Guidelines on the use of ACE Inhibitors (Angiotensin-Converting Enzyme Inhibitors) in Children with cardiac failure or hypertension

Indications
ACE Angiotensin-converting enzyme inhibitors (ACEI) inhibit the conversion of angiotensin I to angiotensin II. The main indications of ACEI in children are the following:
- heart failure as a result of: moderate to large VSDs, mitral or aortic incompetence, left ventricular dysfunction associated with cardiomyopathy, myocardial infarction or following relief of left ventricular outflow obstruction
- hypertension usually associated with coarctation of the aorta

Contraindications
- Hypersensitivity to ACE inhibitors (including angioedema)
- Bilateral renovascular disease (ACEI’s reduce or abolish glomerular filtration and are likely to cause severe and progressive renal failure)

Cautions
- Renal impairment
- Concomitant treatment with NSAIDs (increases risk of renal damage) and potassium sparing diuretics or potassium supplements (increases risk of hyperkalaemia)
- Severe or symptomatic aortic stenosis
- Hypertrophic cardiomyopathy
- Primary aldosteronism
- Afro-Caribbean

Mode of action
ACE inhibitors are competitive inhibitors of ACE which is involved in the conversion of angiotensin I to angiotensin II. Angiotensin II promotes the secretion of aldosterone via the adrenal gland.

Angiotensin II is also a potent vasoconstrictor so preventing its production will have a vasodilatory effect resulting in a decrease in blood pressure. The beneficial effects of ACE inhibitors in stable heart failure arise from the lack of aldosterone. Aldosterone promotes the retention of sodium and water. A reduction in the secretion of aldosterone will promote the excretion of sodium and water, thereby lowering the volume of blood the heart has to pump, so, again, blood pressure will be lowered.
Baseline Monitoring

- Urea and Creatinine (U&Es)
- Liver function tests (LFTs) (marked evaluation of hepatic enzymes or jaundice increase risk of hepatic necrosis)
- Full blood count (FBC) (risk of agranulocytosis is possibly increased in collagen vascular disease)

Dosing Regimen

CAPTOPRIL\textsuperscript{1,2}
Captopril is not licensed for use in children less than 18 years old

Preparations available
Captopril oral solution 25mg in 5mL (kept on stock on ward 51)
Captopril tablets 12.5mg (half a tablet = 6.25mg, quarter a tablet = 3.125mg)
Captopril oral solution 5mg in 5mL (for neonatal use or named patients only)

Acute dosing regimen - to be used for patients in de-compensated heart failure, patients who are inotrope dependent and /or patients who need a slow titration of dose of an ACEI

Note: Captopril should be used in caution in neonates, particularly preterm neonates due to risk of renal failure, anuria and hypotension

Step 1: Give 100micrograms/Kg as a test dose (max. 6.25mg) and observe the patient every 15 minutes for the first 2 hours for effects of severe hypotension.

When using captopril suspension 25mg in 5mL, then use the guide below:
2Kg to 2.9Kg: 250micrograms STAT
3Kg to 5.9Kg: 500microgram STAT
Over 6Kg: 100microgram/Kg/dose STAT max. 6.25mg

Step 2: If tolerated, give 100-300micrograms/Kg/dose three times a day
Step 3: If a higher dose is required increase to 500microgram/Kg/dose (max 25mg) three times a day
Step 4: If a higher dose is required increase to 1mg/Kg/dose (max 50mg) three times a day

Stable dosing regimen - to be used in patients with stable heart failure or hypertension associated with coarctation of the aorta. DO NOT USE IN NEONATES.

Step 1 Start on 500microgram/Kg/dose (max 25mg) three times a day
Step 2 If a higher dose is required increase to 1mg/Kg/dose (max 50mg) three times a day
Lisinopril is not licensed for use in children less than 18 years old

Preparations available
Lisinopril tablets 2.5mg, 5mg, 10mg and 20mg

For children over 6 years old (and over 20Kg)

Acute dosing regimen - to be used for patients in de-compensated heart failure, patients who are inotrope dependent and/or patients who need a slow titration of dose of an ACEI

Step 1: Give 100micrograms/Kg of CAPTOPRIL as a test dose (max. 6.25mg) and observe the patient every 15 minutes for the first 2 hours for effects of severe hypotension.

Step 2: If tolerated, change to LISINOPRIL and give 2.5mg daily

Step 3: Then increase LISINOPRIL dose slowly to a maximum of 0.5 - 1mg /Kg/dose daily (max. 35mg daily)

Stable dosing regimen - to be used in patients with stable heart failure or hypertension associated with coarctation of the aorta.

Step 1: Start on LISINOPRIL 2.5mg daily

Step 2: Then increase LISINOPRIL dose slowly to a maximum of 0.5 - 1mg /Kg/dose daily (max. 35mg daily)

Note: In exceptional cases Lisinopril could be used in children less than 20Kg and over 10Kg (6). In these children start them on captopril and then convert to Lisinopril 2.5mg daily, once a dose of 500microgram/kg/dose three times a day has been reached.

Administration
Captopril tablets can be dispersed in water.

Parameters to Monitor
- Baseline U&E’s, LFT’s and FBC
- Blood pressure:
  - For captopril; every 15minutes for the first 2 hours after test dose or changes in dose and then 12 hourly thereafter.
  - For lisinopril; 4 hours after initial dose or change of doses and then 12 hourly thereafter.
- After each dose change the patient must be assessed for worsening renal function and increase vasodilation. These should be done by doing the above blood pressure monitoring and U & E’s.
- If a child is on spironolactone or amiloride watch carefully for hyperkalaemia.

NOTE: If Urea and Creatinine increase from baseline, then consider fluid allowance and diuretic management of the patient. By increasing fluid allowance and reducing diuretics, this may be sufficient to allow continuation of ACEI therapy. If only urea is increased from baseline, then consider continuing with the same ACEI dose and monitor carefully.
**Pharmacokinetics** (3,4,5)

- **Captopril:**
  - Time to peak plasma concentration is 60 to 90 minutes.
  - The presence of food in the gastrointestinal tract reduces absorption by about 30-40%.
  - About 25 to 30% of the circulating drug is bound to plasma proteins.
  - The elimination half-life of unchanged captopril in blood is about 2 hours.
  - Impaired renal function could result in drug accumulation.

- **Lisinopril:**
  - Following oral administration of lisinopril, peak serum concentrations occur within about 7 hours.
  - The elimination half-life of lisinopril is about 12 hours.
  - Lisinopril does not undergo metabolism and is excreted entirely unchanged into the urine.
  - The conversion from captopril to lisinopril is:
    - 5mg total daily dose of captopril : 1mg total daily dose of lisinopril

**Side effects** (1,2,3,4)
Hypotension, renal impairment, persistent dry cough, angioedema, pancreatitis, upper respiratory-tract symptoms, gastro-intestinal disturbances, altered LFTs, hyperkalaemia and hypoglycaemia.

**References**
1. BNF for Children (online), accessed 19/8/19
2. Evelina London Paediatric Formulary (online), accessed 19/8/19
3. Noyada 25mg per 5mL oral solution, Summary of Product Characteristics, accessed 19/8/19
4. Lisinopril tablet, Summary of Product Characteristics, accessed 19/8/19

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