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HOSPITAL MANAGEMENT OF DIABETES (G UMPIERREZ, SECTION EDITOR)

The Use of Non-Insulin Anti-Diabetic Agents to Improve Glycemia Without Hypoglycemia in the Hospital Setting: Focus on Incretins

Stanley Schwartz · Ralph A. DeFronzo

Abstract Patients with hyperglycemia in hospital have increased adverse outcomes compared with patients with normoglycemia, and the pathophysiological causes seem relatively well understood. Thus, a rationale for excellent glycemic control exists. Benefits of control with intensive insulin regimes are highly likely based on multiple published studies. However, hypoglycemia frequency increases and adverse outcomes of hypoglycemia accrue. This has resulted in a 'push' for therapeutic nihilism, accepting higher glycemic levels to avoid hypoglycemia. One would ideally prefer to optimize glycemia, treating hyperglycemia while minimizing or avoiding hypoglycemia. Thus, one would welcome therapies and processes of care to optimize this benefit/ risk ratio. We review the logic and early studies that suggest that incretin therapy use in-hospital can achieve this ideal. We strongly urge randomized prospective controlled studies to test our proposal and we offer a process of care to facilitate this research and their use in our hospitalized patients.

Keywords In-hospital diabetes control · Incretins · DPP-4 inhibitors · GLP-1 receptor agonists · Intensive insulin therapy · Noninsulin anti-diabetic agents · Glycemia · Hypoglycemia

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R. A. DeFronzo
Diabetes Division, UTHSCSA, San Antonio, TX, USA

S. Schwartz
Main Line Health System, University of Pennsylvania, Philadelphia, PA, USA

S. Schwartz (✉)
Suite 305, 233 E. Lancaster Ave, Ardmore, PA 19003, USA
e-mail: stschwar@gmail.com

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Introduction

Type 2 diabetes mellitus continues to increase at epidemic rates and, as a result, the proportion of hospitalized patients who have stress-induced hyperglycemia and overt diabetes is increasing [1–3]. Several recent studies [4–6] have failed to show any benefit of intensive glycemic control on mortality in critically ill, hospitalized patients, and some studies [7–9] have demonstrated an increased incidence of side effects, especially hypoglycemia. This has resulted in an active debate about the risk/benefit ratio of aggressive glucose control in critically ill, hospitalized patients. One can make a strong argument that these negative findings largely resulted from processes of care and use of anti-diabetic agents (insulin and sulfonylureas) that cause undue hypoglycemia, thereby obliterating any potential benefit of the intervention. Although unproven, one could argue that intensive glycemic control is appropriate in hospitalized patients with hyperglycemia as long as one employs processes of care and anti-diabetic agents that do not cause, or minimize, undue hypoglycemia. We will briefly review this debate and focus on data, where it exists, and logic [10], of using anti-diabetic agents that would obviate the need for sulfonylureas and possibly insulin in hospitalized patients, while potentially reducing the detrimental effects of hyperglycemia, glycemic variability, cardiovascular (CV) risk, and adverse outcomes in these patients.

Risks/Benefits of Intensive Therapy in Diabetic Patients: Intensive Insulin Therapy in Hospitalized and Critically Ill Patients

Hospitalized patients with stress-induced diabetes and overt type 2 diabetes mellitus experience adverse outcomes at a rate that rises in proportion to the severity of hyperglycemia [3, 11, 12]. Although some studies have demonstrated the benefit of

