Review

Treatment of diabetic ketoacidosis with subcutaneous insulin lispro: A review of the current evidence from clinical studies

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Abstract

Aim. – Low-dose intravenous infusions of regular insulin, usually initiated in the emergency department and continued in the intensive care unit (ICU), are the standard care for patients with diabetic ketoacidosis (DKA) to ensure rapid resolution of hyperglycaemia and ketoacidosis. Several studies have evaluated whether subcutaneous injections of the rapid-acting analogue insulin lispro may be an alternative to intravenous insulin infusion for avoiding ICU admissions of uncomplicated DKA cases.

Methods. – This review summarizes the current clinical evidence for the effectiveness and safety of subcutaneous insulin lispro injections in non-severe DKA patients. Relevant studies were identified by a systematic literature search through the PubMed database.

Results. – To date, four small randomized studies (156 patients overall; three studies in adults and one in paediatric patients with diabetes) have directly compared subcutaneous insulin lispro injections every 1–2 h *vs* continuous intravenous infusions of regular insulin. Patients with severe complications were excluded. In all studies, the mean time to resolution of DKA was similar in both treatment groups [range (three studies): lispro 10–14.8 h; regular insulin 11–13.2 h]. The mean time to resolution of hyperglycaemia, total insulin doses required, number of hospitalization days and number of hypoglycaemic episodes were similar in both treatment groups; no severe complications or DKA recurrences were reported, and one study showed a 39% cost reduction for the insulin lispro group.

Conclusion. – In patients with mild-to-moderate DKA, subcutaneous injections of insulin lispro every 1–2 h offer a feasible alternative to continuous intravenous infusions of regular insulin, and should now be evaluated in larger, more appropriately powered studies.
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Keywords: Diabetic ketoacidosis; Insulin lispro; Rapid-acting insulin analogue; Review

Résumé

Traitement de l'acidocétose diabétique par insuline lispro en sous-cutanée : revue de la littérature.

But. – La perfusion IVSE d'insuline rapide humaine, débutée au service des urgences et poursuivie en soins intensifs, constitue l'approche thérapeutique standard pour traiter rapidement et efficacement l'acidocétose diabétique. Plusieurs études ont évalué la possibilité de remplacer l'insuline en IVSE par des injections sous-cutanées de l'analogue ultrarapide de l'insuline lispro dans l'acidocétose diabétique non compliquée.

Méthode. – Cette revue résume les données cliniques existantes en matière d'efficacité et d'innocuité des injections sous-cutanées d'insuline lispro chez les patients présentant une acidocétose non compliquée. Une recherche systématique dans la base de données PubMed a permis d'identifier les études pertinentes.

Résultats. – À ce jour, quatre études randomisées (156 patients au total) ont comparé directement l'injection sous-cutanée d'insuline lispro toutes les une à deux heures à la perfusion d'insuline rapide humaine IVSE (trois chez l'adulte et une chez l'enfant). Les patients présentant des complications sévères ont été exclus. Dans toutes les études, le temps de résolution moyen de l'acidocétose a été similaire dans les deux groupes ([trois études] : insuline lispro : dix à 14,8 heures ; insuline « régulière » : 11 à 13,2 heures). Le temps moyen de résolution de l'hyperglycémie, la dose totale d'insuline, la durée d'hospitalisation et le nombre d'hypoglycémies étaient identiques dans les deux groupes. Aucune complication sévère ou récidive de l'acidocétose n'a été rapportée. De plus, une des études a montré une réduction des coûts de 39 % pour le groupe traité par insuline lispro.

