



REVIEW

Advances in safe insulin infusions

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Abstract

Hyperglycaemia is recognized as a marker of adverse clinical outcomes for hospitalized patients with and without diabetes, including mortality, morbidity, increased length of stay, infections and overall complications. In some cases, intravenous (IV) insulin infusions are the optimal intervention and, to date, these have been compounded in hospital pharmacy departments or, alternatively, at the point of care, when timeliness is a concern or the pharmacy is closed. However, in-house compounding of high-risk medications such as IV insulin poses risks both for patients and institutions. The critical nature of certain high-risk therapies has led to the development of ready-to-administer products to improve the

safety, timeliness, efficacy and efficiency of critical infusions. Recently, IV insulin, a high-alert therapy, has been added to the ready-to-use armamentarium. This narrative review explores the expanding indications, risks and opportunities associated with insulin infusions and potential options for improved safety.

Keywords: insulin, insulin infusion, IV insulin, patient safety, Myxredlin.

Citation

Massoomi F, Burger M, de Vries C. Advances in safe insulin infusions. *Drugs in Context* 2021; 10: 2021-1-6. DOI: 10.7573/dic.2021-1-6

Introduction

The importance of glycaemic control for clinical outcomes in acute care settings has been well established in numerous studies. Hyperglycaemia is recognized as a marker of adverse clinical outcomes, such as mortality, morbidity, increased length of stay, infections and overall complications, in hospitalized patients with and without diabetes.¹ Intravenous (IV) insulin infusion protocols are recommended for diverse patient types not just for patients in critical care. This narrative review explores the expanding indications, risks and opportunities associated with insulin infusions and the potential options for improved safety.

IV insulin infusions are predominantly compounded in hospital pharmacy departments or at the point of care, when timeliness is a concern or the pharmacy is closed. Over time, pharmacy manufacturers have recognized the critical nature of certain therapies and have introduced ready-to-administer products to improve the safety, timeliness, efficacy and efficiency of critical infusions commonly found in 'code carts' for emergent life-saving therapies where timeliness is critical (e.g. dopamine, dobutamine, lidocaine, heparin). A recent survey on insulin infusion practices revealed opportunities for hospital

pharmacies as well as pharmacy manufacturing to improve the safety of insulin infusions.²

This narrative review reports the expanded indications for IV insulin use in acute care settings and their impact on acute care, with a focus on concerns about timeliness, patient safety and product safety that warrant further discussion. Further, new options for IV insulin infusion therapy in the acute care setting may offer solutions to these challenges with varying degrees of safety; these options are reviewed herein.

Methods

A search of publications in the PubMed database from 2018 to 2021 including terms related to the management of diabetes in hospitalized patients, indications for IV insulin, options for IV insulin preparation and delivery, and medication errors associated with high-risk medications, including IV insulin, was undertaken to assess the scope of the problem.^{1,3-8} Expert guidelines for insulin use⁹⁻¹⁵ and expert consensus recommendations for in-house compounding *versus* manufacturer preparations of high-risk medications¹⁶⁻²⁹ were reviewed to identify best practices. A recent new option for IV insulin was assessed in the context of best practices.³⁰ Finally,

a survey of hospital pharmacists was undertaken to assess the current state of IV insulin preparation and use in hospitals, compared with best practices.²

Review

Insulin infusions for hyperglycaemia

The number of people in the United States diagnosed with diabetes is expected to increase from 22.3 million (9.1%) in 2014 to 39.7 million (13.9%) in 2030 and corresponding increases in hospitalizations are projected.³ Studies on patients with and without a prior diagnosis of diabetes demonstrate a correlation between elevated blood glucose levels and increased mortality, ICU admissions, length of stay, infection rates, and nursing home or transitional care admissions for patients admitted to general medical, surgical and critical care departments, especially those with cardiovascular disease, cardiac surgery or neurological disorders.¹ Most recently, an observational study indicated that improvement in glycaemic control results in lower rates of hospital complications and mortality in COVID-19 illness.⁴

IV insulin versus insulin injections

IV insulin is the treatment of choice when a rapid, easily titrated effect is needed and there are relatively no contraindications to its use. Insulin infusions are used for critically ill patients and commonly used in hyperglycaemic emergencies, following cardiac or solid organ transplant surgery, for patients on *nil per os* status and for patients in labour and delivery.⁹ Continuous insulin infusions may also be used to control hyperglycaemia associated with parenteral nutrition.¹⁰

Protocols using IV insulin to keep blood sugar within a reasonable range can reduce both mortality and morbidity. In critically ill patients, insulin given by continuous infusion is the preferred way to attain and maintain recommended glycaemic targets and has advantages over subcutaneous insulin injections.¹¹ The short half-life of IV insulin allows for quick changes in insulin dose associated with insulin sensitivity seen during critical illness.¹² Improved glycaemic control with IV insulin therapy is related to improvement of the hormonal and pro-inflammatory changes associated with stress hyperglycaemia.

