Challenges With Insulin in the Inpatient Setting

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IN BRIEF This article reviews potential challenges to and necessary considerations for ensuring the safe and effective use of insulin in the hospital setting. It offers practical suggestions for managing insulin-related issues regarding medication reconciliation, general inpatient management, and the use of concentrated insulin products.

More than 29 million Americans have diabetes (1). It is one of the most common disease states encountered in the inpatient setting. From 1998 to 2009, the number of hospital discharges that listed diabetes as a diagnosis rose from 2.8 million to nearly 5.5 million (2). One may assume that number is higher today given the consistent increase in diagnosing diabetes.

In most clinical situations, insulin is the preferred method for hyperglycemia management in the inpatient setting (3). The most common concentration ordered to control blood glucose, regardless of its pharmacokinetic profile, is U-100 (100 units/mL) (4). Dosing of U-100 generally ranges from 0.2 to 1 units/kg/day, with some patients requiring ≥3 units/kg/day. Higher doses result in multiple daily injections, and problems with absorption and administration often arise. Regular U-500 insulin (500 units/mL) is five times more potent than U-100 insulin and is typically used in patients with type 1 or type 2 diabetes who are severely insulin resistant and cannot achieve glycemic control. Until recently, regular U-500 insulin was the only concentrated insulin available (5–7). The advent of newer concentrated insulins is appealing to both prescribers and patients because a smaller volume is required per injection when high doses of insulin are needed. However, there are no current clinical guidelines to assist prescribers with concentrated insulins within the inpatient setting.

Insulin is identified as a high-alert medication by the Institute for Safe Medication Practices (ISMP) and is commonly involved in medication errors in inpatient settings (8). Insulin-related medication errors can cause serious harm—sometimes even fatal harm—and can occur in all hospital settings (i.e., emergency departments, critical care units, medical-surgical units, and the perioperative setting). Adverse events related to insulin are also a major reason for presentation to the emergency department.

In 2013, the American Society of Health-System Pharmacists released recommendations from an expert panel for enhancing the safety of insulin use across the medication process in hospitals (9). The panel identified the following phases in which errors involving insulin occur during the medication process: prescribing, transcribing, dispensing and storage, administering, and monitoring. With the recent approvals

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of newer and concentrated insulin formulations, inpatient management may become even more challenging, increasing the potential for medication errors.

This article provides guidance on insulin therapies and challenges specific to the inpatient setting and addresses medication reconciliation, considerations that practitioners face with inpatient insulin management, and challenges regarding the use of concentrated insulin products.

Medication Reconciliation

Medication reconciliation is a process to which many health care professionals (HCPs) are exposed. It occurs at admission, discharge, and any transition of care (i.e., from the intensive care unit to the medical-surgical floor or from the operating room to the medical-surgical floor). Transitioning patients who are on insulin therapy from the outpatient to the inpatient setting and vice versa can be challenging. If not performed correctly, it may result in harm to patients.

Medication reconciliation is designed to prevent medication errors from occurring at all levels of care (10). Its goal is to obtain the most complete and accurate list possible of all medications, including over-the-counter and herbal products, that a patient is currently taking. The names, doses, routes, frequency, and purpose of each medication ideally should be obtained for all medications (11).

When obtaining information about patients' preadmission insulin regimen, it is strongly suggested to confirm both the dose in units and the volume (e.g., insulin glargine 20 units equals 0.2 mL) (4,9). Unlike the U-100 forms of insulin, the concentrated formulations do not correspond to the dose markings on a regular U-100 insulin syringe. If possible, having patients demonstrate or verbally describe their dose on the syringe they use can assist in dose validation (12). Insulin products also may be reconciled by calling patients' preferred outpatient pharmacy to verify the formulation and strength they have received. Confirming the insulin name and concentration is also crucial to preventing errors (13). For example, insulin degludec is available in concentrations of U-100 and U-200, but both concentrations are marketed as Tresiba (14). One also cannot assume that insulin glargine means Lantus because the concentrated insulin glargine U-300, marketed as Toujeo, is now also available (15). The U.S. Food and Drug Administration (FDA) also approved Basaglar, another insulin glargine U-100 formulation, in December 2015 (16).

Once a complete medication list has been obtained, the prescriber should review and act on each medication (11). The list should also be compared to medications already ordered for the patient to identify and resolve discrepancies. Several factors such as infection, concomitant medications known to increase blood glucose, and stressors also should be taken into consideration because they may warrant additional insulin to control hyperglycemia (4). Management strategies will be discussed later in this article.

