Subcutaneous Insulin for DKA

Introduction

1. Available literature indicates that low-dose insulin therapy is effective for treatment of DKA regardless of the route of administration (intravenous vs intramuscular vs subcutaneous)
2. Traditionally, intravenous insulin has been the preferred treatment method for DKA given the concern about delayed response to subcutaneous insulin
3. The development of rapid acting insulin has provided an attractive alternative to treatment of mild to moderate DKA

Pharmacology			
	Insulin Lispro	**Insulin Regular (subcutaneous)**	**Insulin Regular (intravenous)**
Dose	0.1-0.3 units/kg	0.1-0.2 units/kg	0.1 units/kg initial bolus (if desired) followed by 0.1 units/kg/hr continuous infusion; or 0.14 units/kg/hr continuous infusion
Administration	Subcutaneous	Subcutaneous	Intravenous
PK/PD	Onset: <15 minutes Peak effect: 0.5-1.5 hours Duration: 3-5 hours	Onset: ~30 minutes Peak effect: ~1.5-3.5 hours Duration: ~8 hours	Onset: ~10-21 minutes Peak effect: ~5 hours Duration: 1.5 hours after drip D/C
Adverse Effects	Hypoglycemia, hypokalemia, injection/infusion site reactions		

Overview of Evidence

Study	Design/ sample size	Intervention & Comparison	Outcome
Umpierrez, et al; 2004	Prospective, randomized trial of patients with DKA defined as BGL >250 mg/dL, serum bicarbonate <15 mEq/L, blood pH <7.3, positive serum ketone level, and serum B-hydroxybutyrate level > 31 mg/dL N = 40	**Subcutaneous insulin lispro** (n = 20) ▪ 0.3 units/kg x 1 followed by 0.1 units/kg every hour until BGL <250 mg/dL, then 0.05 units/kg every hour until resolution of DKA vs **Intravenous insulin infusion** (n = 20) ▪ Initial bolus of 0.1 units/kg, followed by continuous infusion at 0.1 unit/kg/hr until BGL <250 mg/dL, then 0.05 units/kg/hr until resolution of DKA	There was no significant difference amongst: ▪ hospital length of stay ▪ duration of treatment until resolution of hyperglycemia ▪ duration of therapy until resolution of diabetic ketoacidosis ▪ amount of insulin until resolution of diabetic ketoacidosis ▪ Episodes of hypoglycemia during therapy ▪ Recurrence of diabetic ketoacidosis Treatment of DKA in a non-intensive care setting was associated with a 39% lower hospitalization charge compared to that in an intensive care setting with intravenous insulin infusion

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Della Manna, et al; 2005	Randomized controlled trial of children with BGL > 300 mg/dL, pH <7.3 and/or serum bicarbonate <15 mmol/L, and ketonuria > ++ N = 60	**Subcutaneous insulin lispro** (n = 30) ▪ 0.15 units/kg every 2 hours until BGL < 250 mg/dL, then 0.15 units/kg every 4 hours for the next 24 hours vs **Intravenous insulin infusion** (n = 30) ▪ 0.1 units/kg/hr until BGL <250 mg/dL, then 0.15 units/kg subcutaneously every 4 hours for the next 24 hours	**At 2 hours and time when BGL reached <250 mg/dL**, there was no significant difference in blood glucose, pH, serum bicarbonate levels, or beta-hydroxybutyrate levels **At 6 hours after BGL reached <250 mg/dL**, blood glucose levels were significantly lower in the infusion group, however pH, serum bicarbonate, and beta-hydroxybutyrate levels were similar **At 12 hours after BGL reached <250 mg/dL**, pH was significantly higher in the infusion group, however blood glucose, serum bicarbonate, and beta-hydroxybutyrate levels were similar **At 24 hours after BGL reached <250 mg/dL**, there was no significant difference in blood glucose, pH, serum bicarbonate levels, or beta-hydroxybutyrate levels
Ersoz, et al; 2006	Prospective, randomized, open trial of patients with mild or moderate DKA defined as BGL >250 mg/dL, beta-hydroxybutyrate level >1.6 mmol/L, pH <7.3, serum bicarbonate level <25 mmolL, and positive urine ketones N = 20	**Subcutaneous insulin lispro** (n = 10) ▪ Initial bolus of 0.15 units/kg IV, followed by 0.075 units/kg subcutaneous every hour until resolution vs **Intravenous insulin infusion** (n = 10) ▪ Initial bolus of 0.15 units/kg IV, followed by IV insulin infusion until resolution	There was no significant difference amongst: ▪ Time to BGL <200 mg/dL ▪ Time to pH <7.3 ▪ Time to serum bicarbonate >18 mEq/L ▪ Time to beta-hydroxybutyrate <0.6 mmol/L ▪ Time to urine ketone negative ▪ Total amount of insulin delivered until resolution of DKA ▪ Hypoglycemic events ▪ Mortality ▪ Recurrence of ketoacidosis
Karoli, et al; 2011	Prospective, randomized, open trial of patients with mild to moderate DKA N = 50	**Subcutaneous insulin lispro** (n = 25) ▪ 0.3 units/kg x 1 followed by 0.2 units/kg every 2 hours until BGL <250 mg/dL, then 0.1 units/kf every 2 hours until resolution vs **Intravenous insulin infusion** (n = 25) ▪ Initial bolus of 0.1 units/kg followed by 0.1 units/kg/hr until BGL <250 mg/dL, then 0.05 units/kg/hr until resolution	There was no significant difference amongst: ▪ Duration of therapy until BGL <250 mg/dL ▪ Duration of therapy until resolution of DKA ▪ Amount of insulin until BGL <250 mg/dL ▪ Amount of insulin until resolution of DKA ▪ Duration of hospital stay ▪ Hypoglycemic events ▪ Mortality ▪ Recurrence of ketoacidosis
Cohen, et al; 2017	Retrospective review of children with DKA defined as BGL >200 mg/dL, pH <7.3 or serum bicarbonate <15 mmol/L, and ketonemia or ketonuria N = 76	**Subcutaneous regular insulin** ▪ 0.8-1 unit/kg divided by 6 and given every 4 hours, titrated by 10-20% according to stepwise protocol based on blood glucose level prior to insulin injection until resolution	Median time to resolution of DKA was 10.3 hours ▪ The time to DKA resolution was longer in those with moderate or severe DKA One patient experienced hypoglycemia There were no cases of severe morbidity or mortality
Griffey, et al; 2023	Prospective pre-post study N = 177	**Subcutaneous insulin lispro** (n = 78) ▪ 0.2 units/kg every 2 hours until BGL <250 mg/dL, then 0.1 units/kg every 2 hours until resolution vs **Intravenous insulin infusion** (n = 99) ▪ Initial bolus of 0.1 units/kg x 1 then 0.1 units/kg/hr titrated per protocol	Median ED length of stay was significantly shorter for the subcutaneous insulin cohort compared to the intravenous insulin infusion group There were no differences in hypoglycemic events

Conclusions

Subcutaneous rapid-acting insulin appears to be a safe and effective alternative to a continuous insulin infusion in patients with mild to moderate DKA and has cost-saving potential. The optimal dose has not been established, but initial doses of 0.1-0.3 units/kg have been studied and shown to be effective in this patient population.

References

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