Insulin before surgery

(NOVEMBER 2013)

TO THE EDITOR: We appreciated the thoughtful 1-Minute Consult by Drs. Dobri and Lansang, "How should we manage insulin therapy before surgery?"[1] We agree with them in regard to the benefits of perioperative control of blood glucose levels. However, we disagree in general with their assertion that the full dose of the patient's home dose of basal insulin be administered while the patient is *nil per os* (NPO) before surgery, with a reduction to 75% of the home dose only if the patient has a history of hypoglycemia, a recommendation that did not differentiate between patients with type 1 and type 2 diabetes mellitus.

The RABBIT 2 Surgery trial,[2] which showed superiority of basal-bolus insulin over sliding scale insulin in surgical patients with type 2 diabetes mellitus, also showed a surprisingly high rate of hypoglycemia—24 (23.1%) of 104 patients had blood glucose levels lower than 70 mg/dL, compared with a similar trial in nonsurgical patients in which 2 (3.1%) of 65 patients had a blood glucose level less than 60 mg/dL.[3] The authors of the two studies explained[2] that "differences in hypoglycemic events between the two trials could be in part explained by reduced nutritional intake in surgical patients…"

Although patients with well-controlled type 1 diabetes mellitus may tolerate their full dose of basal insulin while NPO, we contend that patients with type 2 diabetes mellitus should be prescribed a reduced dose of basal insulin while NPO, regardless of the dose distribution or the patient's overall glycemic control. It is routine practice on our consult service to reduce the basal insulin dose in such patients by roughly half.

KAITLIN DITCH, MD
Department of Internal Medicine
University of Kansas School of Medicine-Wichita

JUSTIN MOORE, MD
Department of Internal Medicine
University of Kansas School of Medicine-Wichita

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IN REPLY: We appreciate the kind words of Drs. Ditch and Moore, as well as their opinion.

Our article was intentionally brief—a 1-Minute Consult—and so could not cover all specific situations we encounter in clinical practice. We meant only to provide a general approach in this matter.

Quite often before surgery, patients receive less basal insulin than needed, or none at all, rather than too much. It has to be borne in mind that perioperative hyperglycemia—not just hypoglycemia—is linked with poor outcomes in cardiac[1] and noncardiac surgery.[2,3]

Through our scenarios and suggestions, we have taken steps to err on the side of preventing hypoglycemia while averting hyperglycemia, at the same time making it easy to calculate the dose. In a scenario in which the basal insulin dose is about the same as the total of the prandial boluses, we have not yet seen evidence that raises concern for hypoglycemia, maybe because many of the patients with type 2 diabetes seen in our institution for surgery take, in addition to insulin, oral agents or noninsulin injections (which are appropriately withheld before surgery), and have suboptimal glycemic control on their home regimen. But if a physician has concerns for hypoglycemia, a dose reduction should be made.

There were some differences between the RABBIT 2 trial in medical patients[4] and the RABBIT 2 Surgery trial[5] that would make the results not completely comparable. In RABBIT 2, the medical patients included were on diet alone or any combination of oral antidiabetic agents (not on insulin), and

they were started on a total daily dose of insulin of either 0.4 or 0.5 U/kg/day, depending on the glucose level. In RABBIT 2 Surgery, patients who were on insulin at home with a total daily dose of 0.4 U/kg or less were also included, and the starting daily dose of insulin was 0.5 U/kg (unless they were older or had a high serum creatinine).

In view of all the above, we agree with Drs. Ditch and Moore that if there is concern for hypoglycemia, the clinician should reduce the insulin dose in the manner that evidence from the local practice suggests, without causing undue hyperglycemia and postsurgical complications.