tight glycemic control with insulin on mortality/morbidity in hospitalized critically ill patients including individuals undergoing CABG [13], patients in the surgical intensive care unit [14], and postmyocardial infarction patients [15]. However, these results have not been consistent. VISEP [7], Glucontrol [8], and NICE-Sugar [6] trials have found increased mortality/morbidity in patients treated with intensive insulin regimens. Hypoglycemia has been a major side effect in all studies that have attempted to achieve tight glycemic control with insulin in hospitalized, severely ill patients and this adverse event may account for the negative outcomes seen in the above trials [5, 6, 8, 9, 16–21]. Hypoglycemia has many potential deleterious effects on the CV system [22], including prolongation of the QT- interval [23], which can last for extended periods of time [24]. Hypoglycemia stimulates catecholamine release [24], and this can precipitate angina, cause ischemic EKG changes, and arrhythmias [25, 26], and result in sudden death [23, 27]. Not surprisingly, insulin is the most common cause of drug-related medication errors in hospitalized patients [28]. Not surprisingly, considerable debate exists concerning in-hospital glycemic goals and the value of intensive insulin therapy. The ADA/EASD consensus conference advocates a plasma glucose concentration between 140–180 mg% as a reasonable goal to balance the risks (primarily hypoglycemia) and benefits of intensive insulin therapy in hospitalized patients [29]. However, many experts believe that tighter glycemic control would be beneficial if it could be achieved without undue hypoglycemia [30].

Insulin as Standard of Care

At the present time, insulin represents the standard-of-care for hospitalized patients [31–33]. However, targeting tight glycemic control with intensified insulin therapy to achieve a BG target within normal limits produces unacceptable rates of hypoglycemia. With the advent of basal-bolus insulin approaches using insulin analogs, a reduction in the incidence of hypoglycemia has been achieved. Avoidance of sliding scales [34, 35] has further improved the benefit/risk ratio in achieving good control without hypoglycemia. In addition, basic principles of care—careful glucose monitoring, timing of insulin boluses in relation to meals have been shown to reduce the risk of hypoglycemia.

Given the above considerations, newer glycemic goals of therapy have been defined. The newest guidelines from the Critical Care Society and Endocrine Society are a very reasonable synthesis [32, 33] and states that initiation of therapy occur with >180 mg/dL, aim for <140–150 mg /dL, and assiduously avoid numbers <70 mg/dL.

However, we believe that there is room for improvement, and propose medications and processes of care that have the potential to further reduce in-hospital hypoglycemia and overall morbidity and mortality.

Alternative Therapies To Insulin - Key Principles

The ideal characteristics of any medication proposed to replace insulin include: (I) rapid onset and offset of action; (II) effectively reduce hyperglycemia by correcting the underlying abnormalities responsible for stress-induced hyperglycemia and diabetes; (III) obviate the need for insulin completely and be complementary to insulin if insulin is required; (IV) engender no undue hypoglycemia in absence of insulin or a sulfonylurea; (V) not increase cardiovascular risk and possibly reduce CV risk; (VI) have acceptable and manageable side effects; (VII) be easy to use by physicians and nursing personnel. The incretin class of drugs most closely fulfills these characteristics.

Incretin Therapies

Incretin-based therapy (glucagon-like peptide-1 [GLP-1] receptor agonists and DPP-4 inhibitors) satisfy the key principles described above and can be used throughout the continuum of care of hospitalized patients with hyperglycemia, ranging from severely ill patients with diabetes in the intensive care unit to hospitalized patients on noncritical floors, as well as in hospitalized patients with stress-induced hyperglycemia.

GLP-1 is secreted by the L-cells of the gastrointestinal tract and, in conjunction with glucose-dependent insulinotropic polypeptide (GIP), accounts for >90 % of the ‘incretin effect’, ie, the 2–3-fold greater release of insulin from beta cells following oral vs intravenous glucose administration [36]. In T2DM patients the incretin effect is markedly reduced due to beta cell resistance to the stimulatory effect of GLP-1 (and GIP) on insulin secretion [37]. The stimulatory effect of GLP-1 on insulin secretion, as well as its inhibitory effect on glucagon secretion, is glucose dependent [36]. Thus, as the plasma glucose concentration declines to normoglycemic levels, the stimulatory effect of GLP-1 on insulin secretion wanes, as does its inhibitory effect on glucagon secretion. This provides a normal physiologic mechanism to prevent hypoglycemia.

Of particular note, in the hospitalized patient undergoing significant pathophysiological stress, it’s been shown that the adverse hyperglycemic effects of steroids, both endogenous as well as exogenous, occur in part through a mechanism that can be overcome by the GLP-1 pathway in the beta-cell [38, 39]. Thus, incretins offer unique value to patients with ‘stress-induced’ and ‘steroid-induced’ hyperglycemia. Moreover, considerable data indicate that GLP-1 exerts beneficial effects on the heart [40, 41], and preliminary analyses suggest that

incretin therapy may reduce cardiovascular outcomes in diabetic patients [42–45].