Most institutions have a limited formulary for insulin products. At one institution, for example, the preferred rapid-acting insulin is insulin lispro and the preferred long-acting insulin is insulin glargine. For patients who are receiving other formulations before admission, most institutions transition to the preferred formulary agent. This ensures patient safety and streamlines product usage throughout the inpatient setting. However, the availability of newer concentrated insulins will make this transition challenging for patients who were prescribed these agents before admission. How to transition patients who were receiving a concentrated insulin before admission is discussed later in this article.

At discharge, the reconciled pre-admission medication list should be compared to physicians' discharge orders and the medication administration record, and differences should be resolved before discharge. The purpose, dosage, administration times, and frequency of each medication should be reviewed with patients (4). The following topics also should be reviewed with patients: *1*) the HCP who is responsible for diabetes management after discharge; *2*) patients' level of understanding related to the diabetes diagnosis, self-monitoring of blood glucose, and home blood glucose goals; *3*) the definition, recognition, treatment, and prevention of hypoglycemia and hyperglycemia; *4*) patients' nutrition and diet habits; *5*) when and how to administer insulin; *6*) sick-day management; and *7*) the proper use and disposal of needles and syringes (3,17). Additionally, patients who are prescribed concentrated insulins should be counseled about and demonstrate their understanding of how to use their syringe of choice (tuberculin or regular insulin syringe) (12). This is especially important for patients who were injecting U-100 insulin before admission but are changing to U-500 insulin at discharge. However, U-500 insulin soon will also be available as a pen, mitigating any confusion regarding doses or volumes to be administered (18). Newer insulins such as U-200 and U-300 will only be available as pens (14,15). Regardless of the strength prescribed at the time of discharge, patients should be counseled about and demonstrate proper pen administration technique before leaving the hospital (3,9). Providing comprehensive reviews of insulin administration and the differences between U-100 insulin and the concentrated insulin being prescribed also will assist in assessing patients' knowledge and understanding and help to prevent adverse reactions (4).

Diabetes educators, nurses, and pharmacists can play pivotal roles in the discharge process. In addition, a pharmacist, social worker, or case manager should confirm that patients' preferred outpatient pharmacy has

the concentrated insulin being prescribed in stock or can acquire it before discharge (4). Some hospital policies may also allow a temporary supply to be dispensed to patients at discharge. Both strategies ensure adequate glycemic coverage and continuity of care. Close follow-up also should be arranged with a primary care provider, endocrinologist, or diabetes educator no later than 1 month after discharge, especially for patients newly initiated on insulin (3,17). Providing copies of discharge summaries or communicating directly with these providers can facilitate safe transitions to the outpatient setting. Information provided should include reasons for hyperglycemia or the plan for determining its etiology, related complications or comorbidities, and recommended treatments to assist in outpatient management (3).

General Considerations for Inpatient Insulin Management

About 25% of hospitalized patients have a confirmed diagnosis of diabetes at admission; 12% of patients have unrecognized diabetes or hospital-related hyperglycemia (19). Several factors challenge the inpatient management of hyperglycemia. Nutritional status should be considered at the time of initiation of an insulin regimen and throughout a patient's length of stay (LOS) (4). Decreases in appetite or caloric intake during a patient's LOS can lead to lower insulin requirements. In addition, an NPO ("nothing-by-mouth") status before scheduled procedures or surgeries should be taken into account (3). Both situations may prompt changes in insulin needs. During these times, it is recommended to continue basal insulin and discontinue prandial insulin orders. If additional coverage is necessary based on blood glucose values, correctional insulin doses may be ordered to reduce fluctuations in blood glucose levels. However, sole reliance on sliding-scale insulin (SSI) is strongly discouraged for hyperglycemia management in this patient population (3). SSI refers to gradual increases in premeal insulin doses based on predefined blood glucose levels (20). This reactive approach fails to take into account the amount of carbohydrate in the meal to be consumed or the patient's weight, previous insulin needs, and degree of insulin sensitivity or resistance. Failing to consider these factors may lead to further episodes of hyperglycemia and hypoglycemia.

With the exception of patients in critical care units, all hospitalized patients with hyperglycemia should be prescribed scheduled insulin therapy (3). For individuals with adequate nutrition, a regimen of subcutaneous insulin that delivers basal, prandial, and correctional components is recommended. Order sets and protocol-driven orders can assist with this process, as can glucose monitoring during planned and unplanned interruptions of nutrition in the inpatient setting. Registered dietitians can assist in providing recommendations when a patient's nutritional issues are complex.