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Conclusion. – Chez les patients présentant une acidocétose non compliquée, légère à modérée, les injections sous-cutanées d'insuline lispro toutes les une à deux heures constituent une alternative à la perfusion d'insuline rapide humaine IVSE. Ces données doivent cependant être confirmées sur un plus grand nombre de patients.
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1. Introduction

Diabetic ketoacidosis (DKA) is the most serious hyperglycaemic emergency in patients with diabetes. Because patients with DKA are in a state of insulin deficiency, exogenous insulin has to be provided. Continuous intravenous (i.v.) infusion of low-dose regular human insulin is the current standard of care, as stated by the American Diabetes Association (ADA) [1], the International Diabetes Federation (IDF) and the International Society for Pediatric and Adolescent Diabetes (ISPAD) [2,3]. The i.v. infusion is preferred over intramuscular (i.m.) or subcutaneous (s.c.) injections to avoid any delay in the onset of insulin action due to slower uptake and to take advantage of the short insulin half-life after i.v. infusion, which also allows more flexible dose adjustment. Intravenous insulin acts within minutes and has a half-life of only 9 min [4], ensuring rapid resolution of the hyperglycaemic crisis and easy titration to achieve glycaemic control. In contrast, following s.c. injection of regular insulin, the onset of action takes up to 1 h, and the duration of action is 4–6 h [4]. In clinical studies, s.c. injections of regular insulin were less effective than i.v. infusions [5]. However, i.v. infusions are associated with higher hospitalization costs and resource requirements [6] compared with s.c. injections. Patients receiving i.v. insulin infusions are usually required to either stay in the emergency department (ED) or be managed in an intensive care unit (ICU) because they need to be followed by close (hourly) monitoring. In some institutions, policies prevent the use of i.v. insulin infusions outside of the ICU setting [6]. For these reasons, i.v. insulin infusions may be more appropriate for severely ill patients who already require ICU care because of the precipitating cause of their DKA, such as myocardial infarction or severe infection. In cases of severe DKA, i.v. infusions of insulin are preferred over s.c. or i.m. injections because of the concomitant hypovolaemic state and/or poor tissue perfusion [7].

However, for non-severe cases of DKA, an alternative approach that avoids i.v. insulin infusions may help to save on costs and resources. The rapid-acting analogue insulin lispro has been used in the treatment of diabetes for more than 15 years. The pharmacokinetic profile of insulin lispro following s.c. injection suggests that it might be a feasible alternative at least in uncomplicated cases of DKA: its onset of action occurs within 1–20 min; insulin peak concentrations are reached within 30–90 min; and the duration of action is 3–4 h [8]. In 2004, a study performed in patients with DKA suggested that s.c. injections of insulin lispro could replace the i.v. insulin infusion, offering an opportunity to avoid cost-intensive ICU admissions at least in cases of uncomplicated DKA [9]. Few additional studies have been performed to date. Thus, the aim of the present review was to summarize the current clinical evidence for the efficacy and safety of s.c. insulin lispro injections in adult and paediatric patients with non-severe DKA, when compared with the current standard i.v. infusions of regular insulin.

2. Methods

A systematic literature search was performed of the PubMed database from its inception in 1966 to June 2012, using the key words "insulin lispro" and "ketoacidosis" to identify any relevant published reports on this topic. One of the present authors (M.V.) identified the relevant studies by title and abstract review. In addition, all relevant publications were hand-searched to detect any additional studies. The results of the identified studies are summarized below.

3. Results

3.1. Studies

To date, four randomized studies of the use of s.c. insulin lispro injections for DKA have been published. They included a total of 156 patients (s.c. lispro: 80 patients; i.v. regular insulin: 76 patients) with 170 episodes of DKA overall. The studies were conducted in the United States [9], Brazil [10], Turkey [11] and India [12]. Three studies enrolled adults only (110 patients overall) and one study, by della Manna et al. [10], evaluated 60 DKA episodes in 46 children and adolescents with diabetes. All of the adult studies compared s.c. insulin lispro injections every 1–2 h *vs* continuous i.v. infusions of regular insulin. In the paediatric study [10], insulin lispro injections were reduced from every 2 h to every 4 h once blood glucose levels fell to < 250 mg/dL. The results are summarized below and details are presented in Table 1 .