Because the half-life of GLP-1 is short, ~2 minutes, incretin-based therapies rely upon administration of exogenous GLP-1 receptor agonists that are resistant to DPP4 or the inhibition of dipeptidyl peptidase 4, the enzyme that inactivates endogenously secreted GLP-1. Three GLP-1 receptor agonists (exenatide bid, exenatide qw, liraglutide) and 5 DPP4 inhibitors (sitagliptin, saxagliptin, linagliptin, vildagliptin, alogliptin) currently are available. The increase in plasma GLP-1 levels with DPP4 inhibitors is quite modest compared with the fold greater increase observed with the GLP-2 analogues [46]. Not surprisingly, the GLP-1 receptor agonists are more potent in reducing HbA1c than the DPP4 inhibitors [47].

Incretins in Hospital: Pilot Study Data

In hospitalized patients with stress-induced and steroid-induced diabetes, as well as in patients with overt diabetes, we have found that GLP-1 receptor agonists and DPP-4 inhibitors (I) effectively reduce the mean blood glucose level while minimizing the risk of hypoglycemia; (II) decrease excessive glycemic excursions that result from the release of stress hormones (glucagon and glucocorticoids); (III) reduce or eliminate the need for insulin (both the basal insulin requirement and the need for prandial insulin boluses); (IV) reduce glycemic variability, which has been postulated to increase adverse outcomes in hospitalized patients; and (V) have no undue cardiovascular side effects [48–50].

These impressions are supported by multiple pilot studies looking at glycemic and CV benefits of incretins in the hospital.

GLP-1 Infusion

As early as 2004 [50], GLP-1 infusion was used to control hyperglycemia in patients undergoing major surgery and showed increases in insulin and C-peptide, a decrease in plasma glucagon concentration and improved glycemic control with no undue nausea. We treated 40 patients (36 nondiabetic and 4 diabetic) undergoing cardiac surgery and observed a 15 mg/dL decrease in plasma glucose during the procedure in those that concentrations without significant nausea [48].

A 72-hour infusion of GLP-1 added to standard therapy in patients with acute MI and without diabetes (n=10) significantly improved left ventricular ejection fraction (LVEF) from 29 % to 39 % (P<0.01) compared with controls (n=11), measured by echocardiogram, after reperfusion [51]. Further, GLP-1 infusion in the peri-MI has been shown to improve regional functional recovery in the peri-infarct zone in humans (n=10) [51]. Sokos et al [52] investigated the effect of a continuous 48-hour infusion of GLP-1 beginning 12 hours before coronary artery bypass graft (CABG) surgery in 10 patients with coronary heart disease and preserved LV function. This resulted in a reduced need for vasopressors, decreased incidence of arrhythmias, and significantly better glycemic control in the pre- and perioperative periods (95 mg/dL vs 140 mg/dL, P<0.02), despite a 45 % reduction in insulin requirement compared with the control group (n=10) and no undue nausea [52]. Similar results were reported by Mussig following cardiac surgery [53]. GLP-1·infusiion also has been shown to markedly attenuate the glycemic response to small intestinal nutrition [54, 55] and in-hospital test meals [56]. Deane [57] and others [58•, 59] have reviewed the use of glucagon-like peptide-1 in the critically ill.

Exenatide, which is approved for the treatment of type 2 diabetes mimic the effects of native GLP-1.

Marso et al [60] administered intravenous exenatide as a prime (0.05 ug/min for 30 minutes)-and then continuous (0.025 ug/min) infusion to 40 adults admitted to the cardiac ICU. It took 3.9 hours to reduce and maintain the plasma glucose from 199 mg/dL to 140 mg/dL for the subsequent 48 hours. Blood glucose levels <70 mg/dL were uncommon. Lonberg used IV exenatide peri-MI and showed reduced infarct size [61]. Subcutaneous exenatide has been shown to treat critically ill pediatric burn patients with improved glycemic control and a significant reduction in insulin requirement [62•]. In G1 Japanese type 2 diabetic patients scheduled for elective surgery, institution of liraglutide therapy prior to admission resulted in good pre-, peri- and postoperative glycemic control without any cases of hypoglycemia [63].

