging incontinence, urgency, and frequency. The drug is an M3 (muscarinic) receptor blocker that increases urinary capacity and decreases urinary episodes and frequency of incontinence, along with feelings of urgency. Darifenacin, which is already available in Europe, will be marketed in the United States as Enablex.

Drugs approved under the FDAs accelerated approval program are often approved on the basis of surrogate end points, such as tumor markers that would indicate the likelihood of clinical benefit. The FDA, however, requires that cancer drugs in particular, must document clinical benefit in subsequent studies to remain marketable. A recent case-in-point is AstraZeneca's gefitnib (Iressa), which was approved for treatment of non small cell lung cancer in patients who failed other courses of cancer therapy. A recent study of gefitnib involving nearly 1700 patients failed to show a survival benefit better than placebo. The drug, which was initially approved in 2003, now faces a FDA review to determine whether the drug will be removed from the market. In a letter to physicians, AstraZeneca "urges you to consider other treatment options in recurrent non small cell lung cancer patient population." In the meantime, Genentech and Roche's erlotinib (Tarceva), which has shown survival benefit for the same patient population, remains a viable option.

The FDA has issued a Public Health Advisory regarding the use of anti-inflammatories including COX-2 inhibitors because of recent indications that the drugs may increase the risk of cardiovascular disease and stroke. The agency is requiring evaluation of all prevention studies that involve the COX-2 inhibitors celecoxib (Celebrex) and valdecoxib (Bextra) to ensure that adequate precautions are in place. Several prevention studies regarding potential benefit of these drugs on colon polyps and Alzheimer's disease are either in progress or planned in the near future. Meanwhile, the agency is recommending that physicians should prescribed Celebrex or Bextra with caution, particularly in patients at risk for cardiovascular disease, and should weigh the risk vs benefits.

The FDA is also recommending that consumers should use over-the-counter anti-inflammatories in strict accordance with the label directions, taking them for no longer than 10 days without consulting a physician. ■