Diabetic emergencies in children

Peter-Marc Fortune

INTRODUCTION

Diabetic ketoacidosis (DKA), a common paediatric presentation, carries a significant mortality primarily as a result of cerebral oedema. The aetiology remains poorly understood. However, an understanding of the process of treatment and current guidelines discussed in this article is essential to maximize good outcome.

Diabetes was first described in 1550 BC. Therapy first became available in the 1920s when Banting, Best and Collip isolated insulin and produced an exogenous replacement (Canadian Diabetes Association, 2003). Since then people with insulin-dependent diabetes mellitus (IDDM) have managed their condition by administering an insulin dose modulated by their diet and activity. On occasion this control fails leading to an acute metabolic crisis.

DKA caused by a relative insufficiency of insulin is the commonest metabolic emergency for which children are referred for hospital treatment (Campbell and McIntosh, 2003). Around 1% of treated episodes develop cerebral oedema, carrying a mortality of 21–24% (Carlotti et al, 2003). Despite this the best management for DKA is unknown (Inward and Chambers, 2002). Hypoglycaemia, secondary to insulin excess, is also very common. However, its treatment is straightforward and without significant complication, so it will only be briefly considered. The focus of this discussion will be the management of DKA. It will be structured around the current consensus guidelines issued by the British Society of Paediatric Endocrinology and Diabetes (BSPED) (Edge, 2001) with additional reference to areas of debate where appropriate.

HYPOGLYCAEMIA

Low blood glucose concentrations occur when insulin is administered in excess to requirement. Individuals manifest clinical features at different concentrations. A diagnosis of hypoglycaemia may be made for glucose concentrations <2.2 mmol/litre (Campbell and McIntosh, 2003). Symptoms include obtundation, sweating and tachycardia.

Plasma glucose should be elevated as soon as possible. In a conscious child a sugary drink may be taken. Where this is not possible 40% glucose gel (Hypostop, Bio-Diagnostics Ltd, Worcester UK) may be applied to the buccal mucosa or an intramuscular injection of glucagon given. Where intravenous (IV) access is available, 10% dextrose 5 ml/kg should be administered parenterally (Advanced Life Support Group, 2000).

Ideally blood glucose measurement should be performed before corrective therapy but must not be allowed to delay it. Treatment on clinical grounds alone is unlikely to cause harm if the child is, in fact, hyperglycaemic. Bedside tests are inaccurate at low values and therefore laboratory samples are preferred. Once the child responds to the initial treatment, attention should be turned to the aetiology of the episode and action taken to prevent recurrence.

DIABETIC KETOACIDOSIS

DKA may occur in a patient with known IDDM or be the initial presentation of the condition. Presentation is often associated with a mild infectious illness.

Pathophysiology

Insulin promotes anabolism. It directly stimulates cellular uptake and metabolism of glucose, glycogenesis, lipogenesis and protein production. It forms part of the feedback pathways for a number of counter-regulatory hormones, notably glucagon, cortisol and growth hormone (Inward and Chambers, 2002).

The absence of insulin usually only occurs in the absence of glucose and signals a starvation state. In DKA insulin is low, despite an abundance of glucose, so the processes to utilize glucose and store it are downregulated. The increased levels of glucagon result in endogenous glucose being generated by gluconeogenesis and alternative energy sources, such as ketone bodies, being mobilized from the breakdown of fat.

As blood glucose concentration rises, the renal threshold is exceeded (approximately 10–15 mmol/litre) and glycosuria occurs which promotes an osmotic diuresis causing dehydration. The ketone bodies generated cause a metabolic acidosis. Excess hydrogen ions in the plasma are exchanged with intracellular potassium ions as they equilibrate across the cell membrane. The liberated potassium is then excreted by the kidneys to maintain normal plasma levels. The net result is a tissue and plasma acidosis with whole body depletion of potassium.

As intravascular depletion develops, the secretion of catecholamines, growth hormone, cortisol, renin, aldosterone and vasopressin is stimulated. These hormones promote insulin resistance, compounding the situation. With the loss of normal hormonal control and an obligate loss of anions with ketone bodies in the urine, disturbances in sodium homeostasis occur, usually manifested as overall depletion.

