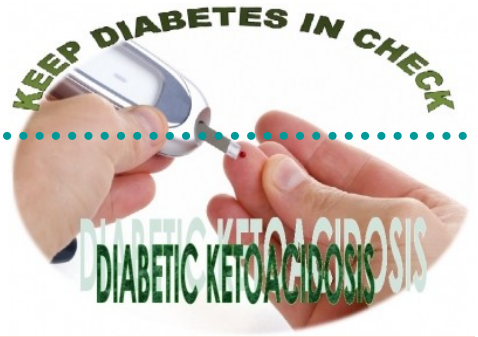
Buletin Farmasi Hospital Segamat



What is diabetic ketoacidosis (DKA)?

Volume 1/2014

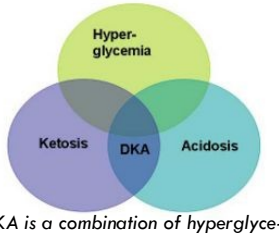
DKA is defined as an acute, major, life-threatening complication of diabetes.[1] It is a state of absolute or relative insulin deficiency aggravated by ensuing hyperglycemia, dehydration, and acidosis-producing derangements in intermediary metabolism.[1] It is defined by the biochemical triad of ketonaemia, hyperglycemia, and acidaemia.[3] Clinically, it is an acute state of severe uncontrolled diabetes associated with ketoacidosis that requires emergency treatment with insulin and intravenous fluids.[1]

It is much more common in young children and adolescents than it is in adults.[1] Most patients with DKA have Type 1 Diabetes Mellitus (DM). In the United Kingdom (UK), more than 11% of patients with Type 1 DM had an episode of DKA between year 2004 to 2009. However, those with Type 2 DM are also at risk during catabolic stress of an acute illness.[2]

The most common causes of DKA are underlying or concomitant infections (40%), disruption of insulin treatment (25%), and newly diagnosed diabetes (15%).[1]

Despite improvements in diabetic care, DKA remains a life-threatening condition. Mortality rate is high in developing countries and among non-hospitalized patients. In the UK, mortality rate is approximately 2%. The most common cause of mortality, particularly in children and adolescents is cerebral oedema.[1,3]

However, death is potentially avoidable. It is important to raise awareness of DKA and improve patient education and compliance towards follow-up at clinics.[3]



DKA is a combination of hyperglycemia, ketonaemia, and acidaemia.

Causes of DKA[1,2]

Type 1 DM	• Acute insulin deficiency • Poor compliance • Bacteria (*Klebsiella penumoniae*) infection and intercurrent illness • Medical, surgical, or emotional stress • Brittle diabetes • Idiopathic • IVI insulin catheter blockage or mechanical failure of infusion pump
Type 2 DM	• Medication eg. Corticosteroids, clozapine, thiazides, pentamidine • Intercurrent illness eg. UTI

Signs and symptoms of DKA

The most common early symptoms of DKA includes polydipsia, and polyuria, both of which are signs of hyperglycemia. Before the development of ketoacidosis, the patient may experience generalized weakness, fatigue, nausea and vomiting, decreased appetite, and rapid weight loss (in newly diagnosed Type 1 DM). Symptoms associated with possible intercurrent infection are fever, dysuria, coughing, chills, shortness of breath. Acute chest pain and palpitation may be present in association with myocardial infarction.

DKA patient may be present with dry skin, decreased skin tugor, dry mucous membrane, increased capillary refill time, and hypotension, all of which are signs of dehydration. Patient may also have characteristic acetone breath odor. Signs of acidosis include shallow rapid breathing, disturbed consciousness, coma, and abdominal tenderness.

Inside this issue:

Pathophysiology of DKA

DKA is a complex disordered metabolic state characterized by hyperglycemia, ketoacidosis, and ketonuria.1,2 It usually occurs as a consequence of absolute or relative insulin deficiency. This is accompanied by an increase in counter-regulatory hormones (eg. glucagon, cortisol, growth hormone, and epinephrine) as a result of impairment in carbohydrate utilization. This hormone imbalance enhances gluconeogenesis, glycogenolysis, and lipolysis. Overall, the metabolism in DKA shifts from a normal fed state - carbohydrate metabolism, to a fasting state - fat metabolism.[1]

Impaired glucose utilization in peripheral tissues, gluconeogenesis and glycogenolysis leads to severe hyperglycemia; whereas lipolysis increases serum free fatty acid levels with increased activity of tissue lipase.[1,2] Excessive acetyl coenzyme A generated from β-oxidation of serum free fatty acids is then rerouted to ketogenesis due to inhibition of citric acid cycle (TCA) resulting in the accumulation of ketones (acetone, β-hydroxybutyrate, and acetoacetate) causing ketonemia. β-hydroxybutyrate causes nausea and vomiting; whilst acetone induces fruity odor of breath. When the body threshold to extract ketones is exceeded, they will overflow into urine (ketouria). If untreated, further accumulation of this organic acid will lead to a subsequent drop in blood pH and serum bicarbonate levels causing ketoacidosis. Rapid shallow breathing (Kussmaul respirations) is observed as respiratory compensation for this acidotic condition.[1,2,3]

