1995
3. Ohta M, Obayashi H, Takahashi K, Kitagawa Y, Nakano K, Matsuo S, Nishimura M, Itoh N, Ohta K: Radioimmunoprecipitation assay for glutamic acid decarboxylase antibodies evaluated clinically with sera from patients with insulin-dependent diabetes mellitus. *Clin Chem* 42:1975–1978, 1996
4. Fukui M, Nakano K, Shigeta H, Yoshimori K, Fujii M, Kitagawa Y, Mori H, Kajiyama S, Nakamura N, Abe N, Obayashi H, Fukui I, Ohta K, Ohta M, Kondo M: Antibodies to glutamic acid decarboxylase in Japanese diabetic patients with secondary failure of oral hypoglycaemic therapy. *Diabet Med* 14:148–152, 1997
5. Awata T, Kuzuya T, Matsuba A, Iwamoto Y, Kanazawa Y: Genetic analysis of HLA class 2 alleles and susceptibility to type 1 (insulin-dependent) diabetes mellitus in Japanese subjects. *Diabetologia* 35:419–424, 1992

# Constant Infused Glucose Regimen During the Recovery Phase of Diabetic Ketoacidosis in Children and Adolescents With IDDM

In a recent issue of *Diabetes Care*, Wiggam et al. (1) have suggested that an extended insulin regimen for diabetic ketoacidosis (DKA) can be effectively applied with the 20% glucose at a variable rate to avoid hypoglycemia and that this regimen may produce a more rapid resolution of ketosis during the recovery phase than the conventional regimen. Many physicians may agree to any regimen involving extra insulin during the recovery phase of DKA, since the reduced dose of insulin may prolong recovery, as also demonstrated by Krentz et al. (2), who used 10% glucose infusion as extra glucose with additional insulin, in comparison with the conventional 5% glucose infusion.

However, the extended insulin regimen used by Wiggam et al. (1) may cause electrolytes and fluid imbalances due to a constantly large amount of infused insulin, almost 2 U · $kg^{-1}$ body wt · $day^{-1}$. The 20% glucose at a variable rate appears to be a reasonable approach to avoid hypoglycemia, but it remains empirical, since no guideline for the infusion rate was mentioned except for the hourly monitoring of the blood glucose levels. On the other hand, the 10% glucose regimen, a constant concentration of infused glucose, used by Krentz et al. (2) seems to offer a contradiction in terms of the amount of glucose to be infused per hour versus the time course of fluid replacement. As seen in an example of fluid therapy for DKA found in textbooks for pediatric (3) and adult (4) patients, the infusion rate of fluid replacement for the calculated deficit within the first 12 h, the early recovery phase, may be double that for the remaining deficit and maintenance during the next 24 h, the late recovery phase. Thus, the amount of glucose infused per hour during the late recovery phase may be halved in comparison with that during the early recovery phase. Contrarily, the patient may require a larger amount of infused glucose per hour during the late recovery phase, since the hepatic glucose output may be suppressed, and the insulin resistance, or glucolipotoxicity, may be reducing.

We have therefore suggested a constant amount of infused glucose per hour (5,6), which is based on the basal hepatic glucose output according to Bier et al. (7) (Table 1). These amounts for infancy to adulthood can also account for the amount of infused glucose calculated for the late recovery phase of DKA in the above example if using a 10% glucose infusate in any age-groups. In our experience (5), the ratio of infused glucose to insulin per hour became higher at a variable rate of infused insulin, determined on the basis of 1- to 2-hourly adjustment to keep near normoglycemic levels as DKA was improving. This ratio during the recovery phase was also useful as an index of metabolic stability or insulin sensitivity. At the endpoint, the median ratio was 7 g glucose/1 U insulin, regardless of age-group. This regimen was superior to the conventional therapy using a 5% glucose infusate in regard to the disappearance rate in serum ketone bodies. Further, such a therapy based on the constant amount of glucose, as indicated above, has also been applied safely and effectively in a prolonged fasting state of IDDM on sick days or during surgery.