3.2. Patient populations

In the three adult studies, inclusion criteria were similar and largely based on ADA criteria for mild DKA [1]: plasma glucose levels > 250 mg/dL; positive results for serum or urine ketones with blood pH < 7.3; and serum bicarbonate < 15 or < 18 mmol/L. Patients with severe DKA according to ADA criteria (plasma glucose > 600 mg/dL, blood pH < 7.0, serum bicarbonate < 10 mmol/L) were excluded from two of the three studies [11,12] (see Table 1 for details). Patients with severe complications (such as persistent hypotension) or severe cardiac or renal diseases were also excluded from the three adult studies.

Table 1
Summary of studies comparing subcutaneous injections of insulin lispro *vs* continuous infusion of regular insulin in diabetic ketoacidosis (DKA) patients.

	Study (country)							
	Studies in adult patients						Paediatric patients	
	Umpierrez et al., 2004 [9] (USA)		Ersöz et al., 2006 [11] (Turkey)		Karoli et al., 2011 [12] (India)		della Manna et al., 2005 [10] (Brazil)	
Insulin arm	Lispro	Regular	Lispro	Regular	Lispro	Regular	Lispro	Regular
n	20	20	10	10	25	25	25[c]	21[c]
Age and diabetes duration, mean years (SD)	37 (12) 7 (5)	39 (14) 7 (4)	39 (20) 4 (5)	49 (18) 5 (4)	34 (13) 7 (4)	35 (11) 6 (5)	11 (4) Range 3–17	12 (3) Range 5–18
Inclusion criteria	DKA: PG ≥ 250 mg/dL; blood pH < 7.3, bicarbonate < 15 mmol/L, positive serum ketone level, β-hydroxy-butyrate > 3 mmol/L		DKA (mild or moderate only): serum G > 250 mg/dL, arterial pH < 7.3, bicarbonate < 15 mmol/L, β-hydroxy-butyrate > 1.6 mmol/L, ketonuria		DKA (mild-to-moderate only, ADA criteria)		DKA: BG > 300 mg/dL, pH < 7.3, and/or bicarbonate < 15 mmol/L, or > ++ ketonuria	
Exclusion criteria	Persistent hypotension; comatose state; acute myocardial ischaemia, heart failure, end-stage renal disease, anasarca, dementia, pregnancy		PG > 600 mg/dL, pH < 7.0, bicarbonate < 10 mmol/L; persistent hypotension; hypothermia; severe concomitant illness		Severe DKA requiring ICU admission; loss of consciousness, acute myocardial ischaemia, congestive heart failure, end-stage renal disease, anasarca, pregnancy, serious co-morbidities, persistent hypotension		Surgery, glucocorticoid or immune-suppressive treatment required	
Regimen	Bolus 0.3 IU/kg s.c., then 0.1 IU/kg s.c. every 1 h until BG < 250 mg/dL, then 0.05 IU/kg s.c. every 1 h	Bolus 0.1 IU/kg, then continuous infusion at 0.1 IU/kg/h until BG < 250 mg/dL, then 0.05 IU/kg/h	0.15 IU/kg bolus of regular insulin, then 0.075 IU/kg lispro s.c. every 1 h	0.15 IU/kg bolus, followed by continuous infusion	0.3 IU/kg s.c. bolus, then 0.2 IU/kg s.c. after 1 h, then 0.2 IU/kg s.c. every 2 h until BG < 250 mg/dL, then 0.1 IU/kg	0.1 IU/kg bolus, then continuous infusion at 0.1 IU/kg/h until BG < 250 mg/dL, then 0.05 IU/kg/h	0.15 IU/kg s.c. every 2 h until BG < 250 mg/dL, then every 4 h	0.1 IU/kg/h, continuous infusion until BG < 250 mg/dL

Table 1 (*Continued*)