Severe electrolyte disturbance occurs as a result of hyperglycemia, serum hyperosmolarity, osmotic diuresis, and metabolic acidosis combined with ketone-induced severe nausea and vomiting. The most prominent is total body potassium (K+) loss. However this loss is not mirrored in serum (K+) loss, which may be low, within reference range, or even high. Loss of K+ is a result of shift of K+ from the intracellular to the extracellular space in exchange with hydrogen ions that accumulate in the extracellular during acidosis. Osmotic diuresis then leads to loss of the shifted extracellular K+ in the urine. Overall serum electrolyte loss are typically 200-500mEq/L of potassium, 300-700 mEq/L of sodium, and 350-500 mEq/L of chloride.[1]

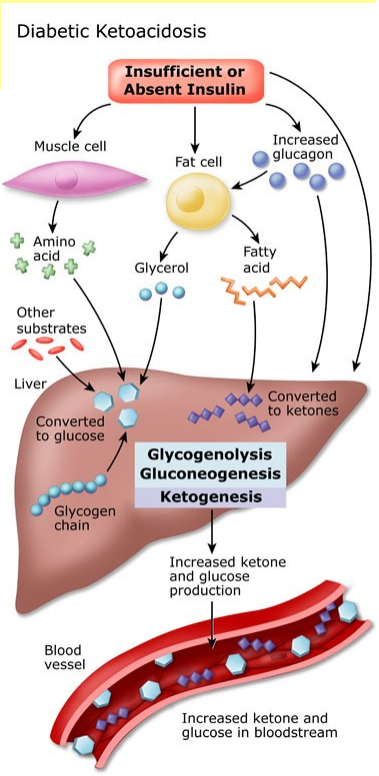


Diagram of pathophysiology of diabetic ketoacidosis in a molecular level

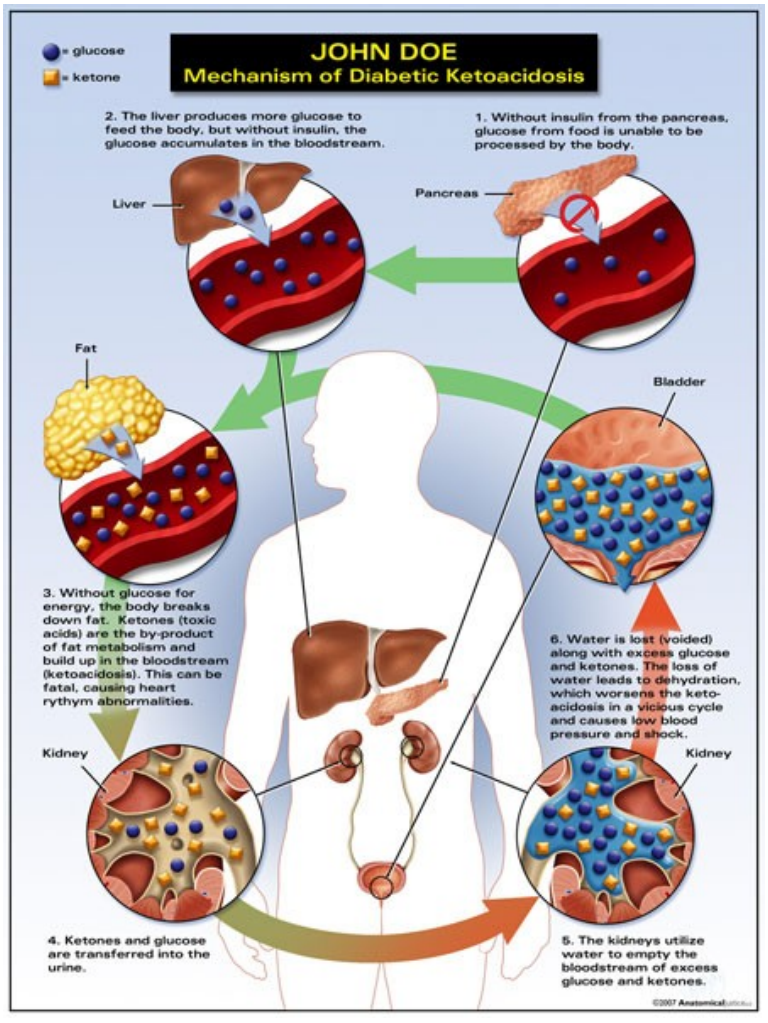


Diagram showing the mechanism of diabetic ketoacidosis

> ***"On admission, serum potassium levels may be high or within reference range due to shift of potassium from intracellular to extracellular due to acidemia, insulin deficiency, and hypertonicity."***

Severe hyperglycemia leads to glycosuria when the renal threshold for glucose absorption is exceeded. As a consequent, osmotic diuresis induced by glycosuria increases water loss in urine. This results in severe dehydration, thirst, tissue hypoperfusion, and possibly lactic acidosis. Typical water loss in DKA is approximately six litres or 100mL/kg body weight.[1]