**Table 1—*The amount of glucose to be infused during the recovery phase after reducing blood glucose below 240 mg/dl in diabetic ketoacidosis***

| Age-group | Body weight (kg) | Estimated surface area ($m^2$) | Glucose to be infused (mg · $kg^{-1}$ · $min^{-1}$)* |
|---|---|---|---|
| Infant–preschool child | 10 | 0.46 | 8–6 |
| | 17 | 0.70 | 8–6 |
| School aged–adolescent | 17 | 0.70 | 6–4 |
| | 30 | 1.08 | 6–4 |
| | 40 | 1.30 | 6–4 |
| Young adult | 40 | 1.30 | 4–2 |
| | 60 | 1.65 | 4–2 |

*Larger values shown first because the amount of glucose infused is larger in younger than in older patients.

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**References**

1. Wiggam MI, O'Kane MJ, Harper R, Atkinson AB, Hadden DR, Trimble ER, Bell PM: Treatment of diabetic ketoacidosis using normalization of blood 3-hydroxybutyrate concentration as the endpoint of emergency management: a randomized controlled study. *Diabetes Care* 20:1347–1352, 1997
2. Krentz AJ, Halle PJ, Singh BM, Nattrass M: The effect of glucose and insulin infusion on the fall of ketone bodies during treatment of diabetic ketoacidosis. *Diabet Med* 6:31–36, 1989
3. Sperling MA: Diabetes mellitus. In *Nelson's Textbook of Pediatrics*. 15th ed. Berman RL, Kliegman RM, Arvin AM, Eds. Philadelphia, WB Saunders, 1996, p. 1646–1666
4. Marshall AM, Walker M, Alberti KGMM: Diabetic ketoacidosis and hyperglycaemic non-ketotic coma. In *International Textbook of Diabetes Mellitus*. 2nd ed. Alberti KGMM, Zimmet P, DeFronzo RA, Eds. Chichester, U.K., Wiley, 1997, p. 1215–1229
5. Amemiya S: Continuous infusion of insulin therapy: the effect of glucose and insulin infusion in the management of juvenile diabetes mellitus, parts I and II. *J*

*Jpn Pediatr Soc* 86:918–947, 1982
6. Amemiya S, Asayama K, Najjar JL, Kato K: Diabetes mellitus. In *Pediatric Textbook of Fluids and Electrolytes*. Ichikawa I, Ed. Baltimore, MD, Williams & Wilkins, 1990, p. 352–369
7. Bier DM, Leake RD, Haymond MW, Arnold KJ, Gruenke LD, Sperling MA, Kipnis DM: Measurement of "true" glucose production rates in infancy and children with 6,6-dideuteroglucose. *Diabetes* 26:1016–1023, 1977

## Response to Amemiya

We thank Dr. Amemiya (1) for his interest in our study (2). It is worth emphasizing that we studied adult patients with diabetic ketoacidosis and that we do not suggest using our dosage schedule in young children. Dr. Amemiya comments on possible fluid and electrolyte problems with our extended insulin regimen, resulting from a "large amount of infused insulin." We did not experience any difficulties, although there was a tendency for phosphate concentrations to be lower on the extended insulin regimen. If a variable rate glucose infusion of any concentration is used, overall fluid requirements must be considered independently. As outlined in our study, our approach was to give additional normal saline.

Dr. Amemiya also referred to the late recovery phase (12–36 h). Generally, our extended insulin regimen was not required beyond 12 h (mean 10.8, range 6–19). The constant glucose infusion rate recommended by Amemiya for young adults is similar to that with which we start, because 5 U/h insulin is continued after correction of hyperglycemia. Whatever approach (constant insulin or constant glucose) is used, monitoring of plasma glucose will be required and treatment adjusted accordingly.

