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Washington University Emergency Medicine Journal Club
Subcutaneous Insulin in the Treatment of Diabetic Ketoacidosis

Vignette

One afternoon you are working in your emergency department (ED) and walk in to see a new patient. Mr. X is a 24 year-old with a history of type I diabetes who presents with a complaint of weakness. He reports to you that one month ago he lost his job and hence lost his insurance. He has been unable to afford his insulin or syringes and was trying to "stretch them out" by only using one injection per day. He ran out completely 3 days prior to arrival, and in the interim developed polyuria and polydipsia, followed by nausea, vomiting, and generalized weakness. He denies any infectious symptom, abdominal pain, chest pain, or shortness of breath, though he does appear mildly tachypneic. He is also mildly tachycardic, but otherwise afebrile and hemodynamically stable. His exam is unremarkable.

His blood sugar is checked at the bedside and is 540 mg/dL, and his finger-stick ketones are 4.3 mmol/L. You start by giving him a liter of normal saline (NS) while you await his chemistry labs, but you're pretty sure he's in diabetic ketoacidosis (DKA). His labs come back as follows: Na 131, K 4.1, Cl 100, CO2 13, and his anion gap is 22. You realize that you will need to treat his DKA, but are also aware that all of your ICU beds are full, and that you cannot send a patient to the floor on an insulin drip. The patient is also begging you to keep the cost of his care to a minimum, since he has no insurance at the moment. Given the availability of fast-acting insulin analogs (lispro and aspart) you wonder if there is any place for subcutaneous (SC) fast-acting insulin, as an alternative to a continuous infusion of intravenous (IV) regular insulin, in the management of mild to moderate DKA. You decide to do a brief search of PubMed to see if this is even a reasonable question…

PICO Question
Population: Patients (adult or pediatric) with mild to moderate DKA.
Intervention: Subcutaneous fast-acting insulin analog (aspart or lispro)
Comparison: Continuous infusion of intravenous regular insulin.
Outcome: Duration of therapy, ICU admission, ICU length of stay, hospital length of stay, hypoglycemia, recurrence of DKA.

Search Strategy

You use the PubMed advanced search builder to create the following search strategy: (aspart OR lispro) AND ((diabetic ketoacidosis) OR DKA) (http://tinyurl.com/q4neutu). This identifies 38 articles, from which the following 4 most relevant articles are chosen.

Article 1: Umpierrez GE, Cuervo R, Karabell A, Latif K, Freire AX, Kitabchi AE. Treatment of diabetic ketoacidosis with subcutaneous insulin aspart. Diabetes Care. 2004 Aug;27(8):1873-8. Answer Key.

Article 2: Umpierrez GE, Latif K, Stoever J, Cuervo R, Park L, Freire AX, E Kitabchi A. Efficacy of subcutaneous insulin lispro versus continuous intravenous regular insulin for the treatment of patients with diabetic ketoacidosis. Am J Med. 2004. Sep 1;117(5):291-6. Answer Key.

Article 3: Della Manna T, Steinmetz L, Campos PR, Farhat SC, Schvartsman C, Kuperman H, Setian N, Damiani D. Subcutaneous use of a fast-acting insulin analog: an alternative treatment for pediatric patients with diabetic ketoacidosis. Diabetes Care. 2005 Aug;28(8):1856-61. Answer Key.

Article 4: Karoli R, Fatima J, Salman T, Sandhu S, Shankar R. Managing diabetic ketoacidosis in non-intensive care unit setting: Role of insulin analogs. Indian J Pharmacol. 2011 Jul;43(4):398-401. Answer Key.

Bottom Line

DKA is a relatively common and dangerous complication of diabetes in both children and adults, with an estimated mortality of around 13%. In 2009, seven of every 1000 diabetics were admitted to the hospital for DKA. The primary treatment is hydration, electrolyte monitoring, and insulin therapy, traditionally accomplished via IV regular insulin. Both the American Diabetes Association (ADA) and the International Society for Pediatric and Adolescent Diabetes (ISPAD) recommend a continuous infusion of IV regular insulin as standard of care in the management of DKA. These recommendations are based primarily on studies from the 1970s (Menzel 1970, Fisher 1977) that suggested that the delayed onset and longer half-life of SC and IM regular insulin make these routes inadequate for the management of DKA. However, these studies evaluated the use of regular insulin, and pre-dated the development of fast-acting insulin analogs (aspart and lispro), which may be more efficacious in the management of DKA when administered by these alternate routes. Insulin lispro, for example, has an onset of action of 10 to 20 minutes and reaches peak concentration within 30-90 minutes when administered by SC injection (Holleman 1997).

Management of DKA with continuous IV insulin is typically accomplished in an ICU or intermediate-care setting. As the population ages, the demand for ICU beds is increasing, and availability is often limited. ICU admissions also drastically increase the cost of care. While patients in DKA are often critically ill, their care is generally algorithmic, and may not require ICU level care in those without severe DKA. Given that ICU care is often dictated by the use s continuous IV infusion of insulin, an alternative regimen that involves intermittent SC insulin may allow admission to general medical wards or "step-down" units.

The current body of literature comparing IV and SC insulin in DKA is comprised of small, randomized trials (Umpierrez 2004, Umpierrez 2004, Della Manna 2005, Karoli 2011). The outcomes from these studies suggest that the use of SC fast-acting

insulin is both safe and effective at treating mild to moderate DKA. No differences were observed in the duration of therapy required to resolve hyperglycemia or DKA. The incidence of hypoglycemia was low in the all of the studies and similar with either treatment. There were no episodes of recurrent DKA or death were in any of the studies. In adults, an initial SC injection of 0.3 units/kg of insulin aspart or lispro can be given, followed by SC injections either hourly (0.1 units/kg) or every 2 hours (0.2 units/kg). In pediatric patients, it is reasonable to forego the initial bolus, and instead administer 0.15 units/kg every 2 hours.

While these regimens seems to be safe and effective, their benefit over traditional IV strategies is less clear. The primary potential benefit involves eliminating the need for ICU admission, and thereby reducing cost. Only one of these studies assessed the cost of care, and indicated a 39% reduction with subcutaneous insulin (Umpierrez 2004). However, it is quite possible that this cost difference was due to added ICU charges rather than a true difference in the intensity of care required (Haas 2004). Patients receiving SC insulin had blood glucose levels checked every hour, while levels in those receiving IV insulin were only checked every 2 hours. Given the frequency of insulin administration required with a SC strategy - every 1 to 2 hours - the amount of nursing time required may actually increase with SC insulin. If the use of SC insulin does not reduce ICU admissions, then there is no benefit, and IV regular insulin remains a logical treatment option. In a retrospective chart review of DKA patients treated with SC aspart at Rush University Medical Center in Chicago, there was still a mean ICU length of stay of 43.36 hours, indicating that such patients were still admitted to the ICU for initial management.

Perhaps, then, we should alter our question, and instead be asking whether patients with uncomplicated DKA be admitted to the ICU at all, regardless of the route of insulin administration chosen? A review of 67 cases of DKA admitted to the ICU at Truman Medical Center in Kansas City, MO found that over a third of patients did not warrant ICU treatment based on existing admission criteria. These data suggest that increased use of "step-down" or intermediate care units could reduce the need for ICU admission in uncomplicated DKA patients, whether IV or SC insulin strategies are employed.