Successful management of diabetic ketoacidosis: an innovative protocol

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Abstract

As the prevalence of diabetes increases worldwide, so the numbers of hospital admissions with patients suffering complications, such as diabetic ketoacidosis (DKA), have risen. Morbidity and mortality are affected by delays in presentation and diagnosis, and complications of management. In March 2010, the Joint British Diabetes Societies (JBDS) published national UK guidance on the management of DKA, which was updated in 2013. Both national and local surveys performed since have demonstrated high rates of hypoglycaemia and hypokalaemia, potentially life-threatening complications.

The West Suffolk Hospital critical care unit guideline incorporates additional safety features to avoid both hypoglycaemia and hypokalaemia, compared with the JBDS guidelines. Retrospective case note review was performed in May 2015 and May 2017 of patients admitted to the critical care unit in the preceding 18 and 15 months meeting the JBDS diagnostic criteria. Our results showed only 15% and 9% of our patients experienced hypoglycaemia, in contrast with 28% in the national DKA survey. While our incidence of hypokalaemia was similar to the national survey, adjustments to our guideline in December 2015 resulted in a marked decrease in the percentage of time spent hypokalaemic by patients on fixed rate intravenous insulin.

We believe there is capacity for improvement of DKA guidelines to reduce the incidence of complications of management, and encourage adjustment of guidelines following our findings. Copyright © 2018 John Wiley & Sons.

Key words
diabetic ketoacidosis; hypoglycaemia; hypokalaemia

Introduction and epidemiology

About 8.5% of world’s population has diabetes. The disease is on the rise and hence so are the associated emergencies. Diabetic ketoacidosis (DKA) is a severe and, potentially, life-threatening complication of diabetes. Over the past decade in the USA, hospital admissions with DKA have increased by 40%.1

The National Diabetes Inpatient Audit (NaDIA) revealed that 15.3% of patients with diabetes presenting to hospital with a diabetes-specific problem had DKA.2 NaDIA also highlighted that around one in every 25 inpatients with type 1 diabetes develops DKA during their hospital stay.3 This likely reflects inadequate blood glucose monitoring and insulin mismanagement among inpatients.

Recent estimates of mortality among adult inpatients with DKA are <1% to 1.8%.4,5 Gibb et al. showed a significant association between the number of DKA admissions both within a six-year study period and within a patient’s lifetime, and with mortality. While a single lifetime admission with DKA was associated with a 5.2% risk of death during the follow-up period, more than five lifetime admissions were associated with a 23.4% risk of death during follow-up.6

Morbidity and mortality in DKA are largely associated with delays in presentation and thus diagnosis and initiation of treatment. However, complications of the management of DKA itself also play a key role in worsening the outcome.

Pathophysiology

Diabetic ketoacidosis results from either an absolute or relative insulin deficiency, in association with an increase in counter-regulatory hormones (including glucagon, catecholamines, cortisol and growth hormone). The combination of increased gluconeogenesis, increased glycolysis and decreased ability for glucose uptake into cells results in hyperglycaemia. Fat metabolism occurs secondary to insulin deficiency, with the breakdown of triglycerides to free fatty acids and glycerol and, in turn, the β-oxidation of free fatty acids. β-oxidation causes a high
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Care delivery

Diagnosis of DKA

Diabetic ketoacidosis, observed in type 1 and ketosis-prone type 2 diabetes patients, is characterised by the biochemical triad of hyperglycaemia, ketosis and acidemia. However, the diagnostic criteria differ between the UK and USA. The Joint British Diabetes Societies (JBDS) defines DKA as ketonaemia ≥3.0mmol/L or significant ketonuria (more than 2+ on a standard urine stick), blood glucose >11.0mmol/L or known diabetes mellitus and bicarbonate <15mmol/L or venous pH <7.3. Conversely, the American Diabetes Association (ADA) defines DKA as blood glucose >13.9mmol/L, the presence of ketones in serum or urine and pH <7.3 or bicarbonate ≤18.0mmol/L. The ADA further classifies the severity of DKA on the basis of the patient’s mental state and biochemical parameters. Inclusion of hyperosmolality in grading severity of DKA has been suggested.

Euglycaemic DKA (EuDKA), described first in 1973 by JF Munro, presents with severe ketoacidosis with only mildly elevated plasma glucose levels. It may be precipitated by reduced insulin administration in the presence of illness or reduced food intake, in patients with impaired gluconeogenesis due to alcohol abuse or liver failure, and in the context of partially treated DKA. SGLT2 inhibitors, by inducing rapid excretion of urinary glucose, can cause EuDKA in type 2 diabetes patients. It can also be seen in pregnant women with diabetes. According to a paper recently published in The Lancet, the ADA guidelines create the potential to miss both smaller increases in plasma glucose concentration and EuDKA.