When corticosteroids are initiated in the hospital, the duration of therapy and respective pharmacokinetic profile of the corticosteroid should be considered. For example, hyperglycemia attributed to short-acting, once-daily prednisone may be managed with intermediate-acting NPH insulin (21). Long-acting corticosteroids such as dexamethasone may require long-acting insulin or small supplemental doses of NPH for patients who are already managed with a basal and prandial insulin regimen. Blood glucose values should be monitored closely, and correctional insulin should be available to provide supplemental coverage as needed (3,4). Patients discharged on a long steroid taper, as opposed to those receiving a short steroid burst while hospitalized, will require outpatient follow-up with their prescriber to monitor their blood glucose values and make adjustments to their insulin regimen.

Acute illness may cause hyperglycemia during hospitalization in patients with or without a diagnosis of diabetes (22) by increasing the concentration of stress hormones. Not achieving glycemic control during an acute illness can lead to deleterious effects such as decreased immune functioning and wound healing and increased oxidative stress and inflammation.

Acute myocardial infarction is one example of a stressor. The DIGAMI (Diabetes Insulin-Glucose Infusion in Acute Myocardial Infarction) study assessed intensive versus conventional glucose management in the intensive care unit and 3 months after discharge (23). Intensive control was defined as the use of insulin infusion for the first 24 hours (blood glucose goal 126–196 mg/dL), followed by daily subcutaneous injections. This arm had a mean blood glucose level of 173 mg/dL, compared to a mean of 211 mg/dL in the conventional treatment arm (P <0.001). Additionally, 1-year mortality was 29% lower in the intensive arm (P = 0.03) and remained significantly lower at 5 years. Intensive glycemic control in a noncritical care setting demonstrated similar results. Observational studies in surgical patients with strict glucose control showed an association with infection risk reduction (24). Targets followed guideline recommendations of premeal blood glucose <140 mg/dL and random blood glucose <180 mg/dL. Appropriately managing hyperglycemia in the inpatient setting exhibits significant short-term and long-term benefits to overall health status.

The biggest concern related to insulin management is the risk of iatrogenic hypoglycemia. This may occur for several reasons in the inpatient setting (Table 1) (3). Recognizing hypoglycemia is important because it can be a key factor in the review and modification of patients' insulin regimen. One study found that 84% of patients with an episode of severe hypoglyce-

TABLE 1. Reasons for Iatrogenic Hypoglycemia in the Hospital

- Sudden reduction of corticosteroid dose
- Inability of patient to report symptoms
- Reduced oral intake
- Emesis
- New NPO status
- Inappropriate timing of short-acting insulin with regard to meals
- Reduced infusion rates of intravenous dextrose
- Unexpected interruption of oral, enteral, or parenteral feedings

mia (defined as blood glucose <40 mg/dL) had a previous episode of hypoglycemia (defined as blood glucose <70 mg/dL) during the same admission (25). In another study, 78% of patients who experienced hypoglycemia (defined as blood glucose <50 mg/dL) between midnight and 6:00 a.m. were receiving basal insulin (26). Only 25% of patients had their insulin dose adjusted as a result of hypoglycemia before the next scheduled administration of insulin. It is recommended that all hypoglycemic episodes be reviewed as part of a root cause analysis, that treatment regimens be reviewed and modified (if applicable), and that institution-specific protocols be created and implemented for emergent management (3,17).

Challenges of Newer Insulins

Since the first quarter of 2015, four new insulin formulations have been approved by the FDA. As previously mentioned, insulin degludec U-200 (marketed as Tresiba) and insulin glargine U-300 (marketed as Toujeo) are new concentrated basal insulin formulations (14,15). A combination product consisting of 70% insulin degludec and 30% insulin aspart was also approved in the third quarter of 2015, and a new insulin glargine U-100 product (marketed as Basaglar) was approved in December 2015 (16,27). It and the other concentrated insulin products will be available in prefilled pen devices (14–16). This is attractive to providers and patients because regular U-500 insulin historically has been available only in vials. Regular U-500 insulin is now available as a prefilled pen device, allowing for easier administration and dose conversion (18).

