Refractory cancer pain in children: is methadone an alternative?

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Villejuif - June 2012

Cancer pain in children

- Multi factorial
- Difficult to assess: underestimate by parents and professionals, hidden by children and adolescents
- Frequent at end of life, with high doses of endovenous opioids needed for part of this population Sirkia JPSM 1998
- High efficacy of non drugs therapies, at least at early stage
- Lack of knowledge on long term effect on central nervous system of high opioid doses
- Few drugs labelled for children
- Emerging knowledge of long term effect of chronic suffering during childhood
- Few (no?) clinical trials dedicated to that population on cancer pain
- Reserved area for paediatricians? Who is prescribing?
Pain and palliative care in children: conceiving the unconceivable

A narrow pathway between positive effects and side effects

Less experience and structure where it’s most needed

A lot of opinions and few evidence

… expecting for a miracle: is methadone one?

opioids

morphine (1806 )
oxycodone (1916)
hydromorphone (1926)
buprénorphine (1973)
fentanyl (1956-1992)

Erwan treillet, 2011
Methadone as an analgesic drug

- Triple mechanism of action
  - Agonist of μ opioid receptors
  - Inhibit monoamine reuptake
  - Antagonist of NMDA receptors

- Efficacy on neuropathic pain

- Pharmacological specificities of methadone
  - kinetic with double edge: short and long lasting action : around the clock and PRN at the same time
  - Huge interindividual variability and for a same individual among different periods Sawe 1986 clinical pharmacokinetics
  - High ratios variability between methadone and morphine - benelou-narcoo 2006 / pain Sympt Manage
  - Huge drug to drug interactions (cyt P 450) - Wechsules 2008 Pain medicine
  - Steady state obtained in an average of 5 days:
    - Luo 2005 : 1 day to several weeks
    - Freidheim 2008 : 35 to 325 hours (around 2weeks)
    - Leppert 2009 2 to 4 days
    - Gallagher 2009 : for older people 4 to 5 half life that is 80 to 675 hours (3 to 28 days)

Clinical practice: how to start?

<table>
<thead>
<tr>
<th>model</th>
<th>Ratio</th>
<th>Duration</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edmonton model (Bruera)</td>
<td>Fixed</td>
<td>1:10</td>
<td>3 days</td>
</tr>
<tr>
<td>Milan model (Ripamonti)</td>
<td>Variable</td>
<td>1:4 for MDD between 60 and 90 mg 1:6 for MDD between 90 and 300 mg 1:8 for MDD &gt; 300 mg</td>
<td>3 days</td>
</tr>
<tr>
<td>Mercadante and his «Stop and go»</td>
<td>1:5</td>
<td>NC</td>
<td>3 days</td>
</tr>
<tr>
<td>Morley model</td>
<td>10% of the MDD for each dose</td>
<td>6 days</td>
<td>progressively diminish morphine doses répétées avec un intervalle de 3 heures si EMM&gt;300mg dose de méthadone plafonnée à 30mg/prise dose des 48 dernières heures divisées par 9 et répartie en 2 prises par jour</td>
</tr>
<tr>
<td>The Nauck model</td>
<td>No ratio</td>
<td>4 days</td>
<td>- stop morphine - fixed doses every 4 hours and rescue dose each hour if needed - fixed doses between 5 and 10 mg possible increase of dose at 50% per day or day divide in 3 the total dose taken during the last 24h as fixed doses and give rescue doses each 3 hours as needed</td>
</tr>
<tr>
<td>Le modèle anglais de Scholes</td>
<td>10% de l'EMM par prise</td>
<td>Au moins 7 jours</td>
<td>- slow each 3 hours if needed - when dose get stable divide the methadone dose of the last 24 hours in two and add rescue dose as needed each 3 hours</td>
</tr>
</tbody>
</table>
Clinical practice: ratios (1)

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>1 : 1</td>
<td>4:1 for MDD 60-90 mg</td>
<td>5:1 for MDD &lt;400 mg</td>
<td>4:1 for MDD &lt;90 mg</td>
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<tr>
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<td>6:1 for MDD 90-300 mg</td>
<td>10 :1 for MDD &gt;400 mg</td>
<td>8 :1 for MDD 90-300 mg</td>
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<tr>
<td></td>
<td>8:1 for MDD &gt;300 mg</td>
<td></td>
<td>12 :1 for MDD &gt;300 mg</td>
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</tbody>
</table>

- Meta analyse benitez-rosario 2009 shows ratio seems to vary with:
  - the reason for rotation (uncontrolled pain vs opioids side effects)
  - and the previous opioid doses (less or more than 300mg equivalent oral morphine).

