

DIABETIC KETOACIDOSIS ANAESTHESIA TUTORIAL OF THE WEEK 128

6TH APRIL 2009

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SELF-ASSESSMENT QUESTIONS

Please read the following questions. The answers will be found in the article.

1. What are the characteristic metabolic derangements in diabetic ketoacidosis (DKA)?
2. What are the **basic** principles in the management of a patient with DKA?
3. What is the optimal rate of fall of plasma glucose in the management of DKA?
4. What are the risk factors for and early signs of cerebral oedema complicating DKA treatment?
5. When is it appropriate to convert a patient who has been treated for DKA from intravenous insulin infusion to a subcutaneous regime?

DIABETIC KETOACIDOSIS: DEFINITION AND KEY FEATURES

Diabetic ketoacidosis (DKA) is a life threatening medical emergency. It is characterised by hyperglycaemia, dehydration, metabolic acidosis and ketonuria.

The criteria for the diagnosis of DKA includes a blood sugar >14.0 mmol/l, presence of urinary or plasma ketones, a pH < 7.3 and a serum bicarbonate of less than 18 mmol/l. The main differential diagnosis is the hyperosmolar hyperglycaemic syndrome which differs in the extent of dehydration, acidosis and ketosis. Patients with hyperosmolar hyperglycaemic syndrome tend present with a pH > 7.3. Despite significant overlaps between the syndromes the focus of the review will be on the DKA syndrome.

As important differences exist between adults and children as regards their presentation and management of DKA, the treatment in either subgroup will be discussed separately.

FREQUENCY AND CAUSES

Diabetic ketoacidosis (DKA) primarily occurs in patients with Type I diabetes mellitus but it is being recognised in some Type II diabetics.¹ The incidence of DKA is estimated at between 4.6 and 8 episodes per 100 patient years of diabetes.² DKA may be the first presentation of diabetes or may follow a precipitating event. The most common precipitant is an infection however in a large number of cases no identifiable cause can be found (Table 1).

Table 1. Common precipitating events of DKA

Precipitant	Occurrence (%)
Infections (commonly urinary tract)	30
Non-compliance with treatment	15
New diagnosis of type I diabetes	5-15
Other stresses (MI, alcohol, pancreatitis, drugs)	5
No cause found	40

PATHOPHYSIOLOGY

DKA is due to an insulin deficiency, together with an excess of the counter-regulatory hormones, glucagon, growth hormone and the catecholamines. The absence of insulin results in poor glucose utilisation by peripheral tissues. Glucagon, growth hormone and the catecholamines increase triglyceride breakdown into free fatty acids and promote glucose production from hepatic gluconeogenesis. The Ketones, acetoacetate and β hydroxybutyrate are formed by the beta oxidation of the free fatty acids. Hence resulting in hyperglycaemia and the formation of ketoacids which are the primary metabolic derangements in DKA.

The secondary consequences of these primary derangements include metabolic acidosis and an osmotic diuresis. Metabolic acidosis is caused by the production of H^+ ions by the dissociation of ketoacids. The accumulation of ketoacids leads to an elevated anion gap. This is a key feature of DKA. Initially as the blood sugar rises there is a shift of fluid from the intracellular to the extracellular compartment with subsequent dilution. Once the blood sugar level exceeds the renal threshold for glucose, around 12 mmol/l, glycosuria occurs followed by an obligatory osmotic diuresis, resulting in a loss of water from the extracellular compartment. This hyperglycaemia induced osmotic diuresis as well as causing a urinary loss of water and glucose will also cause a loss of, ketones, sodium, potassium and phosphate in the urine. At presentation patients are often severely dehydrated with marked serum electrolyte disturbances.

CLINICAL FEATURES

There is a wide spectrum of severity of illness in patients presenting with DKA. Classically patients present with a history of thirst, polyuria and polydipsia although these are not invariably present. As discussed, Diabetes Mellitus may not have been previously diagnosed.