Insulin arm	Study (country)							
	Studies in adult patients						Paediatric patients	
	Umpierrez et al., 2004 [9] (USA)		Ersöz et al., 2006 [11] (Turkey)		Karoli et al., 2011 [12] (India)		della Manna et al., 2005 [10] (Brazil)	
	Lispro	Regular	Lispro	Regular	Lispro	Regular	Lispro	Regular
Ward	Regular ward or step-down unit	ICU	n.r.	n.r.	ED	ICU	ICU or ED	ICU or ED
Blood glucose decline[a]	7 (3) h to BG < 250 mg/dL (P = 0.29 *vs* regular)	7 (2) h to BG < 250 mg/dL	9.4 (8.9) h to norm. (NS *vs* regular)	12.7 (7.5) h to norm.	7.5 (3) h until BG < 250 mg/dL	7.2 (2) h until BG < 250 mg/dL	−2.9 mmol/L/h	−2.6 mmol/L/h
Time to resolution of DKA[b], mean (SD)	10 (3) h (P = 0.87 *vs* regular)	11 (4) h	14.8 (7.0) h (NS *vs* regular)	13.2 (7.5) h	12 (2.2) h	11 (1.6) h	< 12 h after BG ≤ 250 mg/dL	< 6 h after BG ≤ 250 mg/dL
Total insulin required, mean (SD)	84 (32) IU (P = 0.22 *vs* regular)	98 (26) IU	61.7 (10.9) IU	65.2(12.7) IU	100 (14) IU	104 (12) IU	0.28 (0.19) IU/kg	0.37 (0.24) IU/kg
Hospital days, mean (SD)	4 (2) (P = 0.14 *vs* regular)	4 (1)	n.r.	n.r.	6.0 (1.2)	6.6 (1.5)	n.r.	n.r.
Hypoglycaemia episodes [n (severity)]	1 (mild)	1 (mild)	0	0	1 (mild)	2 (all mild)	4 (all mild)	6 (all mild)
Other safety data	No death		No deaths; no serious side-effects associated with treatment protocols in both groups		No deaths; no complications		No deaths or near-deaths; no cerebral oedema, no mannitol treatment required	
Comments	Non-ICU treatment associated with 39% lower hospitalization charge		No need to switch from lispro s.c. to regular insulin		No need to increase dose or switch from lispro s.c. to regular insulin		Glycaemic control worsened after reducing lispro s.c. injections from every 2 h to every 4 h	

PG: plasma glucose; BG: blood glucose (capillary); ED: emergency department; ICU: intensive care unit; n.r.: not reported; norm.: normalization; NS: not significant; s.c.: subcutaneous; SD: standard deviation.
Note: any BG values published in mmol/L were converted to mg/dL using the formula: mmol/L × 18.0182 = mg/dL.

[a] Mean (SD) unless otherwise stated.

[b] Resolution of DKA defined as follows: Umpierrez et al., 2004: bicarbonate > 18 mmol/L and arterial pH > 7.3; Ersöz et al., 2006: bicarbonate > 18 mmol/L; Karoli et al., 2011: bicarbonate > 18 mmol/L and arterial pH > 7.3; della Manna et al., 2005: patient mentally alert and able to eat, bicarbonate > 15 mmol/L, venous pH > 7.3, anion gap < 16 mmol/L.

[c] 30 episodes.

Similar DKA criteria were also used for the paediatric study except that blood glucose levels > 300 mg/dL were required, and patients were excluded if they needed surgery, glucocorticoids or immunosuppressive treatment.

In all four studies, baseline clinical and biochemical parameters were similar in both treatment groups (Table 1).

3.3. Insulin and fluid-replacement regimens

Insulin regimens were also similar across the studies (Table 1) in accordance with standard dose recommendations for i.v. infusions of regular insulin [1]. In three studies, the i.v. regular insulin infusion was given at 0.1 IU/kg/h until blood glucose decreased to < 250 mg/dL, and it was then continued at a lower dose; only Ersöz et al. [11] used a slightly higher dose of 0.15 IU/kg/h. Subcutaneous insulin lispro injections were given at corresponding dosages: injection regimens were either 0.075 or 0.1 IU/kg every hour, or 0.15 or 0.2 IU/kg every 2 h, with dose reductions once blood glucose dropped to < 250 mg/dL.