Clinical practice: ratio “my favourite”

Simplified methadone conversion.

Simplified calculation: Daily dose of methadone = EDDM /15 + 15
Does this method works??

Dr erwann Treillet, 2011

Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC

The role of methadone

Methadone has often been viewed as an alternative to oral morphine but its specific pharmacokinetic characteristics and a very long and unpredictable half-life require careful individualisation of dosing schedules. Oral methadone is the drug most frequently considered as an option in the practice of opioid switching. In a systematic review by the Cochrane Collaboration, only three RCTs involving 277 patients addressed the comparison of methadone with another step III opioid (one study had a third group receiving transdermal fentanyl). The drugs did not differ in efficacy between patients who were treated with step II opioids or were opioid naive. In one study methadone was associated with a higher incidence of sedation, which led to a high percentage of patients dropping out because of adverse effects. In a previous study, four (59%) of 26 versus two (8%) of 26 patients in the methadone and diamorphine plus cocaine groups, respectively, withdrew because of sedation.

Although methodological limitations were found in these three studies, data consistently show no significant differences in analgesic efficacy between methadone and morphine; the evidence of more frequent CNS side-effects (sedation) with methadone is not consistent across studies. Methadone should be considered an alternative to other oral step III opioids.

Recommendation for use of methadone

Methadone has a complex pharmacokinetic profile with an unpredictably long half-life. The data permit a weak recommendation that it can be used as a step III opioid of first or later choice for moderate to severe cancer pain. It should be used only by experienced professionals.

Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC

Prof Augusto Caraceni MD, Prof Geoffrey Hanks DSc (Med), Prof Stein Kaasa MD, Prof Michael I Bennett MD, Cinzia Brunelli ScD, Prof Nathan Cherny MD, Prof Ola Dale MD, Franco De Conno MD, Prof Marie Fallon MD, Magdi Hanna FCA, Dagny Falkvag Haugen PhD, Gitte Juhl MD, Samuel King MRC Ph, Pål Kvalestad MD, Bjørn A Laugsand MD, Marco Maltoni MD, Sebastiano Mercante MD, Maria Nabal MD, Alessandra Pigni MD, Prof Lukas Radbruch MD, Colette Reid MD, Prof Per Sjogren MD, Patrick C Stone MD, Davide Tassinari MD, Giovambattista Zeppetella FRCP, for the European Palliative Care Research Collaborative (EPCRC), on behalf of the European Association for Palliative Care (EAPC)

The Lancet Oncology - 1 February 2012 ( Vol. 13, Issue 2, Pages e58-e68 )
Practical steps for initiating methadone

- Before starting:
  - Multidisciplinary decision, with experienced professionals
  - ECG,
  - Ionogram,
  - Analyse other drugs potential interactions
- Choose a titration protocol / proceed with « loading » doses
- Start methadone as inpatient or be sure to be able to have a daily follow-up at the beginning
- Control of symptom, side effects, fixed doses and rescue doses from D1 to D3
- Check the overdose from D3 to D5: provide the team with adequate training
- Ensure continuity in care: link with general practitioner, pharmacy, health insurance if necessary

Paediatric use of méthadone (1)

- Literature is spare
- Efficacy of methadone on postoperative pain
  - Methadone IV 0.2 mg/kg versus morphine 0.2 mg/kg: methadone relieves pain and allows a decrease in opioids requirement during 36 hours compared to morphine, without significant side effects
- Efficacy of methadone after traumas, burn, or cancer pain
  - 3954 patients treated by methadone over 5 years, all age and pathology, 12% children: results are good safety, and use mainly in post operative pain – doses vary between 0.2 to 0.4 mg/kg/day
  - 5 clinical cases out of 70 patients – 0.3 to 0.4 mg/kg/day max 0.6 mg/kg/day
Paediatric use of méthadone (2)