The goal of treatment of DKA is the restoration of normal plasma glucose levels, normal acid/base balance, normal sodium and potassium homeostasis, and anabolism without increased morbidity.

The mortality associated with DKA is predominantly attributable to cerebral oedema (70–80%). Those that survive an episode often do so with significant neurological sequelae (Edge et al, 2001). The aetiology of the oedema process is poorly understood (Edge et al, 2001; Inward and Chambers, 2002; Carlotti et al, 2003). It is thought to occur secondarily to the effects of differential movement of osmotically active molecules between neuroglial cells, the interstitial compartments and intravascular fluid. Smaller molecules move rapidly down

Dr Peter-Marc Fortune is Consultant Paediatric Intensivist, Royal Manchester Children's Hospital, Pendlebury, Manchester M27 4HA

concentration gradients as plasma osmolality changes but larger molecules are unable to diffuse across the cell membranes as fast. This results (temporarily) in a raised osmotic potential within cells. Water passes down the osmotic gradient causing oedema (Inward and Chambers, 2002). These shifts may be promoted by the treatment of DKA (Carlotti et al, 2003).

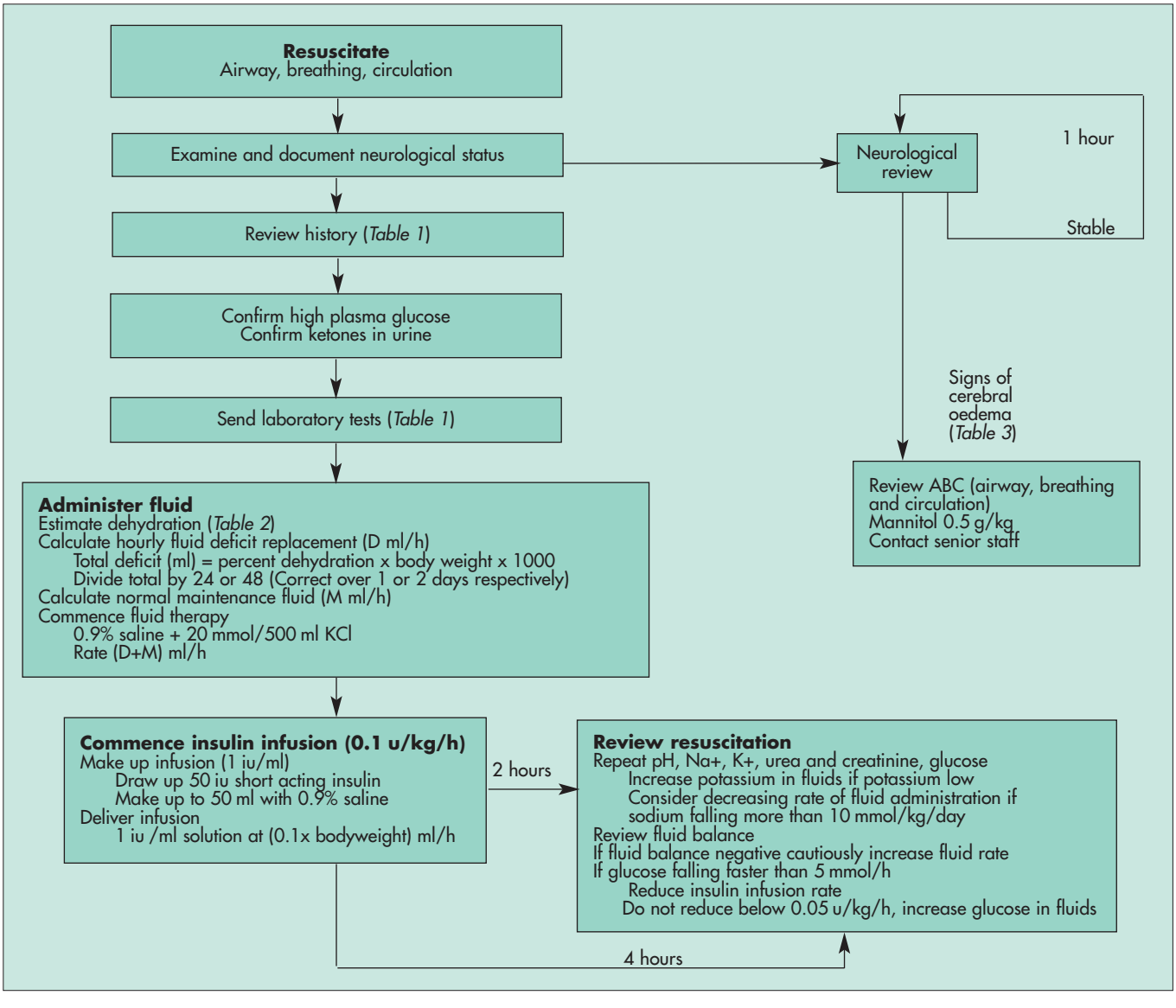
Extrapolating from this model it is reasonable, although unproven, to expect that rapid alterations in the availability of free water, concentrations of the major intra- and extracellular ions (sodium and potassium), and glucose will directly affect the likelihood of triggering cerebral oedema. It may be that the osmotic balance between a subset of or all of these substances holds the key (Carlotti et al, 2003). It is also known that rapid changes in plasma sodium levels can cause central pontine myelinolysis (Soupart and Decaux, 1996; Bonkowsky and Filloux, 2003). Therefore fluid therapy should be meticulously monitored and targeted to correct the metabolic derangement slowly. The limits to the safe rates of change of glucose and ion concentrations are unknown. Currently guidelines do not mitigate the possibility of permanent neurological damage (Bonkowsky and Filloux, 2003).