Alteration in the level of consciousness is a result of the combined effects of serum hyperosmolarity, dehydration, and acidosis.[1]

Degree of dehydration[5]	
Mild, 3%	Only just clinically detectable
Moderate, 5%	Dry mucous membrane, reduced skin tugor
Severe, 8%	Above with sunken eyes, poor capillary return
+ shock	May be severely ill with poor perfusion, thread rapid pulse

Diagnostic criteria

The diagnostic criteria for diabetic ketoacidosis are[5]:

1. History of presentation - polydipsia, polyuria
2. Clinical presentation - acidotic respiration, dehydration, drowsiness, vomiting
3. Biochemical presentation - capillary blood glucose ≥11mmol/L
   - capillary ketones >3mmol/L or urine ketones ≥++
   - venous pH <7.3 and/or serum bicarbonate <15mmol/L

Admission to high-dependency unit or equivalent in the presence of one or more of the following[3]:

1. Blood ketones >6mmol/L
2. Serum bicarbonate <5mmol/L
3. Venous/arterial pH <7.1
4. Hypokalemia on admission (<3.5mmol/L)
5. Glasgow Coma Scale (GCS) <12 or abnormal AVPU (Alert, Voice, Pain, Unresponsive) scale
6. O_2 saturation <92% on air (assuming normal baseline respiratory function)
7. Systolic BP <90mmHg
8. Pulse rate >100 or <60beats/min
9. Anion gap >16 [anion gap = $(Na^+ + K^+) - (Cl^- + HCO_3^-)$]

Management

In the management of DKA, the following points must be considered and monitored closely[1]:

- Correction of fluid loss with intravenous fluids
- Correction of hyperglycemia with insulin
- Correction of electrolyte imbalance, serum K^+ in particular
- Correction of acid-base balance
- Treatment of concurrent infection

1. Fluid replacement

Fluid replacement therapy is a crucial part in the management of DKA.[1] Intravenous fluids replaces extravascular and intravascular fluids and electrolyte losses. Serum glucose level and levels of the circulating counter-regulatory hormones can also be diluted with the administration of intravenous fluids. The main purpose for the first few litres of fluid resuscitation are to :

A) Correct hypotension by restoring the circulatory volume;

B) Clear ketones;

C) Correct electrolyte imbalance.

Fluid should be replaced as crystalloid such as 0.9% sodium chloride rather than colloid as the hypotension in DKA results from a loss of serum electrolytes, therefore it is more physiological to replace fluid with crystalloid. Rate of fluid replacement is recommended be done in caution in small young adults as there is concern that rapid fluid replacement may lead to cerebral oedema.[3]

"Fluid replacement therapy and insulin therapy will almost always lead to hypokalemia."

According to **Medscape**, the recommended schedule for fluid replacement therapy is[1] :

- Administer 1-3L during 1st hour
- Administer 1L during 2nd hour
- Administer 1L during the next 2 hours.
- Administer 1L every 4 hours, based on degree of dehydration and central venous pressure readings.

2. Insulin therapy

Insulin is needed to help switch from a catabolic state to an anabolic state with the uptake glucose in tissues and the reduction of gluconeogenesis as well as free fatty acid and ketone production.

Only short-acting insulin is used to correct hyperglycemia and it is given via intravenous or intramuscular route as the absorption of subcutaneous route is reduced in DKA due to dehydration.

- Insulin therapy should be commenced about an hour after intravenous fluid replacement to evaluate the serum potassium levels.[1]
- Insulin therapy is given via continuous infusion at a rate of 0.1unit/kg/hour.[1-3]
- 50units of human soluble insulin (actrapid) made up to 50mL 0.9% sodium chloride solution. [3]

According to Medscape, the optimal rate of glucose decline is 100mg/dL (5.55mmol/L). Blood glucose level should not be allowed to fall below 200mg/dL (11.1 mmol/L) during the first 4-5 hours of treatment as blood glucose falls rapidly with correction of ketoacidosis.[1,3] Other thing is that rapid correction of hyperglycemia and hyperosmolarity may cause a shift of water rapidly to the hyperosmolar intracellular space and cause cerebral oedema.[1] When serum glucose falls below14mmol/L, intravenous glucose 10% should be added alongside fluid replacement therapy to prevent hypoglycemia.[3]

3. Electrolyte correction

Fluid replacement therapy and insulin therapy will almost always lead to hypokalemia by stimulating cellular potassium uptake in peripheral tissues.[2,3] In severe hypokalemia

(serum potassium less than 3.3mmol/L), insulin infusion should not be started unless potassium replacement therapy has been commenced. This is to prevent potentially serious cardiac dysrhythmia that may result from hypokalemia.[1] The treatment goal is to maintain serum potassium levels at 4-5mmol/L.[2]

- If serum potassium level is more than 6mmol/L, potassium levels need not be corrected.
- If serum potassium level is 4.5-6mmol/L, 10mmol/hour of potassium chloride is given.
- If serum potassium level 3-4.5mmol/L, 20mmol/hour of potassium chloride is administered.