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**References**
1. Amemiya S: Constant infused glucose regimen during the recovery phase of diabetic ketoacidosis in children and adolescents with IDDM (Letter). *Diabetes Care* 21:676–677, 1998
2. Wiggam MI, O'Kane MJ, Harper R, Atkinson AB, Hadden DR, Trimble ER, Bell PM: Treatment of diabetic ketoacidosis using normalization of blood 3-hydroxybutyrate concentration as the endpoint of emergency management: a randomized controlled study. *Diabetes Care* 20:1347–1352, 1997

## Case Report

### Pseudohepatotoxicity of metformin

Metformin (dimethylbiguanide) became available in the U.S. for clinical use in 1995, after extensive experience in foreign markets (1). Since its introduction in the late 1950s, metformin has become the second most prescribed oral hypoglycemic agent in Europe. The drug is generally considered to be safe and effective and has been well received in the U.S. (2). The drug's major side effect is lactic acidosis, and exclusion criteria are weighted toward renal impairment or severe underlying hepatic disease that might predispose the patient to lactic acidosis; the drug is cleared renally (1–3). We wish to report a case of apparent metformin hepatotoxicity that was not confirmed on rechallenge with the drug. We will also briefly review the literature on metformin toxicity and discuss the assessment of an adverse drug reaction.

A 75-year-old white man with a 25-year history of NIDDM was in stable glycemic control on two daily injections of split-and-mixed NPH insulin and regular insulin totaling ~40 U daily. He had no overt diabetic complications and was in general good health, aside from widespread polyostotic Paget's disease of bone (confirmed by radioisotope bone scans and alkaline phosphatase heat fractionation), hypertension, and hyperlipidemia. He was married, did not smoke, and drank one glass of wine with dinner daily. His medications included, in addition to insulin, 325 mg/day enteric-coated aspirin, 180 mg/day diltiazem XR, 800 mg ibuprofen thrice daily as needed, and 60 mg/day lovastatin. In an attempt to improve his glycemic control without increasing his insulin dose, he was started on 500 mg metformin twice daily, with a slight reduction in insulin. He tolerated this dose well, and self-monitored glucose tests demonstrated somewhat improved control (predinner glucose values ranged between 4.44 and 6.66 mmol/l (80 and 120 mg/dl) compared with previous values of 5.55–7.77 mmol/l (100–140 mg/dl), as did $HbA_{1c}$ (7.7% at baseline, 7.3% 3 months later). However, 2 months after initiation of metformin, aspartate aminotransferase (AST) increased from a baseline value of 36 (normal = 8–42) to 322 U/l, while alanine aminotransferase (ALT) increased from a baseline of 33 (normal = 0–55) to 413 U/l. Neither total bilirubin nor albumin changed. Alkaline phosphatase, which was consistently elevated in the 470–510 U/l range (normal = 37–107), peaked at 684 U/l after metformin. He felt well, his exam was unremarkable, and he denied travel, unusual foods, drug exposure (including over-the-counter analgesics), and exposure to ill people. Metformin was discontinued. Hepatitis B surface antigen and core antibodies were negative, as were hepatitis C antibodies and hepatitis A IgM antibodies; ultrasound of the abdomen was remarkable only for gallstones. AST and ALT returned to baseline values. Because of the favorable glycemic response to metformin, the patient agreed to rechallenge with 1 month of metformin therapy, at the same dose as before, with repeat liver function testing at the end of the month. On this occasion, there was no elevation of liver enzymes. It was concluded that metformin could not be confirmed as the cause of liver test abnormalities, but the patient preferred to return to his insulin monotherapy.

The primary toxicity of metformin is lactic acidosis, especially in individuals with impaired renal function. Exclusion criteria for the use of this drug take this into account, although individuals with severe underlying liver disease, which might predispose them to lactic acidosis, are also recommended against using metformin (3,4). Hepatic toxicity in response to metformin is exceptionally rare; there is only one previous citation, which is, unfortunately, in Turkish and unavailable to us for review (5). On the other hand,