Other symptoms may include:

- Weakness and lethargy
- Nausea and vomiting
- Abdominal pain
- Weight loss.

Common general physical signs are:

- Evidence of dehydration
- Tachycardia and hypotension
- Kussmaul respiration (deep rapid respiration to provide respiratory compensation for metabolic acidosis)
- Ketotic breath (fruity acetone smell due to exhaled ketones)
- Temperature is usually normal or low even in the presence of an underlying infection.³
- Altered consciousness and confusion

INVESTIGATIONS

Initial investigations are aimed at confirming the diagnosis, estimating the severity and identifying underlying causes.

Blood glucose measured hourly

This will be grossly elevated at presentation but can rarely be normal if there has been administration of insulin, resulting in correction of the blood sugar but not the acidaemia. When the blood sugar is grossly elevated at presentation, point of care testing can be inaccurate and therefore samples should be sent to the laboratory initially.

Urine test for ketones

If the nitroprusside method is used β hydroxybutyrate will not be measured. As β hydroxybutyrate is the main ketone produced in DKA for on-going assessment of ketonaemia direct measurement of serum β hydroxybutyrate is recommended but is dependent on laboratory availability.

Serum urea and electrolytes

These should be measured every 2-4 hours initially.

Sodium

As already discussed hyperglycaemia will cause a dilutional hyponatraemia. The measured serum Na can be corrected by adding 1.6mmol/l for each 5.5mmol/l elevation of serum glucose over 5.5mmol/l. Correction formula: Corrected Na = Measured Na + 1.6 [(Plasma Glucose (mmol/l) – 5.5/ 5.5]

Potassium

In DKA there is a total body deficit of potassium but because of acidosis and dehydration initial serum levels may be within the normal range or be elevated. Serum levels must be regularly checked because correction of the acidosis and administration of insulin can result in a precipitous drop in serum potassium because of the intracellular movement of potassium.

Urea and creatinine

Renal impairment may be present at presentation. Elevated acetoacetate levels may cause a falsely elevated creatinine level if the calorimetric method is used to measure the serum creatinine.

Serum Osmolality

Calculated as $2(\text{Na}) + \text{Glucose} + \text{Urea}$. If a patient in DKA is comatose with an osmolality less than 330mOsm/kg then other sources for coma should be sought.

Venous or arterial blood gas

This is required every 2-4 hours. Venous blood gases or venous serum bicarbonate are an acceptable alternative to arterial blood gas sampling in the initial management of DKA as studies have confirmed that venous blood pH closely reflects arterial blood pH in these patients. The venous pH is 0.02-0.03 units lower than the arterial pH.⁴

Anion gap

An elevated anion gap metabolic acidosis is a key feature of DKA. Anion gap is calculated as $(\text{Serum Na} + \text{K}) - (\text{Serum HCO}_3 + \text{Cl})$. Normal values are 8 – 12mmol/l.

Full blood count

An increased white blood cell count in the range $10\text{-}15 \times 10^9/\text{l}$ is characteristic of DKA and is not indicative of infection. However a count $>25 \times 10^9$ should raise concern that an infection is present.³

Amylase

Amylase is often raised in the absence of pancreatitis. This may cause diagnostic confusion, especially in the presence of abdominal pain.

Chest X-ray, blood cultures, urine cultures, ECG and cardiac enzymes should be considered to investigate potential underlying causes. Children should be weighed to guide fluid and drug therapy. If this is not possible an estimated weight should be calculated.

MANAGEMENT OF ADULTS IN DIABETIC KETOACIDOSIS

Initial assessment and resuscitation

Patients with DKA may be severely unwell and comatose. Initial assessment involves confirmation of the diagnosis and a rapid assessment of Airway, Breathing, Circulation and Disability. Intravenous access is obtained as soon as possible and blood tests (mentioned above) taken for urgent analysis including blood for culture. There should be application of 100% oxygen via a face mask with a reservoir bag.

