Fluids in young adults with diabetic ketoacidosis

cerebral oedema is real

Dr Andrew Nyman

2014
Goal in DKA: Switch off ketosis

- Unopposed catabolic hormones ↓ Insulin (absolute or relative)
- ↓ Insulin → ↑ Lipase (not inhibited)
- Pancreas → Fat cells
- Fat cells → ↑ Free fatty acids
- Liver → ↑ Hepatic glucose production
- ↓ Peripheral glucose utilization
- ↑ β-OHB
- ↑ Acetoacetate
- 10 mmol/L
- 3 mmol/L
- Acetone* 5 mmol/L
- Excreted by lungs and kidneys

1. Hyperglycemia
2. Ketoacidosis
3. Polyuria (Glucose + Ketones + Electrolytes)

DEHYDRATION
Insulin, glucose production and ketones

% glucose decline after insulin

Max ketones children 4 - 6 mmol/L
< 1 mmol/L after 8 – 12 hrs

Luzi L, Diabetes 37:1470 – 1477, 1988
• DKA admitted to all PICUs in UK 2003 to 2007
• 341 admissions in 330 patients
• Annual increase during this period from 0.54% to 0.67%
• 40% cases aged 11-15 years
• Five deaths (1.5%)
Cerebral oedema in DKA

- Rare but life threatening complication of DKA
- < 1% of diabetics
- 20% mortality
- 33% neurological morbidity

**Clinical signs:**
- Altered level of consciousness
- Headache
- Coma
- Pupillary changes
- Bradycardia
- Papilloedema

Slight alterations in LOC concerning
Pathophysiology of cerebral oedema in DKA

Acidosis
Dehydration
Hypocapnia

Reduced CBF

Sodium concentration

Cytotoxic cerebral oedema

Insulin treatment

BBB permeability

Vasogenic cerebral oedema

Fluid treatment

hypoperfusion

Inflammation complement activation

Poor control (chronic lack of insulin)

Fluid treatment reperfusion

Disease | Therapy
--- | ---
acidosis | rehydration
dehydration | insulin
shock | bicarbonate
low CO2 | osmolar shifts
ischaemia | osmotheraphy
Neural toxins | 

BRAIN SWELLING
Age and cerebral oedema in DKA

Cerebral Edema During Treatment of Diabetic Ketoacidosis in an Adult With New Onset Diabetes

Patrick J. Troy, Roger P. Clark, Sri G. Kakarala, Jocelyn Burns, Isaac E. Silverman and Eric Shore*

The UK case–control study of cerebral oedema complicating diabetic ketoacidosis in children

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>OR</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per year)</td>
<td>1.11</td>
<td>0.86–1.44</td>
<td>0.4</td>
</tr>
<tr>
<td>Female sex</td>
<td>11.9</td>
<td>0.89–158</td>
<td>0.06</td>
</tr>
<tr>
<td>New diagnosis of diabetes</td>
<td>48.8</td>
<td>1.62–1,472</td>
<td>0.025</td>
</tr>
<tr>
<td>Acidosis (lowest vs highest tertile)</td>
<td>0.02</td>
<td>0.002–0.21</td>
<td>0.001</td>
</tr>
<tr>
<td>Blood glucose (per mmol/l)</td>
<td>0.88</td>
<td>0.74–1.04</td>
<td>0.1</td>
</tr>
<tr>
<td>Sodium (uncorrected, per mmol/l)</td>
<td>0.74</td>
<td>0.58–0.94</td>
<td>0.013</td>
</tr>
<tr>
<td>Potassium (per mmol/l)</td>
<td>3.14</td>
<td>0.96–10.22</td>
<td>0.057</td>
</tr>
<tr>
<td>Urea (per mmol/l)</td>
<td>1.68</td>
<td>0.98–2.88</td>
<td>0.055</td>
</tr>
<tr>
<td>p\textsubscript{a}CO\textsubscript{2} (per mmHg)</td>
<td>1.20</td>
<td>1.01–1.43</td>
<td>0.038</td>
</tr>
<tr>
<td>Treated with insulin in hour 1</td>
<td>12.7</td>
<td>1.41–114.5</td>
<td>0.023</td>
</tr>
</tbody>
</table>
Table 4 Category of insulin dose administered over the first 2 h of treatment for DKA