3-β-hydroxybutyrate is the predominant ketone body contributing to acidosis in DKA whereas acetone and acetoacetate are produced in smaller quantities. Point-of-care blood ketone meters directly measure 3-β-hydroxybutyrate; conversely, urine ketone sticks use the nitroprusside reaction to provide a semi-quantitative measure of acetoacetate, but do not reflect 3-β-hydroxybutyrate. As ketosis resolves, 3-β-hydroxybutyrate is oxidised to acetoacetate and this may falsely give the impression of persistent and unresolving ketoacidosis on urine testing. Measurement of urinary ketones also provides the average concentration held in the bladder since the previous micturition; this may be several hours previously and not reflective of the patient’s current ketone status.

A systematic review comparing blood ketone testing to urine testing showed a reduction in time to recovery from DKA and shorter ICU admissions with potential associated cost savings. Limitations of blood ketone meters include their poor performance at high levels, but as these results are rarely used in isolation, their advantages are felt to outweigh these issues.

Management of DKA and associated challenges

In 2013, the JBDS published an updated guideline for the management of DKA. It recommended measurement of blood ketones, venous pH and bicarbonate to aid diagnosis and management. The key components of recommended management were fluid resuscitation and the use of weight-based fixed rate insulin intravenous infusion (FRIII) to promote the clearance of ketones. It also recommended continuation of long-acting basal insulin analogues to prevent rebound hyperglycaemia.

Hypercglycaemia and hypokalaemia are undesired and potentially life-threatening complications of the management of DKA. An association between episodes of hyperglycaemia and prolonged hospital admissions, and increased risk of death has been well-documented. Although a causal relationship has not been proved between hyperglycaemia and increased risk of death, such a relationship is feasible, with impaired autonomic function, altered composition and flow of blood, vasoconstriction, and the release of inflammatory mediators and cytokines. Furthermore, there is an independent association between severe hyperglycaemia in people with type 1 diabetes and QTc interval prolongation, which may result in fatal arrhythmias.

Hypokalaemia results in hyperpolarisation of the cell membrane, making it more difficult for action potentials to be generated and propagated. Therefore, effects on the neuromuscular and cardiopulmonary systems may be seen. Classical ECG changes include flattened or inverted T-waves, increased PR-interval, U-waves and ST-segment depression; hypokalaemia may precipitate cardiac arrest. Furthermore, hypokalaemia has also been associated with muscle necrosis, ascending paralysis and respiratory compromise in the context of DKA.

To prevent hypokalaemia, the JBDS guideline recommended initiation of a 10% glucose infusion when blood glucose falls below 14mmol/L. For prevention of hypokalaemia, it recommended that 0.9% sodium chloride pre-mixed with 40mmol/L potassium be prescribed, as long as the serum potassium level is below 5.5mmol/L and the patient is passing urine.

In a UK national survey of the management of DKA, hyperglycaemia (blood glucose <4mmol/L) was observed in 28% of patients whereas the incidence of hypokalaemia (serum potassium <4mmol/L) was as high as 67%. In another study...

### Table 1. Primary outcomes of retrospective case note review

<table>
<thead>
<tr>
<th></th>
<th>Hypoglycaemia* on FRIII; no. (%)</th>
<th>Hypokalaemia** at 24 hours; no. (%)</th>
<th>DKA resolution in &lt;24 hours; no. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>May 2015 (n=20)</td>
<td>3 (15%)</td>
<td>13 (65%)</td>
<td>17 (85%)</td>
</tr>
<tr>
<td>May 2017 (n=11)</td>
<td>1 (9%)</td>
<td>5 (50%)*†</td>
<td>10 (91%)</td>
</tr>
</tbody>
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*Hypoglycaemia: blood glucose <4mmol/L. **Hypokalaemia: serum potassium <4mmol/L. †Data not available for one patient. FRIII = fixed rate insulin intravenous infusion.
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The West Suffolk Hospital experience

In 2012, the West Suffolk Hospital critical care unit introduced a protocol for the management of DKA. This reflected the JBDS guidelines regarding the administration of 10% glucose solution when blood glucose was less than 14 mmol/L on FR III, but also advised the administration of 20% glucose solution if blood glucose was to fall below 6 mmol/L.

Furthermore, in order to prevent hyperchloremic metabolic acidosis (HCMA), the critical care protocol advised the use of Hartmann’s solution with the addition of 40 mmol potassium chloride to each one litre bag (instead of 0.9% sodium chloride with pre-mixed potassium chloride).