The basic principles of DKA management are;

- rapid restoration of adequate circulation and perfusion with isotonic intravenous fluids
- gradual rehydration and restoration of depleted electrolytes
- insulin to reverse ketosis and hyperglycaemia
- careful, regular monitoring of clinical signs and laboratory tests to detect and treat complications

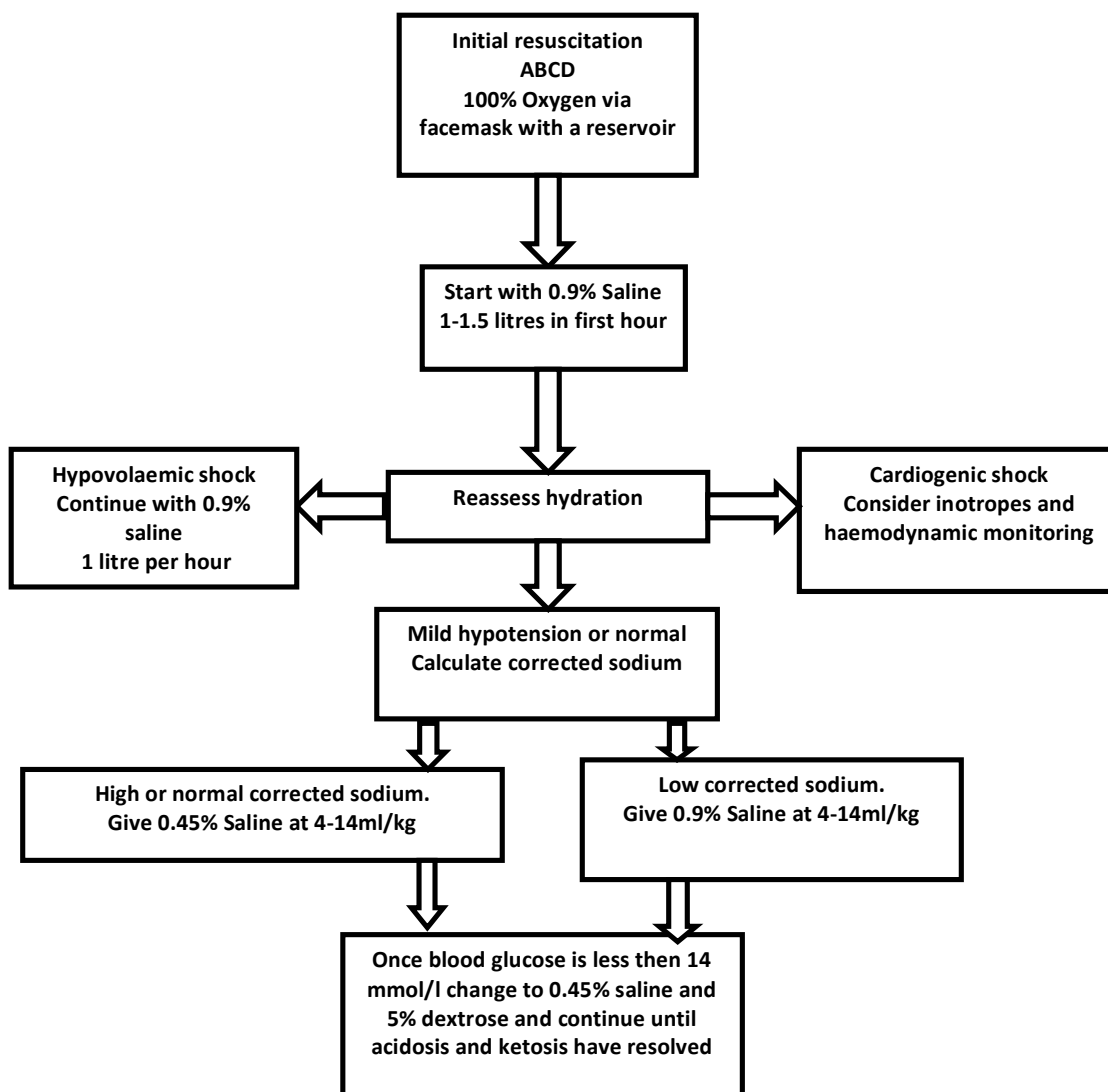
Fluids (see Table 2)

