Role of Milrinone in the Management of Acute Decompensated Heart Failure

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FKUI / Rumah Sakit Pusat Jantung Nasional Harapan Kita
Acute heart failure is a heterogeneous syndrome.

- Right Heart Failure
- Cardiogenic Shock
- High Output Failure
- Hypertensive HF
- PULMONARY EDEMA
- Acute Decompensated CHF


Filippatos 2005
Clinical and pathophysiological classification of acute heart failure

More than 90% of patients hospitalized with heart failure have congestion (wet) and show elevated PCWP1,2

The diagnosis of ADHF should be based primarily on signs and symptoms.

When the diagnosis is uncertain, determination of BNP or NT-proBNP concentration is recommended in patients being evaluated for dyspnea who have signs and symptoms compatible with HF.

The natriuretic peptide concentration should not be interpreted in isolation.
Hospitalization recommended in the presence of:

Evidence of severely decompensated HF, including:
- Hypotension
- Worsening renal failure
- Altered mentation

Dyspnea at rest

Hemodynamically significant arrhythmia
- Including new onset of rapid atrial fibrillation

Acute coronary syndromes  

*Strength of Evidence = C*
HFSA 2010 Practice Guideline

Hospitalization should be considered in the presence of:

Worsened congestion
  - Even without dyspnea

Signs and symptoms of pulmonary or systemic congestion
  - Even in the absence of weight gain

Major electrolyte disturbance

Associated comorbid conditions
  - Pneumonia, PE, diabetic ketoacidosis, TIA or stroke

Repeated ICD firings

Previously undiagnosed HF with systemic or pulmonary congestion
HFSA 2010 Practice Guideline
Acute HF—Treatment Goals

- Improve symptoms
- Restore normal oxygenation
- Optimize volume status
- Identify etiology
- Identify and address precipitating factors
- Optimize chronic oral therapy
- Minimize side effects
- Identify patients for revascularization or device therapy
- Identify risk need for anticoagulant therapy
- Educate patients concerning HF
- Consider and initiate a disease management program
## Patient Monitoring*

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Value</th>
<th>Specifics</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least daily</td>
<td>Weight</td>
<td>Determine after voiding in the morning</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Account for possible increased food intake due to improved appetite</td>
</tr>
<tr>
<td>At least daily</td>
<td>Fluid intake and output</td>
<td></td>
</tr>
<tr>
<td>More than daily</td>
<td>Vital signs</td>
<td>Orthostatic blood pressure, if indicated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oxygen saturation daily until stable</td>
</tr>
<tr>
<td>At least daily</td>
<td>Signs</td>
<td>Edema, ascites, pulmonary rales, hepatomegaly, increased jugular venous</td>
</tr>
<tr>
<td></td>
<td></td>
<td>pressure, hepatojugular reflux, liver tenderness</td>
</tr>
<tr>
<td>At least daily</td>
<td>Symptoms</td>
<td>Orthopnea, paroxysmal nocturnal dyspnea or cough, nocturnal cough, dyspnea,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>fatigue, lightheadedness</td>
</tr>
<tr>
<td>At least daily</td>
<td>Electrolytes</td>
<td>Potassium, sodium</td>
</tr>
<tr>
<td>At least daily</td>
<td>Renal function</td>
<td>BUN, serum creatinine</td>
</tr>
</tbody>
</table>

*All Recommended, Strength of Evidence = C
Intravenous inotropes (milrinone or dobutamine) may be considered to relieve symptoms and improve end-organ function in advanced HF characterized by:

- LV dilation
- Reduced LVEF
- And diminished peripheral perfusion or end-organ dysfunction (low output syndrome)

Particularly if these patients:

- Have marginal systolic blood pressure (<90 mm Hg),
- Have symptomatic hypotension despite adequate filling pressure,
- Or are unresponsive to, or intolerant of, intravenous vasodilators.
These agents may be considered in similar patients with evidence of fluid overload if they respond poorly to intravenous diuretics or manifest diminished or worsening renal function.

Intravenous inotropes (milrinone or dobutamine) are not recommended unless left heart filling pressures are known to be elevated or cardiac index is severely impaired based on direct measurement or clear clinical signs.
HFSA 2010 Practice Guideline
Acute HF—IV Inotropes

It is recommended that administration of intravenous inotropes (milrinone or dobutamine) in the setting of ADHF be accompanied by continuous or frequent blood pressure monitoring and continuous monitoring of cardiac rhythm.

If symptomatic hypotension or worsening tachyarrhythmias develop during administration of these agents, discontinuation or dose reduction should be considered.
The routine use of invasive hemodynamic monitoring in patients with ADHF is not recommended.