GEORGIANA A. DOBRI, MD
Department of Endocrinology, Diabetes, and Metabolism
Endocrinology and Metabolism Institute
Cleveland Clinic

M. CECILIA LANSANG, MD, MPH
Department of Endocrinology, Diabetes, and Metabolism
Endocrinology and Metabolism Institute
Cleveland Clinic
Cleveland Clinic Lerner College of Medicine of Case Western Reserve University

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A comment on a CME test question

(DECEMBER 2013)

TO THE EDITOR: Question 1 of the December 2013 CME test "Can an ARB be given to patients who have had angioedema on an ACE inhibitor?" presents the case of a 73-year-old woman with angioedema thought to be due to her taking enalapril; in addition, she takes hydrochlorothiazide. Her blood pressure is 118/72 mm Hg, and her heart rate is not specified. The question is what the next best step would be to manage her blood pressure medications. The "correct" answer is given as "substitute metoprolol for enalapril in her regimen."

While this answer is the best choice given, I would take issue with it for two reasons. First, many elderly hypertension patients are overmedicated. With a blood pressure of 118/72 on two medications, it is entirely possible that she may not need to replace the enalapril with any other medication to maintain her pressure below the new JNC 8 threshold of 150/90 for the elderly, or even the 140/90 level specified in other guidelines.

I would recheck her pressure daily on her diuretic alone before adding back a second medication. If she does require a second blood pressure medication, JNC 8 (in agreement with other recent guidelines) recommends adding a calcium channel blocker. Beta-blockers are not recommended by any recent guidelines for first-line or second-line treatment of hypertension for elderly patients without special indications, such as tachyarrhythmias or history of myocardial infarction. No special indications for a beta-blocker were mentioned in this case. Indeed, elderly hypertensive patients often have slow-normal heart rates, or even mild resting bradycardia, which would make the addition of metoprolol contraindicated and potentially dangerous.

DAVID L. KELLER, MD
Providence Medical Group
Torrance, CA

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Stress ulcer prophylaxis

(JANUARY 2014)

TO THE EDITOR: In the January 2014 issue, Eisa et al[1] suggested that patients who require prolonged mechanical ventilatory support, ie, for more than 48 hours, should receive stress ulcer prophylaxis. This recommendation came from a study by Cook et al[2] in 1994, which found a significant increase in the risk of gastrointestinal blood loss in this group of patients. Other studies have shown a different result. Zandstra et al[3] found an extremely low rate of stress ulcer-related bleeding in this group in the absence of stress ulcer prophylaxis. Another study[4] in critically ill patients also found no relationship between stress ulcer incidence and prolonged mechanical ventilatory support. Interestingly, that study found that prolonged use of a nasogastric tube is the major risk factor for developing a stress ulcer.[4] The explanation for why newer studies did not demonstrate the relationship between mechanical ventilation and stress ulcer development may lie in the result of a meta-analysis by Marik et al,[5] which showed that stress ulcer prophylaxis may not be required in a patient who receives early enteral nutrition. That practice was not common in the past, including at the time the original study was conducted.

According to current evidence, mechanical ventilation for more than 48 hours does not seem to increase the risk of stress ulcer. The medical community should start questioning the routine practice of stress ulcer prophylaxis in this group of patients. In addition, more studies have identified the adverse effects of acid-suppression therapy in this group of patients, and these effects likely make the harms outweigh the benefits. This notion was confirmed in the most recent meta-analysis by Krag et al.[6] In summary, the practice of routine stress ulcer prophylaxis in all mechanically ventilated patients will likely change in the future, with more focus on patients who are at higher risk.

DAYCH CHONGNARUNGSIN, MD
Cleveland Clinic

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IN REPLY: We welcome the comments from Dr. Chongnarungsin on our article and the opportunity to further discuss our opinions.

In our paper, we discussed current recommendations for prophylaxis of stress ulcer-related bleeding in hospitalized patients and advocated against the blind administration of drugs without risk stratification.

The landmark trial that provides the most-cited definitions and the risk factors for clinically significant stress ulcer-related bleeding in critically ill patients was published in 1994 by Cook et al.[1] In their multicenter prospective cohort study of 2,252 patients, the authors reported that prolonged mechanical ventilation is an important risk factor for clinically significant stress ulcer-related bleeding.