Current consensus suggests that rehydration should take between 24–48 hours. Careful attention must be paid to the rate of change of the concentrations of both glucose and sodium throughout treatment. Glucose should not fall faster than 5 mmol/litre/hour and plasma sodium should not change more than 10–15 mmol/litre/day (Soupart and Decaux, 1996). Sufficient potassium must also be provided to maintain normal plasma concentrations as the acidosis corrects and the ions move back to the intracellular compartment.

Management

The BSPED consensus guidelines for the management of DKA were published in 2001 and are available on their website (Edge, 2001). They are summarized in *Figure 1*. First-line treatment

Figure 1. Management of diabetic ketoacidosis.



and resuscitation follows standard guidelines for airway, breathing and circulation (Advanced Life Support Group, 2000). Once cardiorespiratory stability has been achieved the diagnosis should be confirmed with reference to the signs, symptoms and biochemical tests detailed in *Table 1*. The initial investigations that should be performed are also detailed in this table.

Conscious level must be documented and repeat neurological observations should be performed on an hourly basis. Any deterioration in conscious state should be referred to a senior paediatrician. Prompt consideration should be given to the commencement of treatment for cerebral oedema if there is any indication of onset (see below). It is important to note that irritability or mild depression of conscious level may be the only early warning sign, those that make up Cushing's triad are very late signs and are pre-terminal.

Fluids

The extent of dehydration should be estimated (*Table 2*). Fluid administration rate is calculated by adding normal requirement to the estimated water deficit divided by 24–48 hours. Dehydration is known to be consistently overestimated by clinicians (Inward and Chambers, 2002). Also the standard formula for maintenance fluid requirement assumes the kidneys are unable to concentrate urine and therefore provides an excess over the true basal requirement (Holliday and Segar, 1957). Therefore in the desire for a slow correction of homeostasis dehydration estimation should err on the low side. An example calculation is shown in *Figure 2*.