*Strength of Evidence = A*
Invasive hemodynamic monitoring should be considered in a patient:

- Who is refractory to initial therapy
- Whose volume status and cardiac filling pressures are unclear
- Who has clinically significant hypotension (typically SBP < 80 mm Hg) or worsening renal function during therapy
- Or who is being considered for cardiac transplant
- Or in whom documentation of an adequate hemodynamic response to the inotropic agent is necessary when chronic outpatient infusion is being considered
ADHERE registry: Inotropic agents and mortality in acute heart failure

## Treatment of acute heart failure

### Comparison of various treatment modalities in different guidelines

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ESC</th>
<th>ACC/AHA</th>
<th>Canadian</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oxygen</strong></td>
<td>I C</td>
<td>I C</td>
<td>-</td>
</tr>
<tr>
<td><strong>Loop diuretic</strong></td>
<td>I B</td>
<td>I B</td>
<td>I B</td>
</tr>
<tr>
<td><strong>Vasodilators</strong></td>
<td>I B</td>
<td>IIa C</td>
<td>I B</td>
</tr>
<tr>
<td><strong>Non-invasive ventilation</strong></td>
<td>IIa B</td>
<td>-</td>
<td>IIa B</td>
</tr>
<tr>
<td><strong>Inotropes</strong></td>
<td>IIa B</td>
<td>I C/IIb C</td>
<td>I B</td>
</tr>
<tr>
<td><strong>Invasive monitoring</strong></td>
<td>IIa B/IIa C</td>
<td>I C/IIa C</td>
<td>I B</td>
</tr>
<tr>
<td><strong>Ultrafiltration</strong></td>
<td>IIa B</td>
<td>IIa B</td>
<td>None</td>
</tr>
<tr>
<td><strong>Coronary reperfusion</strong></td>
<td>I C</td>
<td>IIa C</td>
<td>None</td>
</tr>
</tbody>
</table>

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No class of drugs has recommendation level of evidence A!
IV Vasoactive Use—Important Where Begun

Common vasoactives used include:
- Nesiritide 10%
- Nitroglycerin 10%
- Dopamine 6%
- Dobutamine 6%
- Milrinone 3%

The ADHERE Registry 2nd Quarter 2003 National Benchmark Report; Scios Inc.
IV Vasoactive Use—Important Where Begun

In-Hospital Mortality

The ADHERE Registry 2nd Quarter 2003 National Benchmark Report; Scios Inc.
Pulmonary vascular and right ventricular dysfunction in adult critical care: current and emerging options for management: a systematic literature review

Laura C Price, Stephen J Wort, Simon J Finney, Philip S Marino, Stephen J Brett
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Half-life (duration of action)</th>
<th>Potential adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostacyclin (Epoprostenol, Flolan)</td>
<td>Start at 1 ng/kg/min; titrate upward in 2-ng/kg/min increments according to effect</td>
<td>3-5 minutes (10 minutes)</td>
<td>Systemic hypotension, worsening oxygenation (increased V/Q mismatch), antiplatelet effect, headache, flushing, jaw pain, nausea, diarrhea</td>
</tr>
<tr>
<td>Iloprost</td>
<td>1-5 ng/kg/min</td>
<td>30 minutes</td>
<td>Similar to Flolan; also syncope (5%)</td>
</tr>
<tr>
<td>Sildenafil [325] (NB off-license use in hemodynamically unstable patients)</td>
<td>Low dose, 0.05 mg/kg; high dose, 0.43 mg/kg (comes as 0.8 mg/ml)</td>
<td>3-5 hours</td>
<td>Hypotension: caution if fluid depleted, severe LV-outflow obstruction, autonomic dysfunction. Hypoxemia due to V/Q mismatch. Common: headache, flushing, diarrhea, epistaxis, tremor. Rare but important: anterior ischemic optic neuropathy</td>
</tr>
<tr>
<td>Milrinone</td>
<td>50 µg/kg over 10 minutes followed by 0.375-0.75 µg/kg/min infusion</td>
<td>1-2 hours</td>
<td>Tachyarrhythmias, hypotension</td>
</tr>
<tr>
<td>Adenosine</td>
<td>50-350 µg/kg/min, titrate up in 50 µg/kg/min increments</td>
<td>5-10 seconds (2 minutes)</td>
<td>Bradycardia, bronchospasm, chest pain</td>
</tr>
</tbody>
</table>
Report the case of 3 patients in NYHA class IV, who had ECG documented diastolic dysfunction as the main cause of heart failure.

The patients had been receiving maximal medical therapy in an outpatients setting.

The report of additional use of long term milrinone therapy, in order to demonstrate the significant improvement both in invasive hemodynamic indices and in long term survival with good functional therapy.
Intravenous Milrinone in Treatment of Advanced Congestive Heart Failure

Fig. 3 The QTc interval duration before therapy compared with milrinone plus β-blocker therapy (n=51) and with milrinone therapy alone (n=14).