- Efficacy of methadone on paediatric cancer pain
    
    19 children with methadone treatment for cancer pain – initiated at 0.1 mg/kg/4h then up titrate until 0.32 mg/kg/4h max – no ratio – few toxicity – use of methadone as a first line treatment
  
    
    Series of 17 children with cancer pain: 16 had their pain relieved by methadone until death, assessment were « positive tone on pain assessment » – ratios vary from 2 to 60 – no dose/kg calculated
  
    
    Retrospective serie of 41 children with cancer pain, used for neuropathic pain, nociceptive pain unresponsive to opioids, facilitaiton of weaning from opioids. Abstract only, no dose in abstract

Paediatric use of méthadone (3)

- Efficacy of methadone on paediatric cancer pain
  
  - Sabatowski R, Kasper SM, Radbruch L. Patient-controlled analgesia with intravenous L-methadone in a child with cancer pain refractory to high-dose morphine. J Pain Symptom Manage 2002;23:3-5:
    
    One clinical case with use of endovenous methadone
  
    
    Retrospective study of 70 children in palliative care with symptomatic pain. 30 received methadone: 0.27 to 0.89 mg/kg/day per os and 0.34 to 0.46 mg/kg/day endovenous. Efficacy of treatment for 80% of patients.

To conclude:

One RCT
Collection of clinical cases, large range of titration methods
No consensus on doses
Huge differences between countries
« efficacy and safety of oral methadone in children and adolescents with advanced cancer » Alessandra De Grazia1, Sophie Laurent2, Sabine Voisin-Saltiel3, Philippe Poulain4, Martine Gabolde5, Michaela Semeraro1, Agnès Suc6, Nathalie Gaspar1, Laurence Brugières1

1 Paediatric Hematology and Oncology, Institute Gustave-Roussy, Villejuif, France
2 Pain Evaluation and Treatment Centre, Supportive Care department, Institut Gustave Roussy, Villejuif, France
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4 Palliative Care Unit, Clinique de l'Ormeau, Tarbes, France
5 Palliative Care Unit, Paul Brousse hospital, Villejuif, France

- 11 children treated between January 2001 and December 2009
- Age 10 to 21 years (median of 14 years): adolescents and young adults (AYA)
- Methadone given as a second line opioid after previous opioid failure (fentanyl for 5 patients, sufentanil for 3 and morphine for 3)
- Opioid switch done for unrelieved pain for all 11, and also side effects in 5 patients
- Coanalgesics used in all patients (antiepileptic or antidepressant 11/11, ketamine IV 4/11, corticosteroids 8/11)
- 6 mixt pain, 5 neuropathic pain

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<tr>
<th>PATIENTS</th>
<th>SEX</th>
<th>AGE (years)</th>
<th>WEIGHT (kg)</th>
<th>TUMOR</th>
<th>TYPOLOGY OF PAIN</th>
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<td>49</td>
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<td>Mixte</td>
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<td>72</td>
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<td>32</td>
<td>Pelvic Schwannoma</td>
<td>Neuropathic</td>
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**Efficacy and Safety of Oral Methadone in Children and Adolescents with Advanced Cancer**

Alessandra De Grazia, Sophie Laurent, Sabine Voisin-Saltiel, Philippe Poullain, Martine Gabolde, Michaela Semeraro, Agnès Gaspar, Laurence Brugières

