Medicines Management & Pharmacy Services (MMPS)
Guidelines on the use of Carvedilol in Children

Indications

Congestive heart failure (CHF) with left ventricular dysfunction secondary to cardiomyopathy or congenital heart disease for patients:
- Still symptomatic despite maximal therapy with diuretics, angiotensin converting enzyme inhibitors +/- digoxin (unless contraindicated or intolerant)
- With NYHA Class II to IV if >14yrs or Ross CHF Class II to IV if <14 years

Contraindications

- Hepatic impairment
- Asthma or obstructive airways disease*
- 2nd or 3rd degree AV block

* CSM has advised that beta-blockers be contraindicated. However in rare situations where there is no alternative to the use of a beta-blocker then a cardioselective one may be used with extreme caution under specialist supervision.

Cautions

- Acute or decompensated heart failure requiring intravenous inotropes
- Diabetes
- Hypotension for age
- Bradycardia for age

Mode of action

Carvedilol is a non-selective beta-blocker acting on both $\beta_1$ and $\beta_2$ adrenergic receptors. It is thought that the beneficial effects of beta-blockers in CHF arise from their blockade of chronic adrenergic overstimulation\(^1\). Carvedilol also acts as an alpha\(_1\)-receptor blocker, producing vasodilatation, and potentially as an antioxidant\(^2\).

There are currently no large randomised controlled trials (RCT) assessing the benefits of carvedilol in paediatric patients although a number of small trials carried out have noted improved symptoms and left ventricular function\(^3, 4, 5, 6, 7\). A larger RCT is currently underway in the US and will include hospitalisation and mortality data\(^8\). In the adult population a number of large trials have shown a reduction in morbidity and mortality in patients with heart failure\(^9, 10, 11\) and carvedilol is licensed for stable mild, moderate and severe heart failure as an adjunct to standard therapies. It is not licensed for children <18 years old.
Dosing Regimen

Slow titrating of dosage in Outpatient Setting

<table>
<thead>
<tr>
<th>Dose</th>
<th>Initial</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>0.05mg/kg BD</td>
<td>0.1mg/kg BD</td>
<td>0.2mg/kg BD</td>
<td>0.35mg/kg BD</td>
</tr>
<tr>
<td>Maximum Dose</td>
<td>3.125mg</td>
<td>6.25mg</td>
<td>12.5mg</td>
<td>25mg</td>
</tr>
</tbody>
</table>

- Doses may be increased every 4 weeks to a maximum of 0.3 to 0.4mg/kg (25mg) BD or until side effects limit further dose increases e.g. symptoms of worsening CHF.

- Initial dose to be given as an inpatient with subsequent dose increases as an outpatient depending on clinical status.

Quick titrating of dosage in an acute heart failure patient - inpatient only

<table>
<thead>
<tr>
<th>Dose</th>
<th>Initial (Day 1)</th>
<th>Day 3</th>
<th>Day 5</th>
<th>Day 7</th>
<th>Day 9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>0.025mg/kg BD</td>
<td>0.05mg/kg BD</td>
<td>0.1mg/kg BD</td>
<td>0.2mg/kg BD</td>
<td>0.35mg/kg BD</td>
</tr>
<tr>
<td>Maximum Dose</td>
<td>1.5mg</td>
<td>3.125mg</td>
<td>6.25mg</td>
<td>12.5mg</td>
<td>25mg</td>
</tr>
</tbody>
</table>

- Doses may be increased every 2 days if tolerated to a maximum of 0.35 mg/kg to 0.4mg/kg (25mg) BD or until side effects limit further dose increases e.g. symptoms of worsening CHF.

- **NOTE:** If symptoms of worsening CHF occur stop the carvedilol.

Administration

- Carvedilol should be taken with food.
- Tablets (3.125mg; 6.25mg; 12.5mg; 25mg) may be dissolved in water and the appropriate proportion taken to administer the dose. A new tablet should be used for each dose. Dissolve 3.125mg in 3mls of water and then assume the concentration is 1mg/ml.
- Carvedilol oral suspension 5mg/5ml ('Special') is available to order on request. It will not be stocked by LGI due to a short expiry of 28 days.

Parameters to Monitor

- Baseline echo, ECG, U & E’s, liver function tests.
- Heart rate and blood pressure (sitting and standing) at 1 and 2 hours after administration, after each increase in dose.
- After each dose change the patient must be assessed for worsening renal function, heart failure and increased vasodilation. These should be done by doing the above blood pressure monitoring, U & E’s, monitoring of respiratory rate and looking for signs of fluid retention. If there are signs of worsening heart failure then an echo must be done.

- For patients also taking digoxin:
  - Carvedilol may reduce the clearance of digoxin, increasing serum concentrations
Digoxin levels should be taken 7-14 days following the initiation of carvedilol and dose adjusted accordingly.

Patients/carers should be counselled on signs of digoxin toxicity e.g. vomiting, anorexia.

**Pharmacokinetics**

- Time to peak plasma concentration is 0.5-2.5 hours.
- Extensive hepatic metabolism and first pass effect, therefore elimination is via the biliary route (see contraindications).
- Half-life in children averages 2.9 hours and increases with age (cf. healthy adults: 5.2 hours)
- No reduction necessary in renal impairment

**Side effects**

Dizziness, postural hypotension, hypotension, bradycardia, headache, vomiting, fatigue, dyspnoea, peripheral oedema, AV block, atrial flutter, blurred vision, dry mouth, dry eyes, thrombocytopenia, leucopenia.

**References and Provenance**

15. Vaiypathan, B. Is there a role for carvedilol in the management of pediatric heart failure? A meta analysis and e-mail survey of expert opinion. Ann Pediatr Cardiol v.2(1); Jan-Jun 2009
17. BNFC electronic access 2018

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