Another major prospective cohort study observed an incidence rate of clinically significant stress ulcer-related bleeding of 3.5%.[2]

Dr. Chongnarungsin cites another prospective cohort study of 183 patients from the same era,[3] wherein the authors defined stress ulcer-related bleeding as bleeding requiring transfusion of packed red blood cells, found on endoscopy or on postmortem evaluation. This was in contrast to the 1994 study of Cook et al,[1] who had a more rigorous and comprehen-

sive definition for overt and clinically significant stress ulcer-related bleeding, applied by up to three independent adjudicators not involved in the patients' care. Their definition not only entailed a more accurate transfusion-dependent bleeding criterion, but also included hemodynamic and laboratory criteria. As such, the "very low rate" of stress ulcer-related bleeding reported by Zandstra et al[3] should be critically appraised. Of note, the authors in that study did not report the rates of patients who received early enteral feeding, and their patients received cefotaxime for digestive tract decontamination, an important confounder to the interpretation of the study results.

Indeed, the remarkable variation in estimates of the incidence of stress ulcer-related bleeding is probably related to the lack of a uniform definition. Even when rates of endoscopic and occult bleeding are set aside, agreement is lacking as to which category of bleeding is clinically significant.

Dr. Chongnarungsin also cites the study by Ellison et al[4] of a cohort of 874 patients who had no previous gastrointestinal bleeding or peptic ulcer disease and who were enrolled in a multicenter randomized controlled trial of prophylactic intravenous immune globulin to prevent infections associated with an intensive care unit. In a secondary objective, the authors did not identify coagulopathy or prolonged mechanical ventilation as a principal risk factor for bleeding. The authors ascribed this discrepancy with previously published literature to their unique study population, which consisted predominantly of elderly men and rarely included trauma patients. In light of these unique peculiarities of their population, the lack of an association between prolonged mechanical ventilation and stress ulcer-related bleeding cannot be determined. Moreover, that study showed that prolonged nasogastric tube insertion was one of the risk factors for increased risk of gastrointestinal bleeding, and not the risk factor for development of stress ulcer as stated by Dr. Chongnarungsin.

The decrease in the incidence of stress ulcer-related bleeding in critically ill patients over the years could be attributed to an era effect, from advances in critical care medicine and prophylactic methods.[5] We agree with Dr. Chongnarungsin that the increased introduction of early enteral feeding may have also contributed to the reduced incidence of stress ulcer-related bleeding.[6] However, we think the conclusion that "mechanical ventilation for more than 48 hours does not seem to increase the risk of stress ulcer" is overelaborated, and we believe that strong evidence demonstrates this association.[1,2]

Alternatively, we recognize the lack of mortality-benefit evidence for stress ulcer prophylaxis. This notwithstanding, according to recent Surviving Sepsis Campaign guidelines, the use of stress ulcer prophylaxis is listed as a 1B recommendation (strong recommendation) for severely septic patients who require prolonged mechanical ventilation. In addition, the updated 2014 guidelines of the American Society of Health-System Pharmacists[7] continue to recommend stress ulcer prophylaxis in the context of mechanical ventilation, with H2 receptor antagonists being the preferred first-line agents.[8]

It is important to acknowledge that these recommendations were endorsed despite the lack of obvious mortality benefit, and it is our opinion that large randomized controlled studies are needed to evaluate the risks and mortality benefit of these prophylaxis methods.

FATEH BAZERBACHI, MD
University of Minnesota, Minneapolis

NASEEM EISA, MD
Cleveland Clinic

ABDUL HAMID ALRAIYES, MD
Tulane University health Sciences Center, New Orleans, LA

M. CHADI ALRAIES, MD
University of Minnesota, Minneapolis

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Albuminuria

(JANUARY 2014)

TO THE EDITOR: Stephen et al[1] have written a nice review of the implications of albuminuria. However, they are clearly incorrect when they state, "Most of the protein in the urine is albumin filtered from the plasma."[1] First, as they later point out in the article, the normal upper limit of protein excretion is about 150 mg/day, and only about 20 mg/day is normally albumin. Therefore, most of the protein in normally found in urine is not albumin, but instead is mostly a variety of globulins. Tamm-Horsfall mucoprotein or uromodulin is usually the protein found in highest concentration in normal urine.

MICHAEL EMMETT, MD
Baylor University Medical Center,
Dallas, TX

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