Potential Role of Ultrafast-acting Insulin Analogues in the Treatment of Diabetic Ketoacidosis

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Abbreviations: DKA, diabetic ketoacidosis; ICU, intensive care unit; IV, intravenous; sc, subcutaneous.

Despite the progress made in the in-hospital management of diabetes over the past decades, diabetic ketoacidosis (DKA) remains a serious hyperglycemic emergency accompanied by significant rates of mortality and morbidity and high financial burden for health care systems and societies (1). Most national and international guidelines advocate continuous intravenous (IV) infusion of regular human insulin as the standard of care for the treatment of DKA. However, subcutaneous (sc) administration of rapid-acting insulin analogues has recently emerged as an alternative for patients with DKA of mild or moderate severity (2).

An IV insulin infusion is traditionally preferred over other routes of administration because of the rapid onset of insulin action that is necessary for the effective resolution of the hyperglycemic crisis and the suppression of ketogenesis. In addition, the short half-life of IV regimens enables an easy titration to achieve glycemic targets. However, IV administration of insulin usually requires patients to receive treatment in the emergency room or to be admitted to an intensive care unit (ICU) to be closely monitored. Despite the fact that IV insulin infusion is acceptable for many countries to administer in general wards, the safety of such an approach has not been adequately studied. On the other hand, data from the Scottish Intensive Care Society Audit Group show that ICU administration in patients with DKA is related to a high-risk of long-term mortality and also substantial economic costs (3).

A recently published trial aimed to evaluate the safety and efficacy of implementing an sc insulin protocol for the treatment of DKA (4). In a cohort-study design involving 7989 hospitalizations over a 9-year period, Rao et al (4) showed that the sc administration of weight-based lispro every 4 hours led to a reduction by 57% in ICU admission and by 50% in 30-day hospital readmission compared to standard treatment. Moreover, the safety profile of the sc regimen proved to be similar to the standard of care, with no differences in adverse event rates between the intervention and control sites.

The findings of this large trial replicate the results of smaller studies conducted previously. Umberger et al (5) have shown that the use of sc lispro in adult patients with uncomplicated DKA was associated with a similar duration of treatment until correction of hyperglycemia and resolution of ketoacidosis, still with 39% lower hospitalization charges compared to patients in the ICU who received an IV regimen. Another study by the same group did not show differences in mortality rates, incidence of hypoglycemia, length of hospital stay, and total insulin dose until resolution of hyperglycemia or ketoacidosis between patients who received sc aspart every hour or every 2 hours compared to those who were treated with IV infusion of regular insulin (n = 15 in each group) (6). Collectively, these data suggest that the implementation of an sc insulin protocol in individuals with mild to moderate DKA could result in the use of fewer resources including ICU beds, lower rates of complications related to IV lines (eg, thrombophlebitis), and less financial burden on health care systems compared to the traditional approach (2). The findings of a meta-analysis suggested there are neither advantages nor disadvantages when comparing the use of sc rapid-acting insulin vs IV regular insulin for the treatment of mild to moderate severe DKA (7). It should be noted that the quality of the synthesized evidence was low to very low and that the number of included trials and patients was small (5 and 201, respectively).

Ultrarapid-acting insulin analogues are recent additions to the pharmaceutical arsenal against hyperglycemia. Ultrarapid lispro and fast-acting insulin aspart have been shown to provide earlier onset, greater initial exposure, increased initial glucose-lowering effect, as well as earlier offset of exposure and hypoglycemic effect compared to parental molecules. Thus, they match the physiological post meal secretion of human insulin more closely than rapid-acting insulin analogues and their use has been related to improved postprandial glucose control. In people with type 1 diabetes on both multiple daily injections and continuous sc insulin infusion,
ultrarapid lispro decreased the time spent in hypoglycemia compared to classic lispro (8). Based on the aforementioned pharmacokinetic and glucodynamic characteristics, which in theory allow flexible dose adjustment with a lower risk of hypoglycemia between different doses because of shorter time of action, ultrafast-acting insulin analogues deserve a place in future trials evaluating sc regimens in patients with DKA. Whether the benefits of the new analogues related to fewer ICU admissions and relevant complications for patients with mild DKA who are eligible to receive sc insulin can outweigh their increased cost remains an area for future research.

More than a century has passed since the discovery of insulin in 1921. According to the title of Ian Fleming’s famous novel, “You Only Live Twice.” Taking into account recent advances in insulinotherapy, it appears that insulin is not just living a second life, it is probably in its second youth. And this can only give the promise of a better future for people with diabetes and their health care providers.

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Data Availability
Data sharing is not applicable to this article because no data sets were generated or analyzed during the present study.

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