Retrospective case note review was carried out, in May 2015 and May 2017, of patients admitted to the West Suffolk Hospital critical care unit in the preceding 18 and 15 months, respectively. Patients were identified during this time who fulfilled the JBDS DKA diagnostic criteria. The results are shown in Table 1. Following the results of the initial audit, the West Suffolk Hospital critical care guideline was updated in December 2015 (Figure 1) prior to the re-audit performed in May 2017.

**Table 1.**

<table>
<thead>
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<th>Criteria for consideration of acceptance:</th>
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<tr>
<td>• Capillary ketones &gt;6 mmol/L</td>
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<tr>
<td>• Bicarbonate &lt;5 mmol/L</td>
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<tr>
<td>• Blood pH &gt; 7.1</td>
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<td>• K⁺ &lt; 3.5 mmol/L on admission</td>
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<tr>
<td>• GCS &lt; 12 or abnormal AVPU</td>
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<td>• SaO₂ &lt; 95% on air</td>
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<tr>
<td>• Systolic BP &lt; 90 mmHg</td>
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<tr>
<td>• Pulse &gt; 100 or &lt; 60 bpm</td>
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<td>• AKI stage 2 and 3</td>
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**Aim:**

- Fluid resuscitation
- Administer weight based fixed rate insulin until ketotic process is terminated
- Prevent hypoglycaemia and hypokalaemia
- Give additional IV glucose when required
- Administration of normal background insulin (Insulatard, Humulin L, Insuman Basal, Lantus, Levemir, Tesiba)
- Identification of precipitating cause

**Figure 1.** West Suffolk Hospital’s modified critical care guideline for management of diabetic ketoacidosis (December 2015). (Copyright © West Suffolk Hospital NHS Trust. Published in Sidana JK, et al. Therapeutic challenges in the management of diabetic ketoacidosis. *J Intensive Care Soc* 2016;17[4]:353–5)
in both the results of the national survey, where 28% of patients developed hypoglycaemia, and at the teaching hospital, where 40% developed hypoglycaemia. In comparison, our critical care guideline not only advises initiation of 10% glucose infusion when blood glucose is <14 mmol/L, but also recommends introduction of 20% glucose infusion when blood glucose is <6 mmol/L. The effectiveness of our guideline is reflected by only 15% of our patients developing hypoglycaemia during the initial audit, and 9% during the re-audit.

The JBDS guidelines recommend that FRIII should be continued until ketone levels are <0.6 mmol/L. Our initial guideline followed this recommendation. However, as FRIII drives hypoglycaemia, in December 2015, we changed our guideline to state that FRIII should be converted to variable rate intravenous insulin infusion (VRIII) when ketones are <2 mmol/L; this may explain the reduction in patients experiencing hypoglycaemia in our critical care unit.

In an attempt to further reduce the incidence of hypoglycaemia without adversely affecting the time to resolution of DKA, we plan to reduce the rate of FRIII to 0.05 units/kg/hr when blood glucose falls below 12 mmol/L, as discussed by Kitabchi et al.4 This will continue to suppress ketogenesis, while driving hypoglycaemia to a lesser extent.

Like hypoglycaemia, hypokalaemia is also a direct result of the treatment of DKA. Prior to our initial audit, our guideline advised the addition of 40 mmol potassium chloride to each litre bag of Hartmann’s solution given to the patient. This was possible in the critical care unit due to its exemption from National Patient Safety Agency guidance on the storage of strong potassium.19 However, our results showed that 65% of our patients were hypokalaemic at 24 hours, which was similar to the results of the national survey (67%). As our administration rate of potassium was the same as the national guidance, these results were unsurprising. Our updated guideline in December 2015 suggested administration of 3% potassium chloride independently of the resuscitation fluid, which can be given peripherally and titrated to the serum potassium (Figure 1). Hartmann’s solution can thus still be used as the resuscitation fluid, to prevent hyperchloremic metabolic acidosis. Results of the re-audit showed that 50% of our patients were still hypokalaemic at 24 hours, but there was a marked decrease in the percentage of time on FRIII with hypokalaemia – 57.8% in the initial audit, 22.6% following the update to the guideline.

The incidence of hypoglycaemia among patients undergoing DKA treatment in our hospital is markedly lower than that of other published data. We believe that this is due to the additional introduction of 20% glucose infusion if blood glucose falls below 6 mmol/L and conversion to VRIII if ketones are less than 2 mmol/L. We also believe that the use of separate potassium chloride solution that can be titrated to serum potassium should reduce the likelihood and severity of hypokalaemia. Our results are encouraging; however, the recommendations are limited by the small number of patients.

On the other hand, JBDS guidelines are limited in their recommendations for the prevention and treatment of hypoglycaemia and hypokalaemia.

We encourage the writers of the JBDS guidelines to take our findings into account in the next edition of the DKA guidelines, and suggest the incorporation of these findings into local policies.

Declaration of interests

There are no conflicts of interest declared.

References