<table>
<thead>
<tr>
<th>No</th>
<th>Age (years)</th>
<th>Opioid used before methadone</th>
<th>OME (Oral Morphine Equivalent) mg/day</th>
<th>Methadone D1 (mg/kg/day)</th>
<th>Methadone D7 (mg/kg/day)</th>
<th>Ratio D1</th>
<th>Duration (days)</th>
<th>Delay to pain control (days)</th>
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<tr>
<td>19</td>
<td>Fentanyl</td>
<td>480</td>
<td>9.8</td>
<td>50</td>
<td>1.0</td>
<td>9.6</td>
<td>15</td>
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<tr>
<td>17</td>
<td>Morphine</td>
<td>884</td>
<td>13.7</td>
<td>100</td>
<td>6.0</td>
<td>3.3</td>
<td>12</td>
<td>0</td>
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<td>16</td>
<td>Fentanyl</td>
<td>705</td>
<td>9.9</td>
<td>25</td>
<td>0.5</td>
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<td>2.3</td>
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<td>100</td>
<td>8.8</td>
<td>70</td>
<td>2.1</td>
<td>4.6</td>
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<td>Fentanyl</td>
<td>95</td>
<td>1.4</td>
<td>8</td>
<td>0.2</td>
<td>4.6</td>
<td>105</td>
<td>3</td>
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<td>Fentanyl</td>
<td>1300</td>
<td>17.9</td>
<td>120</td>
<td>1.1</td>
<td>11.1</td>
<td>16.7</td>
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<td>11</td>
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<td>27</td>
<td>0.8</td>
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<td>0.7</td>
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<td>3.1</td>
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<td>16.0</td>
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<td>10</td>
<td>Morphine</td>
<td>120</td>
<td>4.0</td>
<td>31</td>
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<td>210</td>
<td>6.6</td>
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<td>1.0</td>
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<td>300</td>
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<td>1.0</td>
<td>5.3</td>
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<td>16</td>
<td>Fentanyl</td>
<td>374</td>
<td>6.8</td>
<td>74</td>
<td>3.5</td>
<td>7.8</td>
<td>7.5</td>
<td>5.8</td>
</tr>
</tbody>
</table>

**DMM before switch:** Mean = 374mg/j or 6.8mg/kg/day, Med = 300mg/day (20-1000)

Ratio M/ME D1: mean = 6.7, med = 5.3 (1.3 – 16)

Ratio M/ME D7: mean = 7.5, Med = 6.9 (0.7 – 16.7)

Ratio M/ME D7 for MDD > 300 mg = 9.8, for MDD< 300mg = 4.8

Dose of ME/kg D1: mean = 1.5 mg/kg/day, med = 1.3 mg/kg/day (0.3 – 6)

Dose of ME/kg D7: mean = 1.5 mg/kg/day, med = 1 mg/kg/day (0.2 – 6)

10 patients out of 11 obtained a relief > 30% on D4

Reasons for late stop of methadone (9/11):
- Pain solved (stop of all opioid treatment) N=1
- Treatment failure N=1
- Oral intake compromised N=2
- Side effects N=2
- Death due to disease N=3
Methadone in children: pro and against

<table>
<thead>
<tr>
<th>pro</th>
<th>against</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less expensive at high doses</td>
<td>Few studies and use in paediatric setting</td>
</tr>
<tr>
<td>Efficacy on neuropathic and nociceptive pain and therefore refractory cancer pain due to a multimodal mechanism</td>
<td>Conversion rate with other opioids unclear</td>
</tr>
<tr>
<td>Few side effects</td>
<td>Long half life and complex pharmacokinetics turning titration complex</td>
</tr>
<tr>
<td>Use not limited by renal failure</td>
<td>Lot of drug to drug interactions</td>
</tr>
<tr>
<td>Oral route alternative for children dependent from complex intravenous treatment allowing them to be discharged home</td>
<td>Off label in France for cancer pain and for patients under 15 years old</td>
</tr>
</tbody>
</table>

discussion

- Use of methadone in children may be beneficial in case of refractory and mixt cancer pain: to be verified
- It allows children to be discharged home but needs an experienced team: where, who?
- Conversion rate is highly variable: titration starting with a dose / kg/day should be considered.
What research on methadone therapy / opioid therapy in paediatric setting?

- **RCT:**
  - Cost: few children by center – multicentric studies
  - Competitive: high prevalence of treatment protocols for cancer: do we have a « fenetre »?
  - Ethics: RCT with active treatment versus placebo at end of life
  - …BUT…

- **Pharmacological studies:**
  - Need for a phase II for methadone in pediatry

- **Titration method:**
  - Retitrate from dose per kilo vs ratio?

What research on methadone therapy / opioid therapy in adult setting?

- **Clinical trials:**
  - Comparing conversion methods: on running trial
  - New trial to measure efficacy of the Plonk method?
  - Advocate for approval at EU level of this drug

- **Pharmacology**

- **Opioids:** go on with recommendations and effects out of analgesia
Thank you

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Zahia Hamdoud
Dr Erwan Treillet
Dr Marion Brugirard

Wellcome in Paris!