While s.c. lispro injections were given mainly in non-ICU wards (except for the paediatric study), the i.v. regular insulin infusions were administered in either an ICU or ED setting.

Fluid and potassium replacement protocols were similar in all four studies, and were largely in agreement with ADA and ISPAD recommendations [1,2]. Isotonic saline (0.9% NaCl) was infused at 20 mL/kg/h or at 500–1000 mL/h for the initial 1–2 h. Subsequent fluid replacement was either adapted individually, depending on the patient's haemodynamics, state of hydration, serum electrolyte levels and urinary output, or reduced to 0.45% NaCl infused at 250–500 mL/h [9] or to 10 mL/kg/h in the paediatric study [10]. Once blood glucose levels had decreased to < 250 mg/dL, 5% dextrose or glucose was added to the saline infusion until resolution of DKA. To prevent hypokalaemia, potassium replacement was initiated when potassium levels dropped to values below prespecified levels of 5.5–6.5 mmol/L [9–11], and in all patients with adequate urinary output [12].

3.4. Resolution of hyperglycaemia and ketoacidosis

None of the four studies reported statistically significant or clinically relevant differences in the speed of blood glucose decline or resolution of DKA symptoms between the s.c. lispro and i.v. regular insulin groups. In the three adult studies, the mean time to blood glucose levels falling to < 250 mg/dL was 7 h *vs* 7 h ($P = 0.29$) [9], 7.5 h *vs* 7.2 h [12] and 9.4 h *vs* 12.7 h [11] in the s.c. lispro *vs* i.v. regular insulin groups, respectively (Table 1). In the paediatric study [10], blood glucose levels decreased by mean rates of 2.9 mmol/L/h *vs* 2.6 mmol/L/h until blood glucose was < 250 mg/dL. However, 6 h after the frequency of s.c. lispro injections had been reduced from every 2 h to every 4 h, the mean (SD) blood glucose concentration was lower in the i.v. regular insulin group than in the s.c. lispro group: 187.4 (86.5) mg/dL *vs* 241.4 (82.9) mg/dL ($P < 0.05$).

Resolution of metabolic ketoacidosis was similarly defined across the studies (see footnote to Table 1). In the three adult studies, mean times to resolution of ketoacidosis were 10 h, 12 h and 15 h with s.c. lispro and 11 h, 11 h and 13 h with i.v. insulin

in the Umpierrez et al., Karoli et al. and Ersöz et al. studies, respectively. In the paediatric study, metabolic acidosis and ketosis resolved within the first 6 h period when blood glucose levels fell to < 250 mg/dL in the i.v. regular insulin group, whereas in the s.c. lispro group, these resolved during the next 6 h interval. However, both groups met DKA recovery criteria with no complications. Alkaline therapy was used in six patients receiving s.c. lispro and in four patients receiving i.v. regular insulin in the paediatric study. Although metabolic haemostasis was not restored within the first 30 h of treatment, all patients were alert and able to tolerate oral food intake.

No statistically significant or clinically relevant differences were reported for any of the additionally reported parameters, such as disappearance of urine ketones, time needed for normalization of blood pH and β-hydroxybutyrate levels. In none of the studies there was a need to change the dose or route of insulin administration because of delayed or inadequate response. No recurrences of DKA during the hospital stay for the respective episode were reported.

3.5. Total insulin doses required

In all four studies, the mean total insulin dose required until resolution of metabolic ketoacidosis was similar for both s.c. lispro and i.v. regular insulin treatment groups. In the three adult studies, the mean total insulin doses were 84 IU *vs* 98 IU ($P = 0.22$) [9], 62 IU *vs* 65 IU [11] and 100 IU *vs* 104 IU [12] for the s.c. lispro and i.v. regular insulin groups, respectively (Table 1).

In the paediatric study [10], total insulin doses of 0.28 IU/kg *vs* 0.37 IU/kg were needed in the s.c. lispro and i.v. regular insulin groups, respectively.