Other insulin concentrations under development include insulin aspart U-500 and BIOD-531 (13). Insulin aspart U-500 is an "ultra-concentrated" insulin analog and has been shown in animal trials to be significantly more rapid-acting in onset and postmeal duration than U-500 regular insulin (28). BIOD-531, an ultra-rapid-acting concentrated U-400 insulin, is currently undergoing phase 2 clinical trials (29). Given the rapid proliferation of these new insulin formulations, challenges will arise for both patients and HCPs trying to optimize safety and efficacy.

As previously mentioned, product identification is a major concern because two different concentrations of insulin are marketed under the same brand name (13). Tresiba (degludec) is an example of this. This may lead to confusion for HCPs prescribing or dispensing the medication. A feasible solution would be to market concentrated insulin formulations under a different brand name from their U-100 counterparts. For example, insulin glargine U-300 is marketed as Toujeo, whereas U-100 glargine is sold as Lantus. Whether this strategy is sufficient to combat the issue remains to be seen. Toujeo recently became available on the market, and monitoring of product identification errors will be underway soon.

As more concentrated basal and prandial insulin formulations receive FDA approval, inpatient management will become more complex because of the variable pharmacokinetics and limited available controlled studies of these products. There is clinical uncertainty regarding the best treatment approaches for inpatient management. Some hospitals recommend reinitiating U-100 insulin in patients whose diabetes has been controlled with concentrated insulin, whereas others recommend maintaining concentrated insulin during hospitalization of medically stable patients whose diabetes was well controlled with it before admission (4). However, if a patient's insulin requirements change, it is unclear how to manage dosage adjustments.

Until clinical guidelines are established, institution-specific protocols should be created and implemented for the inpatient use of concentrated insulins to ensure safety and effectiveness (4). For example, one institution implemented a policy on concentrated insulin use for inpatients (30). Assuming the patient is tolerating a full diet, the recommendation for converting to a basal-prandial regimen is to: *1*) calculate the total dose as 0.6 mg/kg based on actual body weight, *2*) administer half of the total dose as basal insulin, and *3*) administer the remaining half of the total dose as prandial insulin divided among three meals. Additional correctional insulin may be ordered to achieve blood glucose targets. An endocrinology or certified diabetes educator consult is also highly encouraged for all patients when converting a patient's home dose of concentrated insulin to the preferred formulary insulin product. These HCPs can also provide recommendations regarding insulin dose adjustments when achieving normoglycemia after conversion from concentrated insulin to U-100 insulin products is difficult.

When transitioning patients who are already on insulin to Tresiba (degludec) regardless of the formulation chosen, the starting unit dose can be the existing total daily unit

dose of long-acting or intermediate-acting insulin (14). With regard to insulin glargine U-300, the starting dose can be the same as the existing once-daily long-acting insulin dose (15). However, the starting dose of glargine U-300 should be 80% of the existing total daily dose of NPH to prevent hypoglycemia. An endocrinologist or certified diabetes educator can provide further recommendations for transitioning to U-200 or U-300 insulin products.

If patients are continuing their home concentrated insulin regimen while hospitalized, challenges lie in ensuring the correct dose calculation and administration. Before the arrival of newer concentrated insulins, U-500 regular insulin was only available in a vial. As previously mentioned, this can be troublesome because patients who use vials are limited to either a tuberculin syringe or a regular U-100 insulin syringe to draw up their doses (12). Using traditional insulin syringes to inject concentrated insulin involves a large amount of patient education about dosage conversion, as well as an understanding of the difference between fluid by volume (in millimeters) versus "unit marks."

Research published by the U.S. Department of Veterans Affairs observed instinctive selection of the correct insulin syringe (U-500 or U-100) based on a corresponding dose (31). The study population included physicians, experienced patients, and inexperienced patients. The study discovered that when U-500 regular insulin doses were <100 units, the majority of individuals selected the incorrect U-100 insulin syringe. In the physician group, 47% selected the incorrect syringe. This study demonstrated the vulnerabilities with regard to overdosing U-500 insulin because of the perception that the U-100 syringe is more accurate.

Tuberculin syringes are an alternative method of administration endorsed by ISMP (32). This method offers a clearer designation of insulin dose in millimeters. Unfortunately, this approach may not be implemented as frequently because the needles on tuberculin syringes are significantly larger, leading to patient discomfort. Nonadherence also may be a challenge, especially in the ambulatory care setting, because of the larger needles. Additionally, tuberculin syringes are not readily available in the inpatient setting and often are not covered by insurance plans in the outpatient setting.

