Fluid management in children with diabetic ketoacidosis

Sophie McGregor Daniel L. Metzger MD Shazhan Amed MSc MD Ran D. Goldman MD FRCPC

Abstract

Question Previous research has indicated that rapid rehydration in children with type 1 diabetes who present with diabetic ketoacidosis could result in cerebral edema. I have been treating patients with diabetic ketoacidosis with gradual fluid replacement. With the risk of cerebral injury in these patients, should I continue management with slow fluid rehydration?

Answer Recent research has shown that neither fluid infusion rate nor sodium chloride concentration increases risk of cerebral injury. However, it is possible for subtle brain injury to occur during treatment, regardless of the fluid administration strategy. The 2018 International Society for Pediatric and Adolescent Diabetes guidelines have been updated in light of this research.

Prise en charge des liquides chez les enfants atteints d'acidocétose diabétique

Résumé

Question Des recherches antérieures ont indiqué qu'une réhydratation rapide chez les enfants ayant un diabète de type 1 qui présentent une acidocétose diabétique pourrait causer un œdème cérébral. J'ai traité des patients souffrant d'une acidocétose diabétique par un remplacement graduel des liquides. Compte tenu du risque de lésions cérébrales chez ces patients, devrais-je continuer à les prendre en charge par une réhydratation lente avec des liquides?

Réponse De récentes recherches ont démontré que ni le taux de perfusion de liquides ni la concentration du chlorure de sodium n'augmentent le risque de lésions cérébrales. Par ailleurs, il est possible qu'une lésion cérébrale subtile se produise durant le traitement, quelle que soit la stratégie d'administration des liquides. Les lignes directrices de 2018 de l'International Society for Pediatric and Adolescent Diabetes (Société internationale pour le diabète pédiatrique et de l'adolescence) ont été actualisées en fonction de ces recherches.

Diabetic ketoacidosis (DKA) is the most common complication of type 1 diabetes (T1D) in children, with an incidence of 1% to 10% of diabetic patients per year in resource-rich countries.[1] Insufficient insulin levels and subsequent gluconeogenesis, lipolysis, and ketogenesis cause substantial hyperglycemia, which draws sugar and extracellular fluids into the urine, resulting in dehydration, ketones in the blood and urine, and acidosis.[2] The 2018 International Society for Pediatric and Adolescent Diabetes (ISPAD) definition for DKA is a blood glucose level of greater than 11 mmol/L, venous pH of less than 7.3 or serum bicarbonate level of less than 15 mmol/L, and either presence of ketonemia (blood β-hydroxybutyrate level ≥3 mmol/L) or moderate to high ketonuria.[1] A rare but severe complication of pediatric DKA is cerebral injury, occurring in about 1% of cases, with an estimated mortality rate of 20% to 25%.[3]

One-third of children present with DKA at diagnosis of T1D.[4] A 2019 US survey reported that children 18 years of age or younger with a missed diagnosis of T1D at an initial health care visit were 18% more likely to develop DKA (relative risk [RR] = 1.18; 95% CI 1.05 to 1.32; $P<.05$).[5] Thus, a presumptive diagnosis of T1D should be confirmed immediately if possible, although confirmatory testing should not delay treatment.[6]

In patients with established T1D, factors indicating DKA include febrile illness or gastroenteritis[7]; missed insulin injections owing to social and economic factors, as well as insulin compliance[8]; or technical malfunction of an insulin pump.[7] In adolescents, poor compliance with an insulin regimen due to mental health or eating disorders,[9,10] or behaviour like the use of cannabis products or alcohol that results in poor metabolic control, might precipitate DKA.[11,12]

Presentation of DKA might include dehydration, tachycardia, tachypnea, Kussmaul breathing (deep, laboured respirations), nausea, vomiting, abdominal pain, and altered level of consciousness.[1] Common imitators of DKA that can result in a missed diagnosis of diabetes include urinary tract infection, acute abdominal pain, febrile illness, and respiratory illness.[13] Among 118 accounts of DKA in 52 children from a 2014 study, a missed diagnosis of DKA at the initial health care visit was associated with a significantly higher rate of cerebral injury (odds ratio

of 4.47; 95% CI 1.79 to 11.89) and mortality (21% with delayed diagnosis compared with 3% with initial diagnosis; odds ratio of 8.40; 95% CI 1.90 to 58.56).[13]

Cerebral injury risk

Despite efforts to reduce risk of cerebral injury in children with DKA, the rate has remained relatively stable for the past 40 years.[14,15] Subclinical brain swelling, seen as a reduction in ventricle size on magnetic resonance imaging, has been reported in up to 54% of cases of DKA at onset of diagnosis, yet clinically overt cerebral injury often does not develop until 8 to 12 hours after beginning treatment.[16] A previous study suggested that swelling was due to brain parenchyma preserving electrolyte and water balance during DKA, and that rapid rehydration could result in osmotic edema.[15] However, DKA causes a deficit of extracellular fluid that limits peripheral perfusion.[2]

