Effect and safety of morphine use in acute anterior ST-segment elevation myocardial infarction

BONIN Mickaël

BONIN M et al, JAHA, in press
Disclosure Statement of Financial Interest

I currently have, or have had over the last two years, an affiliation or financial interests or interests of any order with a company or I receive compensation or fees or research grants with a commercial company:

Speaker’s name: Mickael, Bonin, Saint-Herblain

☑ I do not have any potential conflict of interest
STE MI Recommendations

ESC 2017

Titrated i.v. opioids should be considered to relieve pain.

ESC 2012

Titrated i.v. opioids are indicated to relieve pain.

Low level of evidence: No randomized study evaluating the clinical impact of morphine use in STEMI
Why the use of morphine has been downgraded to a class IIa recommendation?
Pharmacological interactions

Accumulating evidences of pharmacokinetic and pharmacodynamic interactions with the 3 currently available antiplatelet agents

- Healthy volunteers

- Acute coronary syndromes
Discordant clinical studies (1)

**CRUSADE Registry**  

57,039 high risk NSTEMI between 2001 à 2003

- Morphine use ➔ Increase in mortality, heart failure, cardiogenic shock, ACS recurrence
- BUT many limitations...

**FAST MI Registry (2005 and 2010)**


- No significant difference on MACEs at one year
Prospective non-randomized MRI study

IV morphine = independent predictor of decreased myocardial salvage index

CLINICAL RELEVANCE OF PHARMACOLOGICAL INTERACTIONS?
What about morphine and cardioprotection?
Proof of concept...

In several animal studies, morphine use was associated with a decrease in infarct size

Various mechanisms (mTOR inhibition...)

But no human translation...

Rare studies with low effectives, indirect primary outcomes ➔ limited benefice of morphine

Only one randomized study ➔ negative
Cardioprotection?

Adverse effects?

Patients confort

No disponible alternative treatment
Rule on the EFFECT and SAFETY of morphine in patients presenting with acute ST-segment elevation myocardial infarction
Post hoc analysis on large randomized study population

Intention to treat CIRCUS acute anterior STEMI population

2 groups: morphine use or not before PCI

Composite primary outcome (MACE): CV death, heart failure, cardiogenic shock, stroke, recidivant MI, unstable angina
Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>All Patients (n=967)</th>
<th>Patients With Morphine (n=554)</th>
<th>Patients Without Morphine (n=413)</th>
<th>P Value (Wilcoxon or Fisher’s Test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>60±13</td>
<td>59±13</td>
<td>61±13</td>
<td>0.07</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>82</td>
<td>82</td>
<td>82</td>
<td>0.73</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27±4</td>
<td>27±4</td>
<td>27±4</td>
<td>0.14</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>42</td>
<td>43</td>
<td>41</td>
<td>0.39</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>37</td>
<td>38</td>
<td>37</td>
<td>0.74</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>1.00</td>
</tr>
<tr>
<td>Dyslipidemia, %</td>
<td>38</td>
<td>40</td>
<td>36</td>
<td>0.18</td>
</tr>
<tr>
<td>Previous myocardial infarction, %</td>
<td>6</td>
<td>6</td>
<td>5</td>
<td>0.67</td>
</tr>
<tr>
<td>Previous PCI, %</td>
<td>7</td>
<td>7</td>
<td>6</td>
<td>0.61</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>47±10</td>
<td>47±10</td>
<td>48±10</td>
<td>0.16</td>
</tr>
<tr>
<td>Cyclosporine use before PPCI, %</td>
<td>49</td>
<td>51</td>
<td>46</td>
<td>0.12</td>
</tr>
</tbody>
</table>
## Periprocedural characteristics