<table>
<thead>
<tr>
<th>Insulin dose (U)</th>
<th>n</th>
<th>OR</th>
<th>95% CI</th>
<th>p for trend&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>65</td>
<td>1</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>0.2–1.9</td>
<td>28</td>
<td>1.31</td>
<td>0.30–5.75</td>
<td></td>
</tr>
<tr>
<td>2.0–4.2</td>
<td>28</td>
<td>2.66</td>
<td>0.77–9.12</td>
<td></td>
</tr>
<tr>
<td>4.4–11</td>
<td>26</td>
<td>4.97</td>
<td>1.28–19.32</td>
<td>&lt;0.02</td>
</tr>
</tbody>
</table>

Higher dose and early insulin = higher risk cerebral oedema
Table 3  Tertiles of total fluid volume administered over the first 4 h in cases and controls

<table>
<thead>
<tr>
<th>Time-period/volume tertile</th>
<th>n</th>
<th>OR (95% CI)</th>
<th>p for trend(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–1 h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–171 ml</td>
<td>39</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>175–400 ml</td>
<td>39</td>
<td>3.90 (0.85–17.8)</td>
<td></td>
</tr>
<tr>
<td>440–1,800 ml</td>
<td>38</td>
<td>2.53 (0.52–12.2)</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>0–2 h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20–265 ml</td>
<td>45</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>266–535 ml</td>
<td>43</td>
<td>2.28 (0.58–9.02)</td>
<td></td>
</tr>
<tr>
<td>540–2,800 ml</td>
<td>46</td>
<td>3.4 (0.82–14.0)</td>
<td>&lt;0.09</td>
</tr>
<tr>
<td>0–3 h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40–385 ml</td>
<td>47</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>391–708 ml</td>
<td>46</td>
<td>3.93 (0.90–17.13)</td>
<td></td>
</tr>
<tr>
<td>720–3,800 ml</td>
<td>48</td>
<td>7.30 (1.51–35.12)</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>0–4 h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>76–511</td>
<td>44</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>512–879</td>
<td>44</td>
<td>3.30 (0.71–15.27)</td>
<td></td>
</tr>
</tbody>
</table>
| 892–4,090                  | 45  | 6.55 (1.38–30.97)    | <0.02             

Large volumes fluid in 1\(^{st}\) four hours risk for cerebral oedema

Historically large volume of fluids in children?

- Use of hypotonic fluid in UK (0.18% or 0.45% saline)
- PALS/ APLS guidelines (boluses 20/kg saline)
  - even WITHOUT hypotension
- Repeated boluses for persisting acidosis
- Fluid regimes replace urine output
- Over-evaluation of degree dehydration
Evaluating dehydration

Clinical evaluation of dehydration poor

Iduko. Diabetes Care 2004
Maximum dehydration of 10%
Maintenance if sick is restricted (50-60%)
Don’t replace urine

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Total fluid rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – 9.9</td>
<td>4 ml/kg/hr</td>
</tr>
<tr>
<td>10 – 39.9</td>
<td>3 ml/kg/hr</td>
</tr>
<tr>
<td>&gt; 40 kg</td>
<td>2 ml/kg/hr</td>
</tr>
</tbody>
</table>

Isotonic fluid
Hypotonic fluids
risk for coma
Add KCL
DON’T add Phosphate

www.strs.nhs.uk
Combination insulin with NaHCO$_3$ greatest risk of cerebral oedema

Rose. Pediatr Research. 2007
1. Cannot predict who will get signs of Cerebral oedema
2. Can identify risks
3. Can look out for early markers. How?