4. Intravenous bicarbonate

Severe metabolic acidosis may cause impaired myocardial contractility, cerebral vasodilation and coma, and several gastrointestinal complications. However, rapid alkalinization may cause hypokalemia, paradoxical central nervous system acidosis with resultant alkalosis.[2]

It is recommended to commence bicarbonate therapy in DKA patients with arterial pH of less than 7 or when decompensated acidosis starts to threaten the patient's life especially when associated with sepsis or lactic acidosis.[1,2]

5. Transition to subcutaneous insulin

Continuous infusion of intravenous insulin is given until ketoacidosis is resolved. The criteria for resolution of DKA is as follows[2,3]:

- Blood glucose level <200mg/dL (11.1mmol/L)
- Serum bicarbonate level ≥ 18mmol/L
- Venous pH >7.3
- Calculated anion gap ≤12mEq/L
- Blood ketone <0.3mmol/L

When ketoacidosis is resolved, subcutaneous insulin therapy can be initiated. To avoid recurrence of hyperglycemia or ketoacidosis, allow an overlap of intravenous infusion of insulin for at least 30 minutes after subcutaneous short acting insulin has been given to ensure adequate plasma insulin levels.

When patient is able to eat, split-dose therapy with short-acting and intermediate acting insulin can be given. Patients previously on regular insulin therapy may continue their old insulin regimen prior to DKA. Newly diagnosed patient may be started on initial insulin dose of 0.6unit/kg/day to achieve and maintain metabolic control. If the patient is still unable to eat, continuous intravenous infusion of insulin should be continued while an infusion of dextrose 5% in half-normal saline is given at a rate of 100-200mL/h.[2]

Complications

Hypoglycemia is still reported in 10-25% of DKA patients despite the use of low-dose insulin protocol. Hypoglycemia may lead to rebound ketosis mediated by counter-regulatory hormones, thus increasing the duration of treatment.

The risk factor associated with hypoglycemia during insulin infusion is the failure to reduce the infusion rate of insulin and/or to use dextrose-containing solutions when blood glucose levels reach 250mg/dL or 14mmol/L.

Frequent monitoring of the patient's blood glucose levels is important to ensure recognition of hypoglycemia. This is because many patients with hyperglycemic crisis who experiences hypoglycemia during DKA treatment often do not manifest typical signs and symptoms of hypoglycemia such as sweating, fatigue, hunger, tachycardia, and nervousness despite the low blood glucose levels.[2]

Hypokalemia and **hyperkalemia** are both potentially life-threatening conditions. Patients with DKA is commonly presented with elevated serum potassium levels on admission. However insulin therapy and correction of acidosis will invariably cause hypokalemia due to stimulation of cellular uptake of potassium. Therefore intravenous potassium replacement should be done whenever serum potassium levels drop to ≤5mmol/L.

Patients with DKA who were admitted with low levels of serum potassium should be given intravenous potassium replacement immediately before commencing insulin therapy until the serum potassium level is ≥3.3mmol/L.[2,3]

Cerebral oedema is a rare but serious complication of DKA. It is more common in children. Mortality rate in children is about 40-90%. Cerebral oedema is characterized by a decreasing level of consciousness and headache, followed by seizures, sphincter incontinence, papillary changes, papilledema, bradycardia, and respiratory arrest.[2]

It is suggested that cerebral oedema in DKA is caused by a rapid shift in extracellular and intracellular fluids and changes in osmolality in the brain cells. During treatment, a rapid decrease in extracellular osmolality would cause osmotically mediated swelling of the brain.

Recent data show that cerebral oedema in children with DKA may be related to brain ischemia. Children with DKA who experiences both hypocapnia (causes cerebral vasoconstriction) and extreme dehydration (as presented with high initial serum urea nitrogen) were associated with increased risk for cerebral oedema.

"Frequent monitoring of the patient's blood glucose levels is important to ensure recognition of hypoglycemia."

Cerebral oedema can be treated with intravenous administration of mannitol, reduction of the rate of fluid administration, and possible mechanical ventilation to help reduce brain swelling.[2,3]

The Management of Diabetic Ketoacidosis in Adults

For young people under the age of 18 years use British Society of Paediatric Endocrinology and Diabetes (BSPED) guidelines: http://www.bsped.org.uk/professional/guidelines/docs/DKAGuideline.pdf

Diagnostic criteria: all three of the following must be present

- capillary blood glucose above 11 mmol/L
- capillary ketones above 3 mmol/L or urine ketones ++ or more
- venous pH less than 7.3 and/or bicarbonate less than 15 mmol/L

BOX 1: Immediate management: time 0 to 60 minutes

(T=0 at time intravenous fluids are commenced)

If intravenous access cannot be obtained request critical care support immediately

Action 1: Commence 0.9% sodium chloride solution (use large bore cannula) via infusion pump.
See Box 2 for rate of fluid replacement