Initially fluid therapy is aimed at rapid restoration of the intravascular volume. In the first hour 0.9% saline is given at a rate of 15-20mls/kg or an average 1-1.5 litres. Thereafter further fluid therapy should be administered at a rate sufficient to maintain adequate blood pressure, urine output and mental status. The aim is to correct the estimated water deficit over 24hours, in general a rate of 4-14mls/kg/hour will suffice. Patients in cardiogenic shock will require inotropes and haemodynamic monitoring.

Although some have argued that Hartmann's solution is a better fluid to give during the initial resuscitation as it avoids the hyperchloraemic acidosis. However adverse sequelae from Hartmann's include an increase in the blood glucose from the lactate load, the potassium it contains (5 mmol/l) can elevate the serum potassium dangerously in those already hyperkalaemic and lastly the hypotonicity could precipitate cerebral oedema.

Following the initial period of resuscitation the subsequent choice of fluid will depend on the corrected serum sodium. If normal or elevated then 0.45% saline should be given, if low then saline should be continued. When the blood glucose is 14 mmol/l the fluid should be changed to 5% dextrose with 0.45% saline until the acidosis and ketosis have resolved. Slow correction of metabolic abnormalities, particularly elevated serum sodium and glucose is a goal of treatment. Over rapid or excessive fluid therapy in DKA may precipitate acute cerebral oedema.³

Table 2 Summary of fluid replacement in adults (modified from reference 3)



Insulin

Insulin should be given intravenously and not subcutaneously. Once hypokalaemia has been excluded an intravenous insulin infusion should be commenced (50 units actrapid in 50 mls 0.9% saline) at 0.1 units/kg/hour. Until recently many protocols advised bolus doses of insulin at the time of diagnosis of DKA to allow rapid correction of blood sugar, this is no longer accepted practice. Intravenous fluid resuscitation alone will reduce plasma glucose levels by two methods. It will dilute the blood glucose levels and also the levels of counter-regulatory hormones. Excessive insulin therapy causes inappropriately rapid falls in plasma glucose and risks profound hypokalaemia.

A reasonable target for the fall in plasma glucose is 3-4 mmol/l/hour, if the blood glucose fails to fall at this rate the insulin rate should be doubled every hour until the target decrease is reached. In those in whom the rate of fall of plasma glucose exceeds 5 mmol/l/hr the rate should be reduced to 0.05 units/kg/hr but only for a short time as a rate of 0.1 units/kg/hr is needed to switch off ketone production. When the blood glucose falls to below 14 mmol/l a dextrose containing fluid should be commenced. If hypoglycaemia occurs prior to complete

resolution of DKA the insulin infusion should not be stopped instead extra glucose should be added to the IV fluids.

Potassium replacement

In DKA there is a total body deficit of potassium but despite this at presentation mild to moderate hyperkalaemia is not uncommon. Serum levels will fall once insulin and fluids are started. Adding 20-40 mmol/l KCl will usually result in adequate replacement, keeping the serum potassium around 4.5 mmol/l. If the initial serum potassium is low initially (<3.3 mmol/l) then the insulin infusion should be withheld temporarily. If anuria or peaked ECG T waves are present at presentation then omit potassium in the initial fluid replacement until serum potassium is known. If the serum K is >5.3 mmol/l omit potassium and continue to check the serum potassium every 2 hours.