Critical timeliness to treat hyperglycaemia

The negative physiological effects of hyperglycaemia appear to have a temporal component, as long times outside of the ideal blood sugar range and high levels of hyperglycaemia are associated with increased morbidity and mortality especially in non-diabetic patients.⁵ Therefore, the time required to achieve and maintain glycaemic control is critical to patient outcomes. When the time to target levels is too long, the window to prevent the toxicity of hyperglycaemia may have passed and irreversible damage may already have occurred.¹² Clinicians

must consider potential patient harm from prolonged time to treatment and less time in target range when IV insulin is compounded locally. Even the most rigorous controls on the safety and accuracy of compounding may still leave patients at risk due to process delays during the order review, compounding and delivery of IV insulin to the bedside.

Medication safety of insulin infusions

IV insulin is classified by healthcare institutions as a 'high-alert drug' for safety concerns related to its narrow therapeutic window, the potential for look-alike sound-alike confusion with the numerous variety of commercially available insulin products (especially U-500 insulin), the increased error potential with various dose-scaled syringe types, and the urgency often associated with this therapy.^{6,7} Hypoglycaemia and hyperglycaemia are serious potential consequences with insulin infusions requiring close monitoring and attention to the patient's nutritional status and clinical condition as well as appropriate adjustment of insulin therapy to achieve an individualized patient's euglycaemic goal.¹¹

A variety of clinical guidelines exist to guide insulin infusion therapy and are frequently updated as patient responses, outcomes and safety are evaluated.^{13,14} Nursing and pharmacists play a critical role not only in the clinical management of insulin therapy but also by ensuring the safe and timely availability and administration of insulin infusions.

There are many factors to consider when deciding how to provide IV insulin products for patients, including timeliness, safety and impact on pharmacy operations. Until recently, hospitals had limited options available for providing insulin infusion therapy. IV insulin infusion products were compounded by pharmacy or other healthcare professionals (nursing, anaesthesia)² or outsourced.

Compounding insulin inside the pharmacy

Compounded sterile medications carry many risks for errors, including wrong dose, wrong medication, wrong diluent and/or contamination, exposing patients to significant risk of adverse events or even death.¹⁶ The *USP General Chapter <797> Pharmaceutical Compounding – Sterile Preparations* provides guidance for preparing compounded sterile medications to help ensure patient benefit and reduce risks such as contamination, infection or incorrect dosing.¹⁶ USP standards for compounding sterile preparations have been in place since 2004; however, hospitals continue to struggle with overall compliance and remedial safety standards.³¹ Due to the known issues with compounding, the Food and Drug Administration (FDA) expects healthcare organizations to use FDA-approved drugs and formulations whenever they are commercially available.¹⁷⁻¹⁹ However, the FDA recognizes that, in certain limited situations, it may be clinically necessary to modify commercially available drug products in order to provide a clinically meaningful difference to an individual patient. In such cases, the FDA acknowledges the necessity of drug compounding. In many

healthcare organizations, compounded sterile preparations are batch prepared prior to the scheduled administration time and are stored for extended periods. For IV insulin, stability data supporting batch compounding and any extended storage are limited. The use of published studies limits the beyond-use dates (BUDs) of insulin products and should be validated at each site.^{20,21} The quality and safety of on-demand compounding may be reduced by interruptions and distractions. Medication error prevention during pharmacy compounding is critical, especially for insulin as it is a high-risk medication and has significant potential for patient harm.^{22,23} Sterile compounding errors remain a concern for facilities. A 2020 survey of pharmacy practitioners ($n=634$) noted that they were aware of at least one pharmacy-related compounding error or near-miss within 12 months of the survey, where incorrect dose or concentrations (58%), incorrect base solutions (51%), or incorrect base solution volumes (43%) were the top errors.³¹

Compounding insulin infusions outside the pharmacy

Results from a recent survey of hospital pharmacists about insulin infusion preparation ($n=79$) revealed that 50 of the responding hospital pharmacy departments mixed all insulin infusions but, in 17 hospitals, the preparation was split between pharmacy and nursing and all insulin infusions were made by nursing in 3 hospitals.² Several safety concerns exist when sterile products, especially insulin infusions, are compounded outside the pharmacy.