Action 2: Commence a fixed rate intravenous insulin infusion (IVI). (0.1unit/kg/hr based on estimate of weight) 50 units human soluble insulin (Actrapid® or Humulin S®) made up to 50ml with 0.9% sodium chloride solution. If patient normally takes long acting insulin analogue (Lantus®, Levemir®) continue at usual dose and time

Action 3: Assess patient
- o Respiratory rate; temperature; blood pressure; pulse; oxygen saturation
- o Glasgow Coma Scale
- o Full clinical examination

Action 4: Further investigations
- Capillary and laboratory glucose
- Venous BG
- U & E
- FBC
- Blood cultures
- ECG
- CXR
- MSU

Action 5: Establish monitoring regimen
- Hourly capillary blood glucose
- Hourly capillary ketone measurement if available
- Venous bicarbonate and potassium at 60 minutes, 2 hours and 2 hourly thereafter
- 4 hourly plasma electrolytes
- Continuous cardiac monitoring if required
- Continuous pulse oximetry if required

Action 6: Consider and precipitating causes and treat appropriately

HDU/level 2 facility and/or insertion of central line may be required in following circumstances (request urgent senior review)

- Young people aged 18-25 years
- Elderly
- Pregnant
- Heart or kidney failure
- Other serious co-morbidities
- Severe DKA by following criteria
  - Blood ketones above 6 mmol/L
  - Venous bicarbonate below 5 mmol/L
- Venous pH below 7.1
- Hypokalaemia on admission (below 3.5 mmol/L)
- GCS less than 12
- Oxygen saturation below 92% on air (Arterial blood gases required)
- Systolic BP below 90 mmHg
- Pulse over 100 or below 60 bpm
- Anion gap above16 [Anion Gap = $(Na^+ + K^+) - (Cl^- + HCO_3^-)$]

BOX 2: Initial fluid replacement

Restoration of circulating volume is priority

Systolic BP (SBP) below 90mmHg

Likely to be due to low circulating volume, but consider other causes such as heart failure, sepsis, etc.

- Give 500ml of 0.9% sodium chloride solution over 10-15 minutes. If SBP remains below 90mmHg repeat whilst requesting senior input. Most patients require between 500 to 1000ml given rapidly.
- Consider involving the ITU/critical care team.
- Once SBP above 90mmHg give 1000ml 0.9% sodium chloride over next 60 minutes. Addition of potassium likely to be required in this second litre of fluid

Systolic BP on admission 90 mmHg and over

- Give 1000ml 0.9% sodium chloride over first 60 minutes

Potassium replacement

Potassium level (mmol/L)	Potassium replacement mmol/L of infusion solution
> 5.5	Nil
3.5-5.5	40 mmol/L
< 3.5	senior review – additional potassium required

BOX 3: 60 minutes to 6 hours

Aims of treatment:

- Rate of fall of ketones of at least 0.5 mmol/L/hr OR bicarbonate rise 3 mmol/L/hr and blood glucose fall 3 mmol/L/hr
- Maintain serum potassium in normal range
- Avoid hypoglycaemia

Action 1: Re-assess patient, monitor vital signs

- Hourly blood glucose (lab blood glucose if meter reading 'HI')
- Hourly blood ketones if meter available
- Venous blood gas for pH, bicarbonate and potassium at 60 minutes, 2 hours and 2 hourly thereafter.
- If potassium is outside normal range, re-assess potassium replacement and check hourly. If abnormal after further hour seek immediate senior medical advice

Action 2: Continue fluid replacement via infusion pump as follows:

- 0.9% sodium chloride 1L with potassium chloride over next 2 hours
- 0.9% sodium chloride 1L with potassium chloride over next 2 hours
- 0.9% sodium chloride 1L with potassium chloride over next 4 hours
- Add 10% glucose 125ml/hr if blood glucose falls below 14 mmol/L

More cautious fluid replacement in young people aged 18-25 years, elderly, pregnant, heart or renal failure. (Consider HDU and/or central line)

Action 3: Assess response to treatment

Insulin infusion rate may need review if

- Capillary ketones not falling by at least 0.5 mmol/L/hr
- Venous bicarbonate not rising by at least 3 mmol/L/hr
- Plasma glucose not falling by at least 3 mmol/L/hr
- Continue fixed rate IVI until ketones less than 0.3 mmol/L, venous pH over 7.3 and/or venous bicarbonate over 18 mmol/L.

If ketones and glucose are not falling as expected always check the insulin infusion pump is working and connected and that the correct insulin residual volume is present (to check for pump malfunction).

If equipment working but response to treatment inadequate, increase insulin infusion rate by 1 unit/hr increments hourly until targets achieved.