Sodium bicarbonate

Sodium bicarbonate is rarely, if ever, necessary. If administered, deleterious effects include risk of hypokalaemia, cerebral oedema and reduced tissue oxygenation by its effects on the oxygen dissociation curve. Acidosis will improve with fluid replacement and insulin. Continuing acidosis usually means insufficient resuscitation. Sodium bicarbonate should only be considered in patients with profound acidosis (pH < 6.9) and circulatory failure resistant to inotropes.

Continuing management

Location of care

Patients with DKA require close nursing and medical supervision. This may be best provided in a high dependency or intensive therapy environment if facilities are available. Regular clinical assessment is required to guide fluid therapy and ensure adequate resolution of shock.

Starting an insulin sliding scale and conversion to subcutaneous insulin

Once plasma glucose is < 10 mmol/l patients and the acidosis has resolved the insulin infusion should be changed from a constant rate to a sliding scale. An example of a sliding scale is shown (see table 3). Oral diet should be resumed as soon as the patient is able. Subcutaneous insulin regimes may be commenced when the patient is tolerating an oral diet and the level of ketonuria has fallen to 1+ or 0. This usually corresponds to a pH of > 7.3. Twenty to thirty minutes before a meal subcutaneous insulin should be given and the intravenous insulin continued for another 2 hours.

Table 3. Sliding scale for use in DKA once plasma glucose < 10 mmol/l

Plasma Glucose (mmol/l)	Insulin (units/hr)	Additional action
< 4	0.5	Increase dextrose intake, repeat reading at 30 minutes, alert Doctor if unwell
4.0 – 6.0	1	
6.1 – 8.0	2	
8.1 – 10.0	4	
10.0	6	Alert Doctor if reading remains > 10 mmol/l after second reading

Antibiotic therapy

Occult infections are common precipitants of DKA (Table 1). Evidence of infection should be actively sought and investigations should include blood cultures and urine dipstick testing and cultures. Suspected bacterial infections should be treated aggressively with appropriate antibiotics. The role for prophylactic antibiotics in patients with DKA is an area of debate and clinicians should follow local hospital guidelines.

Thromboprophylaxis

Patients with DKA are at increased risk of thromboembolism. Prophylactic heparin has an accepted role in the management of patients with DKA. It should be continued until the patients are mobile with no evidence of dehydration or elevated serum osmolality. Unfractionated heparin or low molecular weight heparin are suitable treatments.

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Nasogastric tube drainage

DKA causes gastric stasis. Aspiration pneumonitis may occur if vomiting is combined with a reduced level of consciousness. Nasogastric tube drainage should therefore be considered in all patients with DKA. It is mandatory in those with markedly impaired conscious level.

Urinary catheterisation

Strict fluid balance is required in the management of DKA. Measurement of urinary output is simplified by urinary catheterisation.

Continuous ECG monitoring

This is indicated in the presence of significant underlying cardiac disease, significant hyper- or hypokalaemia or severe DKA.

Notes recording

Adequate recording of regular clinical assessments and laboratory test results is vital. This process is made easier by the use of standard ward or high dependency care observation charts and serial results sheets for blood results. This allows staff to rapidly and accurately assess patient progress.

Diabetes team follow up

Prior to discharge from hospital it is recommended that all DKA patients be referred to a member of the diabetes team in order to help determine the cause of the DKA and to review the patient's diabetes knowledge and education.

MANAGEMENT OF CHILDREN AND ADOLESCENTS IN DIABETIC KETOACIDOSIS

Although the pathophysiology behind DKA in children is the same as in adults there are important differences with respect to presentation and management. The young child will be difficult to obtain the classical history of polyuria, polydipsia and weight loss and as a consequence may be misdiagnosed initially. A high proportion of children will present in DKA as newly diagnosed diabetics and in adolescents the leading cause of recurrent DKAs is the omission of insulin.