*P=0.002

Fig. 4 Kaplan-Meier survival curves for patients treated with milrinone plus β-blockers (n=51) versus milrinone alone (n=14) (P <0.0001).
Inotropic effects of PDE inhibitors

β-adrenergic agonists

Calcium channel

Ca++

Adenyl cyclase

ATP

cAMP

Phosphorylated active kinase

Ca++

Increased contractility

Extracellular

Cell membrane

PDE inhibitors

5' AMP

Mg++

Intracellular

Inactive protein kinase

Mechanism of milrinone
Mekanisme Obat Inotropik

Dobutamine

β-receptor

Gs, Gi

ATP

cAMP (active)

Otot Polos Pembuluh Darah

cAMP ▲

MLCK

Fosforilasi myosin otot polos

Relaksasi Otot Polos Pembuluh Darah

PDE III

MILRINONE

AMP (Inactive)

Otot Jantung

cAMP ▲

Meningkatkan Kalsium Intraseluler

Kontraksi

MLCK (Myosin Light Chain Kinase)
Phosphodiesterase Inhibitors

Mechanism of Action
- inhibition of type III phosphodiesterase
  - ↑ intracellular cAMP
  - ↑ activation of protein kinase A
    - Ca²⁺ entry through L type Ca channels
    - inhibition of Ca²⁺ sequestration by SR
- ↑ cardiac output
- ↓ peripheral and pulmonary vascular resistance
- Milrinone is a *positive inotrope* and *vasodilator*, with little chronotropic
- *Different mode action* for either the digitalis glycosides and catecholamines
- Milrinone doesn't *cause desensitization* Beta receptor
- Milrinone's ability increase left ventricle work, *without increase oxygen consumption*
Dosage

- Elimination half-life +/- 2.5 hours, up to 6 – 8 hours if poor renal function*
- Doses:
  - Loading Doses: 50 mcg/kg
  - Maintenance Doses: 0.375 – 0.75 mcg/kg/min
- Adjustment Doses in Renally Impaired Patients
**DOSIS AWAL (LOADING DOSES)**

Cara Pemberian:

1. Loading Doses harus diberikan dalam waktu 10 menit
2. Tambahkan 10 ml atau 20 ml pelarut Dextrose 5% atau NaCl 0.9%, kemudian injeksi selama 10 menit

<table>
<thead>
<tr>
<th>Berat Badan (kg)</th>
<th>30</th>
<th>40</th>
<th>50</th>
<th>60</th>
<th>70</th>
<th>80</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume (ml)</td>
<td>1,5</td>
<td>2,0</td>
<td>2,5</td>
<td>3,0</td>
<td>3,5</td>
<td>3,5</td>
</tr>
</tbody>
</table>
Dosis pemeliharaan (Maintenance Doses)

Cara pemberian:
1. Dianjurkan mulai dengan dosis 0,375 µg/kg/min
2. Larutkan 1 vial (10 ml) INOVAD dalam 40 ml larutan Dextrose 5% atau NaCl 0,9%
   (sehingga diperoleh konsentrasi Milrinone 200 µg/ml)

<table>
<thead>
<tr>
<th>Dosis Pemeliharaan (Maintenance Doses) µg/kg/min</th>
<th>KECEPATAN AUR (ml/jam)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0,375</td>
<td>3,38 4,50 5,63 6,75 7,88 9,00</td>
</tr>
<tr>
<td>0,400</td>
<td>3,60 4,80 6,00 7,20 8,40 9,60</td>
</tr>
<tr>
<td>0,450</td>
<td>4,05 5,40 6,75 8,10 9,45 10,80</td>
</tr>
<tr>
<td>0,500</td>
<td>4,50 6,00 7,50 9,00 10,50 12,00</td>
</tr>
<tr>
<td>0,550</td>
<td>4,95 6,60 8,25 9,90 11,55 13,20</td>
</tr>
<tr>
<td>0,600</td>
<td>5,40 7,20 9,00 10,80 12,60 14,40</td>
</tr>
<tr>
<td>0,650</td>
<td>5,85 7,80 9,75 11,70 13,65 15,60</td>
</tr>
<tr>
<td>0,700</td>
<td>6,30 8,40 10,50 12,60 14,70 16,80</td>
</tr>
<tr>
<td>0,750</td>
<td>6,75 9,00 11,25 13,50 15,75 18,00</td>
</tr>
<tr>
<td>30</td>
<td>40 50 60 70 80</td>
</tr>
</tbody>
</table>

BERAT BADAN (kg)
TERIMA KASIH