3.6. Hypoglycaemia and other safety data

In the three adult studies, hypoglycaemic episodes were rare. Only two episodes with s.c. lispro and three episodes with i.v. regular insulin were reported, all of mild severity. In the paediatric study, four *vs* six hypoglycaemic episodes with s.c. lispro *vs* i.v. regular insulin were reported, all also of mild severity. No deaths, cerebral oedema nor any other severe complications were reported in any of the four studies.

3.7. Resource use and costs of treatment

The mean number of hospital days needed for DKA treatment was reported in only two of the adult studies, with means of 4 *vs* 4 days and 6.0 *vs* 6.6 days for the s.c. lispro and i.v. regular insulin groups, respectively. Umpierrez et al. provided additional data on costs. In their study, the s.c. lispro injections were administered in either a regular ward or a step-down unit, whereas the i.v. insulin infusions had to be administered in the ICU. According to their cost calculations, DKA treatment with s.c. lispro in the non-ICU setting was associated with a 39% lower hospitalization charge compared with the i.v. regular insulin treatment given in the ICU. Mean (SD) hospitalization charges per day

were $3981 ($1067) for the i.v. regular insulin group *vs* $2,682 ($636) for the s.c. lispro group [9].

4. Discussion

Four randomized studies, including 110 adult and 46 paediatric DKA patients in the US, Turkey, Brazil and India, showed that patients with mild uncomplicated DKA can be treated safely and cost-effectively with s.c. injections of insulin lispro, which can be administered in a general ward setting. None of the four small studies available so far revealed any statistically significant or clinically relevant differences versus the standard i.v. regular insulin infusions for any of the standard efficacy parameters evaluated, such as time for blood glucose to fall to < 250 mg/dL, time to resolution of ketoacidosis, and total insulin dose required. No severe treatment complications were reported, hypoglycaemic episodes were rare and of only mild severity.

The patients included were mainly those with "uncomplicated" DKA, largely corresponding to the ADA definition of patients with mild-to-moderate DKA [1]. The presence of concomitant complications was not reported in the three adult studies, but patients with severe complications were generally excluded. Insulin lispro injections were given every 1 or 2 h in two studies each, with no difference in results (Table 1), suggesting that injections at 2 h intervals may be sufficient. Indeed, in the della Manna et al. [10] study, further extension of the injection interval to up to 4 h after the initial decline of blood glucose to < 250 mg/dL led to deterioration of glycaemic control, indicating that injections should be continued with at least 2 h intervals even after an initial improvement in glycaemic control has been achieved.

The results of the present review are consistent with the conclusions of the previous review by Mazer and Chen [13] based on DKA studies comparing s.c. injections of rapid-acting insulin *vs* i.v. regular insulin published up to 2008. Their review reported on three studies evaluating s.c. injections of insulin lispro [9–11] and one additional study evaluating s.c. injections of insulin aspart [14]. The authors concluded that it would be safe and effective to use s.c. administered rapid-acting insulin analogues instead of i.v. regular insulin infusions for patients with uncomplicated DKA. Our present review is limited to only insulin lispro, the first available rapid-acting insulin analogue that has now been in use for more than 15 years. Other short-acting analogues such as aspart and glulisine might also be useful alternatives, but the available data are so far limited [14,15]. The results of the single study of insulin aspart were similar to those of the insulin lispro studies reported here [14]. The glulisine study had a different design: regular insulin and glulisine were both given as i.v. infusions until resolution of DKA, patients were then switched to s.c. basal-bolus regimens with glargine plus glulisine *vs* NPH (neutral protamine Hagedorn) plus regular insulin [15].

Several treatment guidelines are available for the management of DKA in paediatric and adult patients, and offer inconsistent recommendations. The ADA consensus statement from 2009 reflects precisely the current clinical evidence: "Treatment with s.c. rapid-acting insulin analogues such as

lispro every 1–2 h in the non-ICU setting is an effective alternative to the use of i.v. regular insulin, for patients with mild to moderate DKA. However, until these studies are confirmed in routine practice, patients with severe DKA, hypotension, anasarca, or associated severe critical illness should be managed with intravenous regular insulin in the ICU." [1].