The working environment outside the pharmacy is notable for distractions, interruptions and other factors that can contribute to wrong drug, wrong dose and compounding errors. The USP has published the *General Chapter <1066> Physical Environments that Promote Safe Medication Use* to highlight the importance of the interaction between humans and the physical work environments for medication safety.³² One study demonstrated that drug concentration errors occurred approximately 35% of the time when IV medications were prepared by anaesthetists.²⁴ Another study looked at dose errors and treatment delays when IV infusions were prepared at the bedside. The investigators found that infusions made by the pharmacy or manufacturers were 17 times more likely to have the correct drug concentration.²⁵ Wrong drug and wrong dose errors of high-risk drugs can lead to significant patient harm. The American Society of Health-System Pharmacists and the Anesthesia Patient Safety Foundation recommend that all insulin infusions be prepared in the pharmacy department to reduce compounding errors.^{8,15} For these reasons, practitioner-prepared products are the least preferred when compared to ready-to-use products that are FDA approved.²⁶

The expanded indications for insulin infusions, changing compounding standards, the urgency for time-to-treat and time-in-range for hyperglycaemia management, and the patient safety risks have led hospital pharmacies to look for alternative options to improve both the safety and efficiency of insulin infusions.

Product selection of sterile preparations for high-risk medications

The value proposition for FDA-approved ready-to-use products is well established. Several expert consensus panels as well as the Institute for Safe Medical Practice have assessed the state of different IV medication products and processes.^{26–29} These expert panels evaluated the relative safety and cost of IV drug delivery systems for parenteral medications. Included in the evaluation were the use of manufacturer-prepared products, pharmacy-based IV admixture systems, point-of-care activated systems, direct IV administration products (IV push), augmented IV push products and volume-control chambers. The consensus conferences concluded that every medication should be provided to the point of care in the most ready-to-use form. FDA-approved, manufacturer-prepared, ready-to-use products are developed under Current Good Manufacturing Practice regulations that are enforced by the FDA and are considered the safest of the IV drug delivery systems.

The use of manufacturer-prepared formulations has shown improvement in efficiencies while lessening the burden of evolving compounding regulations and overcoming BUD limitations.^{26–29} The first FDA-approved, manufacturer-prepared insulin infusion, Myxredlin (Insulin Human in 0.9% Sodium Chloride Injection, trademark of Baxter International Inc., Deerfield, IL 60015, USA), is indicated to improve glycaemic control in adults and paediatric patients with diabetes mellitus. Myxredlin is delivered in a proprietary container – a non-polyvinyl chloride and non-di(2-ethylhexyl) phthalate system – that enables it to be stored at room temperature (25°C) for 30 days or for 24 months if refrigerated (2–8°C), thus overcoming the BUD limitations noted for compounded sterile preparations.

Further, the commercially available insulin infusion can be safely stored in automated-dispensing cabinets, making it readily available when needed, which would shorten the overall time to initiation of therapy and maintenance of ongoing infusions.³⁰ The availability of an FDA-approved insulin infusion may provide significant efficiencies with enhanced safety.

Conclusion

The incidence of hyperglycaemia is widespread and increasing among acute care patients with and without diabetes. Insulin infusions are commonly utilized for acute care patients with or without a history of diabetes for the management of hyperglycaemia. The turnaround time for initiation and maintenance of insulin infusions may play a critical role in mitigating the risks of hyperglycaemia. The operational aspects of providing safe, timely, efficient and effective insulin infusion therapy can be a challenge to the acute care pharmacy. Healthcare institutions are charged with the mission to provide optimal medications for the best-possible patient outcomes. Premixed and ready-to-use formats of standard doses of commonly prescribed drugs offer efficiencies for

hospitals by simplifying the preparation process and may also enhance patient safety by helping to avoid potential errors or potential contamination that may occur when medications are admixed or compounded. The value of FDA-approved

products, especially for high-risk drugs such as insulin infusion, is well established as a way to reduce the risks associated with compounded sterile products while providing timely treatment to meet patient-outcome goals.

Contributions: FM and MB reviewed the literature, wrote portions of the manuscript and reviewed/edited/approved the full manuscript. CdV provided literature review and wrote a draft of the manuscript. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosure and potential conflicts of interest: The authors declare that they have no conflicts of interest relevant to this manuscript. Visante provides consulting services to companies including Baxter. The authors did not receive any direct compensation from Baxter. The International Committee of Medical Journal Editors (ICMJE) Potential Conflicts of Interests form for the authors is available for download at: <https://www.drugsincontext.com/wp-content/uploads/2021/06/dic.2021-1-6-COI.pdf>

Acknowledgements: None.

Funding declaration: This paper did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Article URL: <https://www.drugsincontext.com/advances-in-safe-insulin-infusions>

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Provenance: Submitted; externally peer reviewed.

Submitted: 19 January 2021; **Accepted:** 9 June 2021; **Publication date:** 15 July 2021.

Drugs in Context is published by BioExcel Publishing Ltd. Registered office: Plaza Building, Lee High Road, London, England, SE13 5PT.

BioExcel Publishing Limited is registered in England Number 10038393. VAT GB 252 7720 07.

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