Initially 0.9% saline solution with 40 mmol/litre of added potassium chloride should be used. In the unusual event that the patient is anuric potassium should be withheld until urinary flow is established. Reexpansion of intravascular volume with fluid will result in a fall in plasma glucose as the anti-insulin hormones are downregulated. Repeat electrolytes must be performed within 2 hours of the initial treatment and thereafter at least 4-hourly. The concentrations of sodium or potassium in the hydration fluid should be reviewed with each result and altered if appropriate. Particular attention should be paid to preventing excessively fast change (as discussed above). Fluid balance should also be regularly reviewed and the rate of fluid administration altered accordingly. It is not uncommon for the large diuresis that occurs in the first few hours of resuscitation to result in a negative fluid balance. In this case the rate should be cautiously increased and then closely monitored so that a small positive balance is maintained.

Insulin

Rapid-acting insulin should be administered by infusion. It may be diluted in normal saline and should be initially administered at 0.1 u/kg/h (Edge, 2001). The plasma glucose should be

TABLE 1.
Features and initial investigation of diabetic ketoacidosis

Diagnosis	History	Polydipsia
		Polyuria
	Examination	Dehydration
		Drowsiness
		Acidotic respiration
		Abdominal pain/vomiting
	Bedside biochemical testing	High blood glucose on finger prick sample
		Ketones in urine
Investigations	Ward	Weight (if possible)
		Cardiac monitor (observe T waves)
	Laboratory investigations	Glucose
		Sodium, potassium, urea and creatinine
		Arterial blood gas
		Full blood count
	Other investigations	Blood culture, chest X-ray or swabs as indicated for concurrent sepsis
		Lumbar puncture should be considered but is contraindicated in a child with impaired level of consciousness

TABLE 2.
Estimation of dehydration

Signs/symptoms	Mild (<5%)	Moderate (5–10%)	Severe (>10%)
Decreased urine output	+	+	+
Dry mouth	+/-	+	+
Sunken fontanel	-	+	+
Sunken eyes	-	+	+
Tachypnoea	-	+/-	+
Tachycardia	-	+/-	+
Drowsiness/irritability Beware possible cerebral oedema	-	+/-	+

Figure 2. Calculation for fluid administration in cases of dehydration.

8-year-old boy, 5% dehydrated, estimated weight 25 kg

Normal maintenance:

100 ml/kg/day for first 10 kg,
50 ml/kg/day for next 10 kg,
20 ml/kg/day for remainder

Thus maintenance = (10 x 100) + (10 x 50) + (5 x 20) = 1600 ml/day

Deficit is 5% of total body weight of 25 kg (litre) = 0.05 x 25 = 1.25 litre = 1250 ml

Thus infusion rate = (maintenance + deficit)/24 = (1600+1250)/24 = 119 ml/h

monitored hourly and the rate of insulin administration titrated to produce a steady fall in plasma glucose not exceeding 5 mmol/litre/h.

Once the glucose concentration is less than 12 mmol/litre 5% dextrose should be added to the IV fluids. The insulin infusion may be titrated as low as 0.05 u/kg/h but if, at this rate, the plasma glucose falls below 7 mmol/litre, the concentration of dextrose in the IV fluids should be increased rather than reducing or stopping the insulin infusion. It is vital to adhere to this guidance to ensure that ketone production does not recommence.

Cerebral oedema

The signs and symptoms of cerebral oedema are listed in *Table 3* (Edge, 2001). Some of these may also occur in the presence of hypoglycaemia which should be excluded. Any suspicion of this complication must be referred to senior staff immediately. If treatment is not successful and cerebral oedema ensues the help of the local paediatric intensive care unit will be required.

A full review of airway, breathing and circulation and appropriate intervention should occur immediately. Mannitol 0.5 g/kg should be given and IV fluids restricted to two-thirds of maintenance. Senior staff will consider the appropriateness of intubation and hyperventilation to control the intracranial pressure. This is an extremely difficult decision as the child with DKA will hyperventilate down to a very low arterial CO_2 to generate a compensatory respiratory alkalosis. Ventilating to similar levels is both unusual and unfamiliar. The need for intubation in order to protect the airway will usually override other considerations. Other measures such as the use of hypertonic saline or cooling may also be considered as neuroprotective strategies but remain untested in terms of both their safety and efficacy in this scenario.