Subtle management differences should be noted compared with an adult. Firstly their smaller size mandates a more precise prescription of fluids and electrolytes. Secondly cerebral oedema is more common in children, occurring in up to 1% with a mortality rate of up to 25%.⁴ It is the concern over ensuing cerebral oedema in children that necessitates a less aggressive fluid replacement, avoiding insulin in the first hour of fluid replacement, avoiding sodium bicarbonate and limiting the rate at which the blood glucose falls.

Resuscitation

Initial management involves confirmation of the diagnosis and resuscitation of the child using an ABCD approach (Airway, Breathing, Circulation, and Disability). Give 100% oxygen via a face mask with a reservoir bag and confirm a patent and protected airway. The child may present comatose, in cerebral oedema, requiring immediate tracheal intubation. Establish intravenous access and assess the circulation (blood pressure, heart rate, pulse volume and capillary refill time (CRT)). If the CRT is prolonged or there are other signs of shock give an initial 10mls/kg of 0.9% saline, followed by a period of assessment. A further 10mls/kg should be repeated if the CRT is still prolonged.⁵

Fluids (see Table 4)

Fast and aggressive fluid replacement may increase the likelihood of cerebral oedema. Fluid replacement is replaced over 48 hours and is calculated using the equation:

Fluid requirement over 48 hours = Maintenance (over 48hours) + Deficit- the volume of fluid used in resuscitation

Where the deficit (in mls) = Body weight (kg) x % dehydration x10

And maintenance= 80 mls/kg/24hours for 3 months -2 years
= 70 mls/kg/24hours for 3-5 years
= 60 mls/kg/24hours for 6-9 years
= 50 mls/kg/24hours for 10-14 years

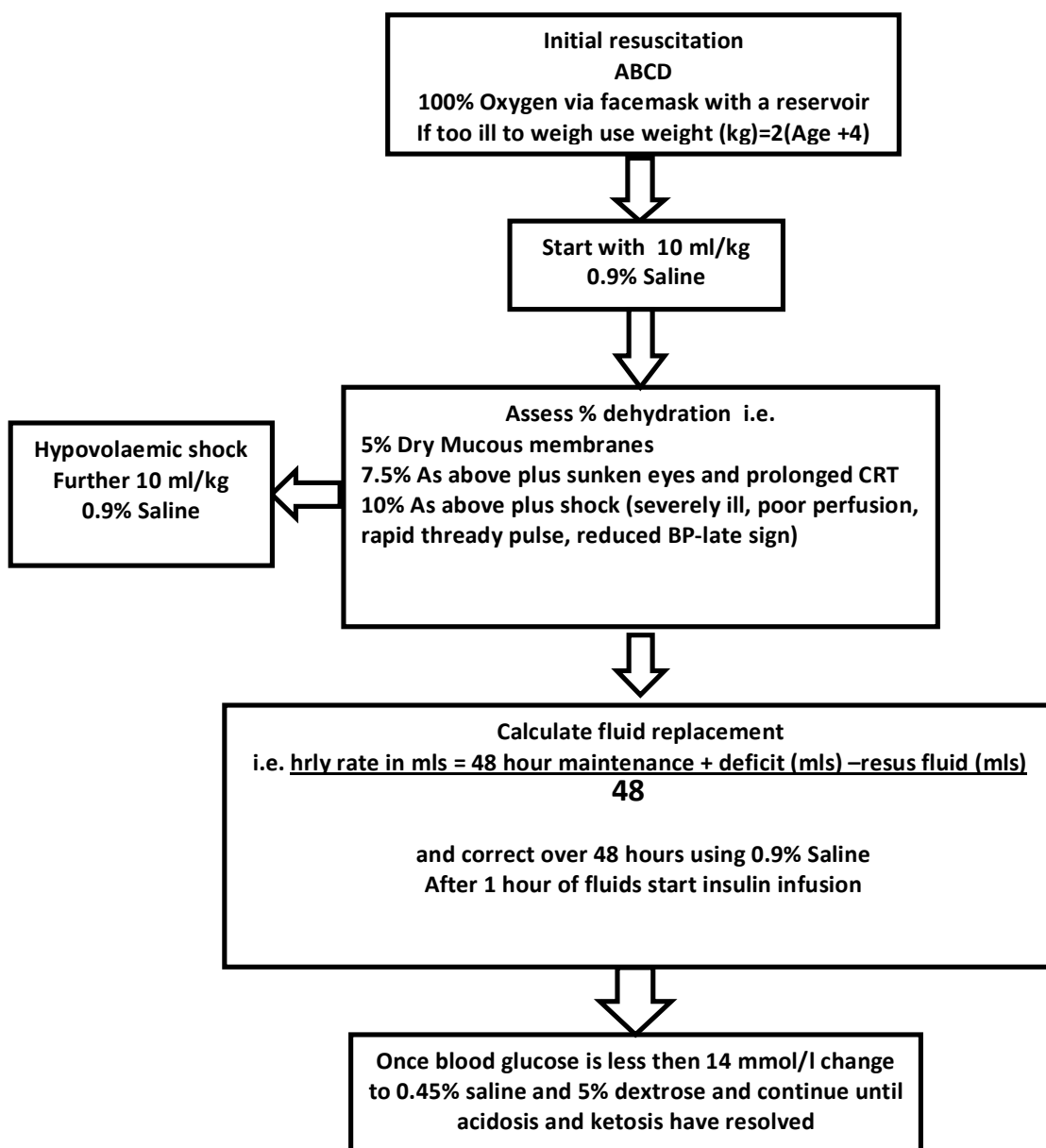
i.e. hourly rate in mls = $\frac{48 \text{ hour maintenance} + \text{deficit (mls)} - \text{resus fluid (mls)}}{48}$