<table>
<thead>
<tr>
<th></th>
<th>Patients With Morphine (n=554)</th>
<th>Patients Without Morphine (n=413)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Killip class at admission</strong></td>
<td>505</td>
<td>353</td>
</tr>
<tr>
<td>Class 1</td>
<td>432 (85.5)</td>
<td>317 (90.0)</td>
</tr>
<tr>
<td>Class 2</td>
<td>57 (11.3)</td>
<td>29 (8.2)</td>
</tr>
<tr>
<td>Class 3</td>
<td>9 (1.8)</td>
<td>7 (2.0)</td>
</tr>
<tr>
<td>Class 4</td>
<td>7 (1.4)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td><strong>Total ischemic time, mean±SD (h)</strong></td>
<td>3.99±2.39</td>
<td>4.94±3.07</td>
</tr>
<tr>
<td>Rentrop Grade 2 or 3</td>
<td>34/554 (6.1)</td>
<td>31/413 (7.5)</td>
</tr>
<tr>
<td>Angiographic thrombus burden ≥3</td>
<td>358/533 (67.2)</td>
<td>267/395 (67.9)</td>
</tr>
<tr>
<td>Area at risk, mean±SD (%)*</td>
<td>36.8±8.4</td>
<td>35.6±8.6</td>
</tr>
<tr>
<td>Proximal localization</td>
<td>252/552 (45.6)</td>
<td>157/403 (38.9)</td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>203/554 (36.6)</td>
<td>154/413 (37.3)</td>
</tr>
<tr>
<td>Thrombolysis rate</td>
<td>33/554 (5.9)</td>
<td>27/413 (6.5)</td>
</tr>
<tr>
<td>Stenting</td>
<td>492/554 (88.8)</td>
<td>362/413 (87.6)</td>
</tr>
</tbody>
</table>
### MACEs (1)

<table>
<thead>
<tr>
<th>Event</th>
<th>Morphine (n=554)</th>
<th>No Morphine (n=413)</th>
<th>$P$ (Fischer’s Test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any MACE*</td>
<td>145 (26.2)</td>
<td>91 (22.0)</td>
<td>0.15</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>29 (5.2)</td>
<td>20 (4.8)</td>
<td>0.88</td>
</tr>
<tr>
<td>Heart failure</td>
<td>110 (19.9)</td>
<td>70 (16.9)</td>
<td>0.28</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>30 (5.4)</td>
<td>19 (4.6)</td>
<td>0.66</td>
</tr>
<tr>
<td>Recurrent myocardial infarction</td>
<td>21 (3.8)</td>
<td>7 (1.7)</td>
<td>0.08</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>15 (2.7)</td>
<td>8 (1.9)</td>
<td>0.53</td>
</tr>
<tr>
<td>Stroke</td>
<td>10 (1.8)</td>
<td>9 (2.2)</td>
<td>0.82</td>
</tr>
</tbody>
</table>
MACEs (2)

- MACE: 26.2% with morphine (n = 554), 22.0% without morphine (n = 413)
- Cardiovascular death: 5.2% with morphine, 4.8% without morphine
- Heart failure: 19.9% with morphine, 16.9% without morphine
- Cardiogenic shock: 5.4% with morphine, 4.6% without morphine
- Myocardial infarction: 3.8% with morphine, 1.7% without morphine
- Unstable angina: 2.7% with morphine, 1.9% without morphine
- Stroke: 1.8% with morphine, 2.2% without morphine
MACEs (3)

Unadjusted HR: 1.25
95% CI [0.96; 1.62]
p = 0.10

Adjusted HR = 1.04
95% CI [0.75; 1.45]
p = 0.82

With morphine (n = 554)
Without morphine (n = 413)
All cause mortality

\[ p = 0.77 \]
**Infarct size**

\[ p = 0.20 \]
No significant adverse nor positive clinical effect associated with morphine use in this new retrospective study, on a large anterior STEMI cohort

Other clinical studies presented conflicting results leading to a low level of evidence

No clear available evidence of clinically relevant adverse effects

No currently available alternative to relief pain and dyspnea, waiting for SCADOL II trial results

Pharmacologic interactions could be decreased by chewing AAP or IV AAP

Morphine should be used without restriction for pain relief during STEMI waiting for an acceptable alternative analgesic treatment.

Particularly if AAP are chewed / IV.

Conclusion in accordance with a recent review

More caution during NSTEMI.