### Venous Acid-base Variables

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 21)</th>
<th>Early Oedema (n = 15)</th>
<th>Late Oedema (n = 17)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial pH</td>
<td>6.94 ± 0.05</td>
<td>6.93 ± 0.11</td>
<td>6.99 ± 0.07</td>
<td>0.06</td>
</tr>
<tr>
<td>Arterial pCO₂ (kPa)</td>
<td>1.6 ± 0.7</td>
<td>1.3 ± 0.9</td>
<td>1.8 ± 0.9</td>
<td>0.30</td>
</tr>
<tr>
<td>Arterial HCO₃ (mmol/L)</td>
<td>2.5 ± 1.1</td>
<td>2.0 ± 1.2</td>
<td>3.2 ± 1.7</td>
<td>0.06</td>
</tr>
<tr>
<td>Arterial Base excess (mmol/L)</td>
<td>-26.6 ± 1.4</td>
<td>-27.3 ± 2.1</td>
<td>-25.3 ± 1.9</td>
<td>0.007</td>
</tr>
<tr>
<td>Anion Gap (mmol/L)</td>
<td>34.3 ± 3.0</td>
<td>35.5 ± 5.9</td>
<td>35.7 ± 5.0</td>
<td>0.60</td>
</tr>
</tbody>
</table>
1. Treat shock cautiously
2. Rehydrate slowly
3. Control glucose
4. Switch off ketosis
5. Eliminate ketones
6. Avoid Cerebral Oedema

Fluid therapy
Insulin / kidneys

Prevention, Recognition & Aggressive therapy for cerebral oedema
Bolus 2 - 3ml/kg of 3% saline (aim for ↑ plasma Na 2-4 mmol/L)

This may be repeated as necessary

Mannitol 0.5 – 1g/kg IVI if no 3% saline

Intubation if failure to respond to osmotherapy

• Ensure hypovolaemia corrected (3% saline is useful here)
• Beware Propofol or Thiopentone (BP fall)
• Aim for normal CO2 (My opinion)

1. Obtain CT scan (this is usually normal despite coma)
2. Reduce IVI fluids if excessive.
3. Ensure no hypotonic fluid.

Need a rigid fluid protocol with careful monitoring!
Tonicity ECF determines ICF volume size

Hypotonic fluid = ICF Expansion

Hypertonic fluid = ICF Shrinkage
<table>
<thead>
<tr>
<th>Children</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normotensive</td>
<td>Comorbidity</td>
</tr>
<tr>
<td>Normal lactate</td>
<td>Common with sepsis &amp; shock</td>
</tr>
<tr>
<td>Rarely sepsis with hypotension</td>
<td>Multi-organ dysfunction</td>
</tr>
<tr>
<td>Minimal co-morbidity</td>
<td>Raised lactate</td>
</tr>
</tbody>
</table>
Does fluid volume in adults matter?

Adrogue. JAMA 1989

14ml/kg/hr

7ml/kg/hr
Avoidance of cerebral oedema

• Avoid risk factors
  – high dose and early insulin
  – large volume of fluids
  – rapid changes in osmolality (drinking water)

• Low threshold to treat with hypertonic saline

• Treat adolescents like children
  – brain receptors maturing
  – At risk of cerebral oedema
1. **Insulin** 0.05 to 0.1 units/kg/hr (switch off ketone production)
   
   $2.5 \times \text{wt (kg)} \text{ units Insulin (Actrapid) in 50 ml 0.9\% Saline gives 1ml/hr} = 0.05 \text{ units/kg/hr}$

2. Follow resolution of ketosis by calculating **Anion Gap** or use **blood ketones** (aim for < 1 mmol/L BOH-B)

3. Urine ketones persist for 24 to 48 hrs and *do not* reflect serum ketonaemia

4. **Base excess and pH are unreliable** as hyperchloraemic acidosis universal

5. **Dont reduce insulin until BLOOD KETOSIS < 1mmol/L**

6. **Bicarbonate has no role**

7. **If slow resolution of acidosis consider other causes (eg sepsis)**
Track acidosis

- Ketones
- Chloride

Anion gap

Base deficit (mmol/L)

Anion gap (mmol/L)

Hours from initiation of therapy