The fluid to be given is 0.9% saline with 20 mmols KCl per 500mls unless the patient is anuric and/or has peaked T waves on the ECG, in which case the KCl is omitted until the serum K is known. During the first hour the blood glucose will fall rapidly but thereafter a reduction of no more 5 mmols/hour should be permitted. If this occurs or the blood glucose falls <14 mmol/l then the fluid should be changed to 0.45% saline/ 5% dextrose plus KCl 20 mmol per 500 mls.⁵

Insulin

After initiating fluid replacement an hour should elapse before starting insulin therapy. As with adults do not use an insulin bolus. Commence an insulin infusion (50 units actrapid in 50 mls 0.9% saline) at 0.1units/kg/hour, with the aim of continuing this rate until the acidosis has resolved (pH>7.3), extra glucose may needed to be added to allow for this. In those in whom the rate of fall of plasma glucose exceeds 5 mmol/l/hr the rate should be temporarily reduced to 0.05 units/kg/hr.⁵

Table 4. Summary of fluid replacement in children and adolescents (modified from reference 5)



COMPLICATIONS OF DKA TREATMENT

Cerebral oedema

Monitoring for any signs of cerebral oedema should start at the time of admission of patients with DKA and continue for at least the first 12 hours of treatment, it typically presents within 2 – 24 hours of treatment for DKA. Early signs are headache, confusion and irritability. Later signs include reduced conscious level and seizures. The exact pathophysiology is poorly understood but risk is related to severity and duration of DKA. Other suggested associated factors include overzealous fluid administration, the administration of sodium bicarbonate and too rapid fall in the blood glucose.

If cerebral oedema is suspected due to an altered level of consciousness hypoglycaemia must be excluded initially. Intravenous mannitol (1.0g/kg = 5.0 ml/kg 20% mannitol) should be given immediately. Fluids should be restricted to 2/3 maintenance and the fluid deficit should be replaced over 72 hours. Transfer the patient to the Intensive Care Unit for intubation, mechanical ventilation and arrangements made for an urgent CT head. If cerebral oedema is present liaise with a neurosurgeon regarding the possibility of intra-cranial pressure monitoring.