In a seminal paper, Umpierrez et al [64•] compared the efficacy of 3 regimens in noncritically ill diabetic patients (patients on diet, oral agents or low-dose insulin (≤ 0.4 u/kg/day with moderately elevated blood glucose levels, <180 mg/dL, and A1c <7.5 % on admission) admitted to general medical and surgical wards: (I) sitagliptin alone; (II) sitagliptin plus supplemental insulin boluses; (III) basal-bolus insulin therapy. There were no differences in glycemic control following randomization and ~50 % of those in the sitagliptin-only group were able to avoid insulin altogether. Since the patient population treated in this study account for about half of all diabetic patients admitted to the hospital, this therapeutic approach has the potential to avoid the use of bolus insulin and associated hypoglycemia in a large number of diabetic patients. Though in patients with significant hyperglycemia the combination of sita+glargine achieved a better mean daily BG and less treatment failures, this is a remarkable achievement. Using Garber's [65] calculation that 12 % in-hospital daily hypoglycemia is due to basal therapy and 88 % is related to bolus therapy, it can be estimated that ~50 % of in-hospital hypoglycemia can be avoided by using a GLP-1 analogue to minimize/avoid bolus insulin therapy. It should be emphasized that the patient population studied by Umpierrez et al

did not include critically ill, ICU patients and his promising results DPP4 inhibitors should not be extrapolated to this patient population. Rather, we factor the use of GLP-1 analogue therapy to control hyperglycemia in this severely ill group of patients.

Incretin Therapy in Hospital Patients: Process of Care

When using incretin therapy (exenatide, liraglutide) in hospitalized patients, the following approach is both simple and practical. We recommend that patients with prediabetes (HbA1c≥5.7 %, fasting plasma glucose=100–125 mg/dL, 2-hour or random postprandial glucose=140–199 mg/dL) who can be expected to become hyperglycemic in the diabetic range with the stresses of the admission/ surgery, those with previously undiagnosed diabetes, or those with known diabetes be identified before elective admission and be started on incretin therapy and continued if previously treated with them. For new starts, it can be done long enough prior to admission to assure tolerability. Thus, the incretin will be 'on-board' pre-, peri- and postoperatively, or in the ICU). Incretin therapy should be continued throughout the hospitalization and after discharge. We favor the use of a GLP-1 receptor agonist, especially in patients who are more critically ill.

If one decides to use a DPP4 inhibitor, the renal-adjusted dose should be administered. DPP4 inhibitors can be given orally or via nasogastric tube, all are approved in combination with insulin and they are not associated with any clinically important side effects. When starting a GLP-1 one can use exenatide, 5 ug bid, with titration as necessary, based on efficacy of this lower dose, (do not use if creatinine clearance is <30 ml/min) or liraglutide, 0.6 mg/day, titrated to 1.2 mg daily the next day (off label) if the first dose of 0.6 mg is well tolerated (no renal adjustment is necessary). Patients on exenatide QW prior to admission should be maintained on the agent; there is no decrement in efficacy if 1 weekly dose is missed while patient is in hospital. Exenatide (Byetta) and liraglutide work quickly with the first dose. Exenatide once weekly (Bydureon) takes several weeks before its hypoglycemic effect becomes manifest and is not effective if started at the time of or after admission to the hospital. Exenatide normally is given by subcutaneous injection but also can be given as a continuous intravenous infusion as described by Marso (68). Exenatide and liraglutide have been approved for use in combination with basal insulin and can be used, albeit 'off-label', with a rapid-acting insulin analog. During the initial 24 hours after initiating GLP-1 analogue therapy, a supplemental order for a rapid acting insulin can be included and after 24 hours this can be changed to a single basal injection of insulin if necessary.