Once clinically stable a computed tomography (CT) scan should be performed to exclude alternative diagnosis. Thrombosis, haemorrhage or infarction may all occur with severe illness and dehydration (Keane et al, 2002).

TABLE 3. Signs of cerebral oedema

Headache		
Confusion		
Irritability		
Reduced conscious level		
Seizures		
Small pupils		
Late signs	Cushing's triad	High blood pressure
		Slow heart rate
		Abnormal breathing pattern
	Papilloedema	

OTHER MEASURES

A nasogastric tube should be passed, aspirated and left on free drainage at an early stage of treatment as these children have gastric stasis and may vomit and aspirate, especially if they are obtunded.

In a conscious, cooperative child a urinary catheter is not required. However, if conscious level is depressed or there is a massive urinary output it may be useful. If used it should be removed as soon as practical.

Sodium bicarbonate infusion is not recommended in the routine treatment of DKA and may be associated with an increased incidence of cerebral oedema. Persistent acidosis is generally caused by insufficient fluid resuscitation. Administration of bicarbonate should only be undertaken under the direction of a paediatric intensivist, usually for the treatment of cardiovascular instability.

Monitoring and ongoing management

Biochemistry, pH and glucose measurements should be repeated within 2 hours of commencing therapy and at least 4-hourly thereafter. Any concerns regarding rapid changes or significant alterations in fluid composition or rate should prompt more frequent testing.

A persistent acidosis is suggestive of insufficient fluid resuscitation. This may be treated by cautiously increasing the rate of fluid administration or a further fluid bolus.

Throughout resuscitation attention to detail is essential. Patience is also vital, providing there is clear evidence of an improvement in biochemistry then it is generally inadvisable to alter therapy significantly. If there is any doubt about any aspect of care senior help must always be immediately sought. HM

Advanced Life Support Group (2000) *Advanced Paediatric Life Support.* 3rd edn. BMJ Publishing Group, London

Bonkowsky JL, Filloux FM (2003) Extrapontine myelinolysis in a pediatric case of diabetic ketoacidosis and cerebral edema. *J Child Neurol* **18:** 144–7

Campbell A, McIntosh N, eds (2003) *Forfar and Arneil's Textbook of Pediatrics,* 5th edn. Churchill Livingstone, New York

Canadian Diabetes Association (2003) Discovery of Insulin. www.discoveryofinsulin.com/Home.htm (accessed 24 February 2004)

Carlotti AP, Bohn D, Halperin ML (2003) Importance of timing of risk factors for cerebral oedema during therapy for diabetic ketoacidosis. *Arch Dis Child* **88:** 170–3

Edge JA (2001) British Society of Paediatric Endocrinology and Diabetes: Recommended DKA Guidelines. www.bsped.org.uk (accessed 24 February 2004)

Edge JA, Hawkins MM, Winter DL, Dunger DB (2001) The risk and outcome of cerebral oedema developing during diabetic ketoacidosis. *Arch Dis Child* **85:** 16–22

Holliday MA, Segar WE (1957) The maintenance need for water in parenteral fluid therapy. *Pediatrics* **19:** 823–31

Inward CD, Chambers TL (2002) Fluid management in diabetic ketoacidosis. *Arch Dis Child* **86:** 443–4

Keane S, Gallagher A, Ackroyd S, McShane MA, Edge JA (2002) Cerebral venous thrombosis during diabetic ketoacidosis. *Arch Dis Child* **86:** 204–5

Soupart A, Decaux G (1996) Therapeutic recommendations for management of severe hyponatraemia: current concepts on pathogenesis and prevention of neurological complications. *Clin Nephrol* **46:** 149–69

KEY POINTS

- Assessment and management of airway, breathing and circulation should be the first priority.
- 0.9% saline should be used for first-line resuscitation and maintenance fluid. Supplemental potassium should be added if passing urine.
- Regular clinical review of fluid and electrolyte status is essential.
- 1-hourly neurological review is mandatory to identify signs of cerebral oedema.
- If cerebral oedema is suspected contact senior staff immediately and treat aggressively.