The recent Joint British Diabetes Societies guideline recommends i.v. administration of regular insulin only [16]. The IDF and ISPAD guidelines for paediatric patients restrict the option of s.c. rapid-acting insulin to only patients in whom i.v. infusion of regular insulin is not possible [2,3]. A recent review by Nyenwe and Kitabchi [17] proposes evidence-based recommendations for the management of hyperglycaemic emergencies in diabetes mellitus. Based on the data from Umpierrez et al. and Ersöz et al. [11,15], the authors state that s.c. insulin analogues may be administered in the medical ward or ED in cases of mild-to-moderate DKA.

The important advantages of using s.c. insulin lispro rather than i.v. regular insulin for patients with mild-to-moderate DKA would be:

- fewer resources are needed, thus allowing healthcare professionals to save on time and materials;
- implantation of an i.v. line and any associated complications such as thrombophlebitis may be avoided for uncomplicated DKA cases that have no need for i.v. rehydration;
- patients can be treated in a general ward rather than an ICU, which may be important if an ICU is not readily available.

All these advantages also suggest a potential for cost savings. In the studies summarized here, the number of hospital days required were similar for both treatments, yet the Umpierrez et al. study showed that hospitalization costs were reduced by 39% simply because the s.c. injections were given in a general ward rather than an ICU unit. It has been previously argued that insulin lispro is more expensive than regular insulin and that – at least in Europe – hospitals could allow i.v. infusions in general medical wards as well [18]. However, continuous i.v. insulin infusions are an accepted standard of care only in the ICU, and their safety and efficacy in the non-ICU setting has yet to be determined [19]. Therefore, even in Europe, many general medical ward units are not allowed to administer i.v. insulin infusions outside of an ICU or ED setting; in other institutions, continuous insulin infusions may not be possible due to a lack of i.v. infusion pumps in regular wards.

Further, insulin lispro s.c. injections may be of particular interest for hospitals in poor and developing countries that have limited access to ICU equipment and tight resource restrictions [20]. In their recent review of DKA management in South Africa, for example, Jivan et al. [21] reported that in their setting, DKA patients are rarely admitted to an ICU, but receive hourly regular insulin bolus injections in the general ward.

A potential disadvantage of using s.c. insulin lispro is that its administration is less flexible than i.v. administration of regular insulin. Flexibility is very important for unstable, fragile and critically ill patients with severe DKA or its associated complications. For this reason, the route of insulin

administration should be discussed for each individual patient based on DKA severity, co-morbidities and the overall situation. Furthermore, larger, more appropriately powered studies are still needed to confirm that s.c. insulin lispro can safely replace i.v. regular insulin.

The data presented in this review have several limitations. First, all four studies were only exploratory and included small patient numbers of 20–50 patients per study. Also, the studies offered a mean time to resolution of DKA only; median values would have been more representative as the time to event data are almost always skewed. In addition, a wide variety of patients was included in each of the studies, and no information regarding the presence of concomitant complications was provided. Patients with severe complications such as hypovolaemic shock or serious acidosis were excluded from all of these studies, so no data were available for these patient populations. However, patients with severe DKA and those who are critically ill or mentally obtunded, or who have severe complications such as hypotension, anasarca or cerebral oedema, require ICU admission anyway to ensure adequate nursing care and quick turnaround of laboratory test results. Replacing i.v. insulin infusions with s.c. injections would offer no advantages in such cases.

In conclusion, s.c. injections of insulin lispro every 1–2 h offer a feasible alternative to continuous i.v. infusions of regular insulin for the treatment of mild-to-moderate DKA and should be evaluated in larger, appropriately powered studies. In hospitals where insulin i.v. infusions can only be performed in the ICU or ED, physicians may consider the use of s.c. injections instead to avoid having to admit patients to the ICU, thereby saving on costs and resources for an equivalent metabolic result.

Disclosure of interest

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