Fluid treatment

The balance between the need to replenish fluids and the fear that rapid rehydration could result in brain swelling has led for many years to a fluid management approach of slow, measured fluid replacement in children with DKA.[15,17] A case review in 1988 with 42 patients younger than 28 (mean age of 11 years) found an inverse correlation between overall rate of fluid administration and time of onset of brain herniation ($r=-0.32$, $P=.04$).[18] However, patients with more severe DKA, who are more dehydrated, are at a higher risk of developing cerebral edema (CE).[4] It is possible that those patients received overaggressive hydration compared with children who presented with milder symptoms.[18]

Case-control studies from 2001 and from 2005 failed to correlate rate of fluid administration with risk of intracerebral complications during treatment of DKA.[3,19] Moreover, evidence from studies of children with DKA and studies of rodent models indicate that DKA-induced hypoperfusion and neuroinflammation might result in vasogenic edema when fluids are administered during treatment, regardless of fluid rate.[16,20] Despite these findings, the 2014 ISPAD clinical practice guidelines recommended that initial fluid replacement take place over 4 to 6 hours in children with DKA to reduce risk of CE.[21]

Shift in fluid treatment

In 2018, Kuppermann et al and the Pediatric Emergency Care Applied Research Network conducted a 13-centre randomized controlled trial of 1389 cases of DKA,[22] with the aim of determining whether the rate of fluid administration was associated with neurologic deterioration. Participants between 0 and 18 years of age were assigned to 1 of 4 fluid replacement regimens: fast rate (20 mL/kg over 12 hours followed by 10 mL/kg over 24 hours) with 0.45% normal saline (NS), slow rate (10 mL/kg over 48 hours) with 0.45% NS, fast rate with 0.9% NS, or slow rate with 0.9% NS. Neither fluid rate nor sodium chloride concentration increased the risk of neurologic deterioration during treatment (RR=0.76; 95% CI 0.44 to 1.33; $P=.34$). Follow-up neurocognitive outcomes 2 to 6 months after DKA also did not differ among intervention groups ($P=.06$). Furthermore, of the 22 patients who were treated for CE, there was no significant difference in incidence of CE between groups (RR=1.43; 95% CI 0.46 to 4.40; $P=.53$). However, they did report that subtle brain injury often occurred during treatment, regardless of fluid administration strategy, supporting the idea that DKA-induced injury and subsequent vasogenic edema occurs independent of fluid-administration rate.[20]

The 2018 ISPAD DKA guidelines have been updated and recommend administration of 0.9% NS of 10 mL/kg over 30 to 60 minutes to restore peripheral circulation.[1] A second fluid bolus of 10 mL/kg might be given over the next 30 minutes if there are still signs of hypoperfusion. The ISPAD protocol recommends replacing the remaining fluid deficit over 24 to 48 hours with an intravenous (IV) drip of 0.9% NS at a rate of 4 to 6.5 mL/kg/hour (depending on the child's weight), with an added 40 mmol/L of potassium chloride. Intravenous insulin should be initiated at a rate of 0.05 to 0.1 units/kg/hour, but not until 1 to 2 hours after IV fluids have begun, since it has also been shown that earlier insulin administration is associated with an increased risk of cerebral injury.[1]

Conclusion

Diabetic ketoacidosis is a serious complication of T1D, caused by a lack of insulin. A severe risk factor of DKA in children is cerebral injury, although its exact pathophysiology remains unknown. It is important for primary care providers and emergency physicians to recognize early signs of insulin deficiency and T1D in order to prevent DKA and reduce the risk of cerebral injury. For many years, fluid replacement in DKA was administered gradually to avoid rapid osmotic changes in the brain. New evidence suggests that neither the infusion rate nor the sodium chloride content of IV fluids affects neurologic outcomes during treatment of DKA, and current guidelines have been updated to reflect this new information.

Competing interests
None declared

Correspondence
Dr Ran D. Goldman; e-mail **rgoldman@cw.bc.ca**

References

1. Wolfsdorf JI, Glaser N, Agus M, Fritsch M, Hanas R, Rewers A, et al. ISPAD clinical practice consensus guidelines 2018: diabetic ketoacidosis and the hyperglycemic hyperosmolar state. *Pediatr Diabetes* 2018;19(Suppl 27):155-77.
2. Foster DW, McGarry JD. The metabolic derangements and treatment of diabetic ketoacidosis. *N Engl J Med* 1983;309(3):159-69.
3. Lawrence SE, Cummings EA, Gaboury I, Daneman D. Population-based study of incidence and risk factors for cerebral edema in pediatric diabetic ketoacidosis. *J Pediatr* 2005;146(5):688-92.
4. Robinson ME, Li P, Rahme E, Simard M, Larocque I, Nakhla MM. Increasing prevalence of diabetic ketoacidosis at diabetes diagnosis among children in Quebec: a population-based retrospective cohort study. *CMAJ Open* 2019;7(2):E300-5.
5. Muñoz C, Floreen A, Garey C, Karlya T, Jelley D, Alonso GT, et al. Misdiagnosis and diabetic ketoacidosis at diagnosis of type 1 diabetes: patient and caregiver perspectives. *Clin Diabetes* 2019;37(3):276-81.