Hypoglycaemia

Hypoglycaemia should be treated with increased dextrose administration. A decreased insulin infusion rate may be necessary temporarily. Insulin infusions should not be stopped before the metabolic acidosis and ketonuria has resolved, as this will delay recovery.

Hypokalaemia

Hypokalaemia should be treated in a standard fashion. Central venous access will allow potassium to be safely administered at a rate more than 40 mmol/hr. Continuous cardiac monitoring is indicated in this setting.

Hypophosphataemia

Hypophosphataemia is common. It seldom requires treatment as levels will correct once oral diet is resumed. The routine replacement of phosphate does not improve the outcome in DKA. However in those with cardiac dysfunction, anaemia or respiratory depression combined potassium and phosphate replacement can be given.

DKA IN PREGNANCY

DKA in pregnancy is of special concern. It tends to occur at lower plasma glucose levels and more rapidly than in non-pregnant patients and usually occurs in the second and third trimesters because of increasing insulin resistance. Fetal mortality rates have previously been reported as high as 30% rising to over 60% in DKA with coma.⁷ However with improvements in diabetic care the figure for fetal loss has been reported as low as 9% in some countries.⁸ Prevention, early recognition and aggressive management are vitally important to try to minimise fetal mortality. It is clear that diabetes and obstetric teams should jointly manage all pregnant patients with DKA.

SUMMARY

DKA is a potentially life threatening complication of Diabetes Mellitus. An understanding of the pathophysiology of the conditions aids appropriate treatment. Initial assessment must involve a rapid assessment of Airway, Breathing and Circulation and obtaining sufficient intravenous access. Initial investigations are aimed at confirming the diagnosis and identifying underlying causes. The diagnosis of DKA requires a blood sugar >14.0 mmol/l, positive urinary or plasma ketones, an arterial pH < 7.3 and serum bicarbonate of < 18mmol/l.

The basic principles of DKA management include rapid restoration of adequate circulation and perfusion with isotonic intravenous fluids, gradual rehydration and restoration of depleted electrolytes, insulin to reverse ketosis and hyperglycaemia and regular monitoring of clinical signs and laboratory tests to detect and treat complications. A target rate of correction of hyperglycaemia is a drop of blood glucose by 3 – 4 mmol/l/hr. Acute cerebral oedema is a potential complication possibly due to excessive fluid therapy or too rapid a fall in blood glucose. Early signs of the development of this potentially fatal complication include headache, irritation and confusion. Prompt recognition and appropriate management may improve prognosis.

REFERENCES

1. Wittlesey CD. Case study: Diabetic ketoacidosis complications in type 2 Diabetes. *Clinical Diabetes* 2000; **18**: 88-90
2. Chiasson J et al. Diagnosis and treatment of diabetic ketoacidosis and the hyperglycaemic hyperosmolar state. *CMAJ* 2003; **168**: 859-66
3. Kitabaci AE, Umpierrez GE, Murphy MB, Kreisberg RA. Hyperglycaemic crises in adult patients with diabetes. A consensus statement from the American diabetes association. *Diabetes Care* 2006; **29**: 2739-2748
4. Brandenburg MA, Dire DJ. Comparison of arterial and venous blood values in the initial emergency evaluation of patients with diabetic ketoacidosis. *Ann Emerg Med.* 1998; **31**: 459—65
5. Glaser NS et al. Frequency of sub-clinical cerebral edema in children with diabetic ketoacidosis. *Pediatr Diabetes* 2007; **8**: 28-43
6. Southwest Diabetes Regional Network Integrated Care Pathway for Children with Diabetic Ketoacidosis 2007.
7. Kyle GC. Diabetes and pregnancy. *Ann Intern Med* 1963; **59**(suppl 3): 1-8
8. American Diabetes Association. Report on the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care* 1999; **22**(Suppl 1): S5