Therefore, regardless of the administration technique implemented, a closed loop of effective communication among physicians, pharmacists, and patients can help decrease medication errors. Most of the newly available concentrated formulations (e.g., insulin glargine U-300) are available in prefilled pen devices, which will be the only means of delivery available (13–15).

Several hospitals have multidisciplinary work groups that create protocols to assist patients and HCPs in administering correct doses of concentrated insulin. To combat the unintentional administration of a more potent insulin formulation, the ISMP released a safety alert in 2007 recommending the use of the word "concentrated" when ordering these insulin formulations (31). Additionally, ISMP has established additional recommendations to reduce the risk of medication errors when using concentrated insulins in the inpatient setting. The following processes address all aspects of medication delivery in the inpatient setting.

Prescribing

When physicians are ordering concentrated insulins, and specifically U-500 insulin, both the units and volume of insulin should be specified to prevent a fivefold increase or decrease in home doses of concentrated insulin (4,9). Additional recommendations include creating different order panels in the computerized physician order entry for U-100 insulin and concentrated insulins. Often, physicians make decisions about insulin dose adjustments without input from patients. Patients' appetite or degree of nausea may be more significant than perceived, thus resulting in a new insulin dose. Patients can help identify and clarify issues regarding meal delivery and the timing of insulin administration.

Storage

To enhance patient safety, the ISMP recommends storing concentrated insulins such as U-500 insulin vials in the central pharmacy in the refrigerator used for controlled substances but in a distinct location apart from other insulins (9). Furthermore, it is not advised to keep concentrated insulin vials as stock on the nursing unit because this significantly increases the risk of selecting the inappropriate insulin vial. When patients are permitted to continue using their personal supply from a prefilled insulin pen, it is common practice to store the pens in patient-specific bins or drawers in the automated dispensing cabinet on the patients' nursing unit. Providers should also consult their institution-specific policies on the use of patient-supplied medications.

Preparation and Dispensing

Distinctive labels for insulin vials can serve as a visual prompt for identifying the incorrect formulation when HCPs are either dispensing or verifying a product (33). Some inpatient settings have implemented additional safeguards such as requiring pharmacists to draw up insulin doses to reduce miscalculations. Each dose that is drawn up in the pharmacy will require a second check of both the dose in units and the volume by two independent pharmacists before dispensing.

Medication Administration

Although patient ratios and long shifts will continue to be obstacles, nurses should be provided adequate inservice training and frequent opportunities for refresher courses regarding insulin management and new formulations (33). Education should

also be performed to demonstrate the administration of U-500 insulin using the syringe of choice (tuberculin or U-100 insulin syringe). A nurse should also double-check doses that are drawn up before administration. When doses are drawn up by pharmacy staff, it is still recommended that nurses triple-check that doses and volumes align with the syringe utilized. This will prevent potential overdose that may occur using a typical insulin syringe (4,34).

For newly approved concentrated insulins that are available in prefilled pen devices, education for pharmacists and nurses is of utmost importance to ensure the preservation of drug integrity and proper administration. For example, U-200 insulin is stable at room temperature for 56 days (8 weeks), whereas U-300 insulin must be discarded after 28 days at room temperature (14,15). Additionally, the pharmacokinetic profile of U-200 insulin grants more flexibility in the timing of administration given its duration of >42 hours, compared to U-300 insulin, which has a duration of ≤36 hours. Understanding these characteristics will allow prescribers to optimize insulin regimens and limit fluctuations in blood glucose during hospitalization. Because of the risk that biological materials and blood can backflow into the insulin cartridge or reservoir, insulin pens should never be shared (9,35).

Although there are advantages to the newer insulins, there are also complexities that may limit their use in the inpatient setting. Institutions will have to review the potential roles and risks of these products, in addition to the information provided above, when considering these products for inclusion in an inpatient formulary.

Conclusion

Insulin is the best approach to managing diabetes and hyperglycemia within the inpatient setting, but management comes with many challenges. It is imperative for practitioners to understand the differences among the newer insulin formulations while also considering other factors that affect safe and effective hyperglycemia management. It will also be important for institutions to formally address the roles of newer and concentrated insulin products through the development of patient care policies. A multidisciplinary approach to transitioning patients from the outpatient setting to the inpatient setting and vice versa will further assist in the delivery of optimal patient education and management.

Duality of Interest

No potential conflicts of interest relevant to this article were reported.

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