6. Diabetes Canada Clinical Practice Guidelines Expert Committee. Diabetes Canada 2018 clinical practice guidelines for the prevention and management of diabetes in Canada. *Can J Diabetes* 2018;42(Suppl 1):S1-325.
7. Dayton KA, Silverstein J. What the primary care provider needs to know to diagnose and care for adolescents with type 1 diabetes. *J Pediatr* 2016;179:249-55.e1.
8. Rewers A, Chase HP, Mackenzie T, Walravens P, Roback M, Rewers M, et al. Predictors of acute complications in children with type 1 diabetes. *JAMA* 2002;287(19):2511-8.
9. Kelly SD, Howe CJ, Hendler JP, Lipman TH. Disordered eating behaviors in youth with type 1 diabetes. *Diabetes Educ* 2005;31(4):572-83.
10. Grey M, Whittemore R, Tamborlane W. Depression in type 1 diabetes in children: natural history and correlates. *J Psychosom Res* 2002;53(4):907-11.
11. Akturk HK, Taylor DD, Camsari UM, Rewers A, Kinney GL, Shah VN. Association between cannabis use and risk for diabetic ketoacidosis in adults with type 1 diabetes. *JAMA Intern Med* 2019;179(1):115-8.
12. Hermann JM, Meusers M, Bachran R, Kuhnle-Krahl U, Jorch N, Hofer SE, et al. Self-reported regular alcohol consumption in adolescents and emerging adults with type 1 diabetes: a neglected risk factor for diabetic ketoacidosis? Multicenter analysis of 29 630 patients from the DPV registry. *Pediatr Diabetes* 2017;18(8):817-23. Epub 2017 Feb 1.
13. Varadarajan P, Suresh S. Delayed diagnosis of diabetic ketoacidosis in children—a cause for concern. *Int J Diabetes Dev Ctries* 2015;35(2):66-70.
14. Hsia DS, Tarai SG, Alimi A, Coss-Bu JA, Haymond MW. Fluid management in pediatric patients with DKA and rates of suspected clinical cerebral edema. *Pediatr Diabetes* 2015;16(5):338-44. Epub 2015 Mar 19.
15. Harris GD, Lohr JW, Fiordalisi I, Acara M. Brain osmoregulation during extreme and moderate dehydration in a rat model of severe DKA. *Life Sci* 1993;53(3):185-91.
16. Glaser NS, Wootton-Gorges SL, Buonocore MH, Marcin JP, Rewers A, Strain J, et al. Frequency of sub-clinical cerebral edema in children with diabetic ketoacidosis. *Pediatr Diabetes* 2006;7(2):75-80.
17. Harris GD, Fiordalisi I. Physiologic management of diabetic ketoacidemia: a 5-year prospective pediatric experience in 231 episodes. *Arch Pediatr Adolesc Med* 1994;148(10):1046-52.
18. Duck SC, Wyatt DT. Factors associated with brain herniation in the treatment of diabetic ketoacidosis. *J Pediatr* 1988;113(1 Pt 1):10-4.
19. Glaser N, Barnett P, McCaslin I, Nelson D, Trainor J, Louie J, et al. Risk factors for cerebral edema in children with diabetic ketoacidosis. The Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics. *N Engl J Med* 2001;344(4):264-9.
20. Ronsley R, Islam N, Ronsley C, Metzger DL, Panagiotopoulos C. Adherence to a pediatric diabetic ketoacidosis protocol in children presenting to a tertiary care hospital. *Pediatr Diabetes* 2018;19(2):333-8. Epub 2017 Jun 30.
21. Sperling MA, Acerini C, Craig ME, de Beaufort C, Maahs DM, Hanas R. *ISPAD clinical practice consensus guidelines 2014*. Berlin, Germany: International Society for Pediatric and Adolescent Diabetes; 2014. Available from: **https://www.ispad.org/page/httpswwwispadorgpageGuidelines2018Chap4?%26hhsearchterms=%222014%22**. Accessed 2020 Oct 20.
22. Kuppermann N, Ghetti S, Schunk JE, Stoner MJ, Rewers A, McManemy JK, et al. Clinical trial of fluid infusion rates for pediatric diabetic ketoacidosis. *N Engl J Med* 2018;378(24):2275-87.

Child Health Update is produced by the Pediatric Research in Emergency Therapeutics (PRETx) program (**www.pretx.org**) at the BC Children's Hospital in Vancouver, BC. **Ms McGregor** and **Drs Metzger** and **Amed** are members, and **Dr Goldman** is Director of the PRETx program. The mission of the PRETx program is to promote child health through evidence-based research in therapeutics in pediatric emergency medicine.

Do you have questions about the effects of drugs, chemicals, radiation, or infections in children? We invite you to submit them to the PRETx program by fax at 604 875-2414; they will be addressed in future **Child Health Updates**. Published **Child Health Updates** are available on the *Canadian Family Physician* website (**www.cfp.ca**).