Additional measures

- Regular observations and Early Warning Score (EWS)
- Accurate fluid balance chart, minimum urine output 0.5ml/kg/hr
- Consider urinary catheterisation if incontinent or anuric (not passed urine by 60 minutes)
- Nasogastric tube with airway protection if patient obtunded or persistently vomiting
- Measure arterial blood gases and repeat chest radiograph if oxygen saturation less than 92%
- Thromboprophylaxis with low molecular weight heparin
- Consider ECG monitoring if potassium abnormal or concerns about cardiac status

BOX 4: 6 to 12 hours

Aims:

- Ensure clinical and biochemical parameters improving
- Continue iv fluid replacement
- Avoid hypoglycaemia
- Assess for complications of treatment e.g. fluid overload, cerebral oedema
- Treat precipitating factors as necessary

Action 1: Re-assess patient, monitor vital signs

- If patient not improving by criteria in Box 3 seek senior advice
- Continue iv fluid via infusion pump at reduced rate
  - o 0.9% sodium chloride 1L with potassium chloride over 4 hours
  - o 0.9% sodium chloride 1L with potassium chloride over 6 hours
- Add 10% glucose 125ml/hr if blood glucose falls below 14 mmol/L

Reassess cardiovascular status at 12 hours; further fluid may be required.

Check for fluid overload

Action 2 – Review biochemical and metabolic parameters

- At 6 hours check venous pH, bicarbonate, potassium, capillary ketones and glucose
- Resolution is defined as ketones less than 0.3 mmol/L, venous pH over 7.3 (do not use bicarbonate as a surrogate at this stage).
- Ensure referral has been made to diabetes team

If DKA not resolved review insulin infusion (see BOX 3 Action 3)
If DKA resolved go to BOX 6

BOX 5: 12 to 24 HOURS

Expectation: By 24 hours the ketonaemia and acidosis should have resolved. Request senior review if not improving

Aim:

- Ensure that clinical and biochemical parameters are continuing to improve or are normal
- Continue iv fluid replacement if not eating and drinking.
- If ketonaemia cleared and patient is not eating and drinking move to a variable rate IVI as per local guidelines
- Re-assess for complications of treatment e.g. fluid overload, cerebral oedema
- Continue to treat precipitating factors
- Transfer to subcutaneous insulin if patient is eating and drinking normally.

Action 1 – Re-assess patient, monitor vital signs
Action 2 – Review biochemical and metabolic parameters

- At 12 hours check venous pH, bicarbonate, potassium, capillary ketones and glucose
- Resolution is defined as ketones <0.3 mmol/L, venous pH>7.3
- If not resolved review fluid **Box 4 Action 1** and insulin infusion **Box 3 Action 3**

If DKA resolved go to Box 6

BOX 6: Resolution of DKA

Expectation: Patient should be eating and drinking and back on normal insulin.
If DKA not resolved identify and treat the reasons for failure to respond.
This situation is unusual and requires senior and specialist input.

Transfer to subcutaneous insulin

Convert to subcutaneous regime when biochemically stable (capillary ketones less than 0.3 mmol/L, pH over 7.3) and the patient is ready and able to eat. **Do not discontinue intravenous insulin infusion until 30 minutes after subcutaneous short acting insulin has been given**
Conversion to subcutaneous insulin should be managed by the Specialist Diabetes Team. If the team is not available use local guidelines. If the patient is newly diagnosed it is essential they are seen by a member of the specialist team prior to discharge.
Arrange follow up with specialist team.

Groups represented: Association of British Clinical Diabetologists; British Society for Endocrinology and Diabetes and Association of Children's Diabetes Clinicians; Diabetes Inpatient Specialist Nurse (DISN) Group; Diabetes UK; NHS Diabetes (England); Northern Irish Diabetologists; Society of Acute Medicine; Welsh Endocrine and Diabetes Society, Scottish Diabetes Group.

FIGURE 1 The management of diabetic ketoacidosis in adults. Summary of the guidelines. Reproduced from NHS Diabetes (2010), with permission of Joint British Diabetes Societies.

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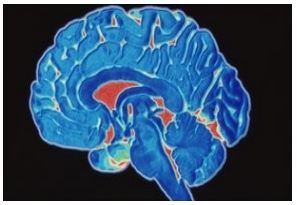
ADVERSE DRUG REACTION REPORT
HOSPITAL SEGAMAT JANUARY — MARCH 2014

DATE	MEDICATIONS	ADR	TREATMENT	REPORTER
21.3.14	Syrup Azithromycin 75mg OD	Generalized body rashes including redness and itchiness	Discontinue syrup azithromycin . T. Piriton and Calamine lotion were given.	Dr. Hazman Bin Jalil
23.3.14	Syrup Cephalexin (3 doses)	Maculopapulor rashes (generalized)	IV hydrocortisone, syrup piriton	Dr. Damia Md Shokor