In our clinical experience, as well as in published in-hospital-use studies [52, 53, 66], the incidence of nausea/vomiting with GLP-1 receptor agonists is low. Hospitalized patients eat less and more slowly, their diet is not high in fat and fiber content, and they should be advised to stop eating when they have the first sense of fullness. Those patients who do report gastrointestinal upset or nausea can be managed with metoclopramide or ondansetron [67]. Incretin use should be avoided in patients with a history of pancreatitis or operative procedures that carry a risk of pancreatitis (ie, Whipple procedure).

Based upon the results of Umpierrez (66), one might select a DPP4 inhibitor in patients who are not critically ill and who are being treated with diet, oral antidiabetic agents, or low doses of insulin, ie, the patient population studied by Umpierrez.

Insulin-treated diabetic patients should be instructed to start incretin therapy prior to hospitalization, and, once their insulin therapy is adjusted, to take their usual dose of basal insulin (glargine, levemir) on the night/day prior to surgery. If incretin therapy is started in the hospital, the dose of insulin can be down titrated to optimize glycemic control while avoiding hypoglycemia. In many patients addition of the GLP-1 analogue may allow insulin to be discontinued. In the face of stress, the glucose lowering efficacy of the DPP-4 inhibitors is equal to ~20–30 units of insulin, while the GLP-1 receptor agonists are equal to ~40–60 units [48]. Thus, for the insulin-treated patient, one must make appropriate reductions in their usual at home insulin dosage regimens. If these prior insulin-treated patients are placed on an insulin drip, the protocols automatically will compensate for the efficacy of the background incretin therapy.

It should be emphasized that incretin therapy can be supplemented with insulin using any protocol/regimen that routinely is employed at one's institution. Thus, our suggested process of care concerning incretin use in the hospital does not require any change of existing insulin protocols or order-sets in order to implement.

Conclusions

Recent clinical trials have failed to demonstrate a benefit in mortality/morbidity in critically ill, hospitalized patients treated with insulin-based therapy. In part, the failure to observe benefit with these intensified insulin regimens can be attributed to side effects of insulin therapy, especially hyperglycemia. In hospitalized patients, both those admitted to general medical/surgical wards, as well as those who are critically ill in intensive care units, we describe an alternate approach utilizing incretinometic agents.

Incretin therapy can achieve normo-/near normoglycemic control (80–140 mg/dL) in hospitalized patients while minimizing the risk of hypoglycemia and capturing those cardiovascular benefits that accrue by achieving tight glycemic

control and that are intrinsic to the incretins themselves. The approach is simple and practical, is not associated with significant side-effects, and does not require alteration of existing in-hospital protocols if concomitant insulin therapy is required. We look forward to, and encourage more clinical research to further validate and gain more experience with our recommended incretin-based therapeutic approach. Based upon (I) evidence-based practice, (II) knowledge about the pathophysiology of stress-induced hyperglycemia in critically ill, hospitalized patients, (III) the known mechanism of action of incretin hormones, (IV) the excellent benefit-risk ratio of incretin therapy, and (V) encouraging published results with incretin-based therapy, we believe that this approach has significant advantages (especially the lack of hypoglycemia) over (and if necessary, in combination with) insulin therapy.

Compliance with Ethics Guidelines

Conflict of Interest Stanley Schwartz serves on the Advisory Boards for Lilly, Bristol-Myers Squibb, Astra-Zeneca, Amylin, Santarus, J&J, Merck, Sanofi-Aventis, Genesis Biotechnology Group, Takeda. He serves on the Speaker's Bureaus for Lilly, Amylin, Santarus, Merck, Sanofi-Aventis, Novo-Nordisk, Boehringer Ingelheim, Bristol Myers Squibb, Astra-Zeneca, Abbvie, Takeda. He has received grant support from CHOP-NIH for Genetics of LADA. He has received honoraria from Delaware ACP, N. Car. AACE. Ralph A. DeFronzo serves on the Advisory Boards: Amylin, Takeda, Bristol-Myers Squibb, Boehringer-Ingelheim, Lexicon, Novo-Nordisk, Janssen. He serves on the Speaker's Bureaus for Novo-Nordisk, Bristol-Myers Squibb, Janssen, Novo-Nordisk. He has grants from Amylin, Takeda, Bristol-Myers Squibb, Boehringer-Ingelheim, Bristol Myers Squibb

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