Sodium Valproate: Risk of Decreased IQ Scores in Children after Fetal Exposure



A recent prospective observational study Neurodevelopmental Effects of Antiepileptic Drugs (NEAD Study) by Meador *et al* published in the Lancet Neurology Journal (March 2013), revealed that children born to mothers who took valproate during pregnancy had IQ scores which were between 8 to 11 points lower at 6 years of age compared to children exposed to carbamazepine, lamotrigine and phenytoin. These effects were dose dependent. According to the Consensus Guidelines on the Management of Epilepsy 2010 by the Epilepsy Council, Malaysian Society of Neurosciences, valproate is an important first-line antiepileptic drug (AED) in adolescents and young adults. Currently there is insufficient evidence of a higher risk of teratogenicity with anyone AED. However, as with most other AEDs, valproate must not be used in women of child-bearing potential unless the benefits outweigh the risks. Valproate is approved in Malaysia for the treatment of epilepsy and mania associated with bipolar disorder. There have been reports of off -label use for the prevention of migraine headaches, however prescribers are reminded not to practice this use. The United States Food and Drug Administration (US FDA) recently contraindicated valproate for migraine use in pregnant women. Ideally, women should be advised not to become pregnant until they are seizure-free and stop taking AEDs. If antiepileptic drug withdrawal is impossible, the treatment plan should aim to avoid polytherapy and use the lowest effective dose of AED. The risk of adverse effects of AEDs should also be taken into consideration when choosing an AED. Women on AEDs should be monitored throughout pregnancy to detect foetal malformations. Children who had foetal exposure to antiepileptic drugs are recommended to have regular assessment of cognitive function.

In Malaysia: Since the year 2000, NPCB has received 175 reports related to sodium valproate, of which only one (1) report involved maternal drug exposure. Meningomyelocele was reported in a three year old child exposed to sodium valproate which his mother took for generalised epilepsy secondary to arrested hydrocephalus, before and during pregnancy. She was also taking folic acid and multi vitamins. The case was given the causality 'possibly-related (C3)'.

Advice to healthcare providers:

• The teratogenic effects of AEDs as well as possible adverse effects of uncontrolled seizures during pregnancy must be discussed with patients well before conception.

• Women of child-bearing potential must use effective contraception during treatment and until AED adjustment is achieved if they wish to conceive.

• Pregnant women currently taking sodium valproate should be advised NOT to stop their medications immediately but should seek medical advice, because sudden discontinuation can lead to serious health problems such as breakthrough seizures.

• Folic acid supplementation of at least 0.4mg daily should be recommended for all women of child-bearing age taking AEDs, starting before conception.

• Any adverse event suspected to be associated with the use of sodium valproate should be reported to the Drug Safety Monitoring Centre, NPCB.

Zithromax®/ Zmax® (azithromycin): Risk of Potentially Fatal Irregular Heart Rhythms

A study published in the New England Journal of Medicine (NEJM) 2012 by Ray, Murray, Hall *et al*. suggested a higher risk of death from cardiovascular or other causes in patients treated with a 5-day course of oral azithromycin compared to those treated with amoxycillin, ciprofloxacin, or no antibacterial drug. In addition, a study was conducted by the product manufacturer to assess the effects of azithromycin on the QT interval in adults, with results showing that the drug prolonged the QTc interval. The Zithromax® and Zmax® local package inserts mention the risk of developing QT interval prolongation and arrhythmias during treatment with azithromycin and other macrolides, under the sections 'Special Warnings and Precautions For Use' as well as 'Undesirable Effects'. On 12 March 2013, the U.S. Food and Drug Administration (FDA) issued a safety announcement warning the public on the risk of azithromycin causing abnormal changes in the electrical activity of the heart which may lead to potentially fatal heart rhythms. The European Medicines Agency (EMA) is also considering strengthening the warnings about this risk in the prescribing information for azithromycin.

In Malaysia

Currently, there are 26 registered products containing azithromycin. Since the year 2000, the NPCB has received 181 reports related to azithromycin. Ten (10) reports were related to heart rate and rhythm disorders, with the following events reported: palpitation (3), tachycardia (3), arrhythmia, bradycardia, heart block, supraventricular tachycardia, and ventricular tachycardia (1 each). This issue will be monitored closely to decide if these warnings need to be further strengthened.

Advice to healthcare providers:

- The risk of torsades de pointes and fatal arrhythmia should be considered when choosing between azithromycin and other antibacterial drugs, especially for patients who are at higher risk of cardiovascular events.
- The potential risk of QT prolongation should be weighed against the side effects of alternative drugs, which may also cause QT prolongation or cause other significant adverse effects.
- Patients should be advised to seek immediate medical attention if they experience an irregular heartbeat, shortness of breath, dizziness or fainting while taking azithromycin.
- Any adverse event suspected to be associated with the use of azithromycin, even those which are common or well-known, should be reported to the National Drug Safety Monitoring Centre, NPCB.

Comparison and Updates on New Oral Anticoagulants (NOACs)

New oral anticoagulants (NOACs) comprise of dabigatran etexilate (Pradaxa®), rivaroxaban (Xarelto®) and apixaban (Eliquis®). They have been developed as an alternative to warfarin (a Vitamin K antagonist) and offer some benefits over warfarin such as do not require blood monitoring as well as dietary restriction. NOACs are indicated for prevention of stroke and embolism in patients with non-valvular atrial fibrillation (NVAF). With the increasing use of these relatively new drugs, post-marketing monitoring is important to ensure safety. Pradaxa®, Xarelto® and Eliquis® were registered in Malaysia since 2009, 2010 and 2013 respectively.

Product Name (Active ingredient)	Pradaxa® (Dabigatran Etexilate)	Xarelto® (Rivaroxaban)	Eliquis® (Apixaban)
Product Registration Holder	Boehringer Ingelheim (M) Sdn. Bhd.	Bayer Co. (M) Sdn. Bhd.	Pfizer (M) Sdn. Bhd.
Malaysian Drug Control Authority (DCA) approved indication	*75mg & 110mg capsule*: Primary prevention of venous thromboembolic events (VTE) in adults with hip or knee replacement surgery *110mg & 150mg capsule:* Reduction of the risk of stroke and systemic embolism in patients with NVAF.	*10mg*: Prevention of VTE in adults with hip or knee replacement surgery. *15mg & 20mg*: Prevention of stroke and systemic embolism in adults with NVAF treatment of DVT, prevention of recurrent DVT and PE following an acute DVT in adults.	*2.5mg*: Prevention of VTE in adults with hip or knee replacement surgery. *2.5mg & 5mg*: Prevention of stroke and systemic embolism in adults with NVAF.
MOH Drug Formulary (*FUKKM*) - approved prescriber category and indication	• Prescriber category: A* • Same as DCA approved indication	• Prescriber category: A* • Same as DCA approved indication	• Not in FUKKM
Contraindication	• Hypersensitivity to the active substance or excipients. • Clinically significant active bleeding. • Hepatic disease which is associated with coagulopathy.		
	• Severe renal impairment (CrCl<30ml/min). • Organic lesion at risk of bleeding. • Haemostasis impairment. • Concomitant treatment with quinidine or ketoconazole. • Prosthetic heart valve.	• Pregnancy. • Breastfeeding.	• Lesion or condition at significant risk of major bleeding. • Concomitant treatment with any other anticoagulant agent.
Use in renal impairment patients	*80% excreted in kidneys*: • Contraindicated in patients with CrCl<30ml/min. • Assess renal function at least once a year in patients with CrCl 30-50ml/min.	*33% excreted in kidneys*: • Not recommended in patients with CrCl <15ml/min. • Use with caution in patients with CrCl 15- <30 ml/min as rivaroxaban plasma concentrations increased. • No dosage adjustment in patients with CrCl 30- ≤80ml/min.	*25% excreted in kidneys*: • Not recommended in dialysis patients or CrCl <15ml/min. • Use with caution in patients with CrCl 15 -29 ml/min as apixaban plasma concentrations increased. • No dosage adjustment in patients with mild or moderate renal impairment.

In Malaysia, **bleeding-related events** are the most reported adverse reaction for NOACs. Statistics from the NPCB Drug Safety Monitoring Centre showed that out of the total ADR reports received for each product, 37 events (33.9%) for Pradaxa® and 16 events (59.3%) for Xarelto® were related to bleeding. As Eliquis® is newly registered in Malaysia, NPCB has only received one report for this product, which was on gastrointestinal and rectal bleeding. There were four reports related to **stroke**, with two each involving Pradaxa® and Xarelto®. Out of the four reports, two were given causality C3 (probable) and the other two were assigned causality C4 (unlikely). Concomitant drugs and concurrent diseases were reported in three cases and no information was provided for the remaining report. One of the reports involved a fatal outcome (post-operative ischaemic stroke), however this case was assigned a causality C4 (unlikely) because the NOAC was stopped one day before the emergency spinal operation and was not continued after the operation. The patient also had concurrent disease and was on other concomitant medications.

Advice for Healthcare Professionals :

- Close clinical surveillance (for signs of bleeding or anaemia) is recommended throughout the treatment period, especially if multiple risk factors are present.
- Renal function should be assessed in all patients before starting dabigatran (Pradaxa®) and at least once a year in patients older than 75 years or those with a suspected decline in renal function.
- The Drug Safety Monitoring Centre, NPCB is conducting further review on the safety of these products. Detailed safety advice will be published once this review has been completed.
- Any adverse events suspected to be associated with the use of NOACs should be reported to the Drug Safety Monitoring Centre, National Pharmaceutical Control Bureau (NPCB), Malaysia.

WELCOME TO PHARMACY DEPARTMENT

Pegawai Farmasi U41 (FRP)

1) Tey Min Nuan
2) Teh Siew Gyn

Penolong Pegawai Farmasi

1) Barimala Rubiny A/P Ravinchandran
2) Noor Liana Bt Zulbahari

Pembantu Tadbir

1) Rozi Binti Atan
2) Roslina Bt Ab Talib

GOODBYE TO

Pegawai Farmasi U41 (FRP)

1) Noziyani
2) Lee Ley Chen

Penolong Pegawai Farmasi

1) Puan Siti Aminah
2) Hj. Basabah

Pembantu Tadbir

1) Norliza bt Abd Karim
2) Sharifah Khadijah bt. Syed Mokhta
3) Munah bt Mahpul

ACTIVITIES OF PHARMACY

Bowling Competition

on 10 January 2014

Photo session at the end of the Bowling competition

Dinner session after the Bowling competition