

Refractory cancer pain in children: is methadone an alternative?

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Villejuif - June 2012

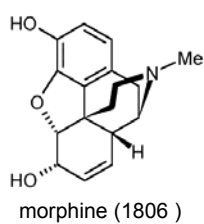
cancer pain in children

- 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?

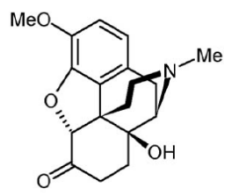
- Pain and palliative care in children: conceiving the unconceivable
- A narrow pathway between positive effects and side effects
- Less experience and structure where it's most needed
- A lot of opinions and few evidence

... expecting for a miracle: is methadone one?

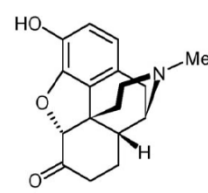
opioids



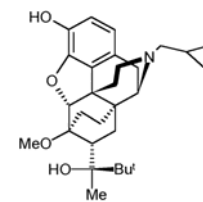
morphine (1806)



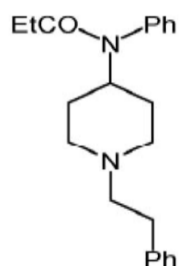
oxycodone (1916)



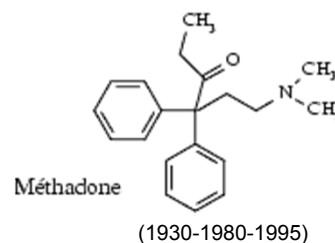
hydromorphone
(1926)



buprenorphine
(1973)



fentanyl (1956-
1992)



Méthadone

(1930-1980-1995)

4

Erwan trellet, 2011

Methadone as an analgesic drug

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

Bruera E, Sweeney C. methadone use in cancer patients with pain: a review. Journal of palliative medicine. 2002 vol5 (1):127-138
- Efficacy on neuropathic pain

Morley JS. 2003 palliative medicine
- 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 periodes Sawe 1986 clinical pharmacokinetics
 - High ratios variability between methadone and morphine - benitez-rosario 2009 J pain Sympt Manage
 - Huge drug to drug interactions (cyt P 450) – Weschules 2008 Pain medicine
 - Steady state obtained in an average of 5 days:
 - Lugo 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 ?

models	Ratio	Duration	Remarque
Edmonton model (Bruera)	Fixe : 1 :10	3 days	-3 fixed doses each 8 hours -rescue doses of morphine the first two days then 10% of the total methadone daily dose
Milan model (Ripamonti)	Variable : 1:4 for MDD between 60 and 90 mg 1:6 for MDD between 90 and 300 mg 1:8 for MDD > 300 mg	3 days	-3 fixed doses each 8 hours -rescue doses of 10% of daily dose of methadone -progressive stop of morphine over 3 days
Mercadante and his « Stop and go »	1:5	NC	-3 fixed doses each 8 hours - Stop morphine when starting methadone - Useful for MDD between 30 and 180 mg
Morley model	10% of the MDD for each dose	6 days	-progressively diminish morphine -doses répétés avec un intervalle de 3 heures -si EMO>300mg dose de méthadone plafonnée à 30mg/prise -dose des 48 dernières heures divisées par 4 et répartie en 2 prises par jour
The Nauck model	No ratio	4 days	-stop morphine -fixed doses every 4 hours and rescue dose each hour if needed -dose between 5 and 10 mg -possible increase of dose of 30% per day -4 th day divide in 3 the total dose taken during the last 24h as fixed doses and give rescue doses each 3 hours as needed
Le modèle anglais de Scholes	10% de l'EMO par prise	Au moins 3 jours	-dose 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

Clinical practice: ratios (1)

Eddy (1949)	Ripamonti (1998)	Benitez rosario (2004)	Mercadantes (2001)
1 :1	4:1 for MDD 60-90 mg 6:1 for MDD 90-300 mg 8:1 for MDD > 300 mg	5 :1 for MDD <400 mg 10 :1 for MDD >400 mg	4:1 for MDD <90 mg 8 :1 for MDD 90-300 mg 12 :1 for MDD >300 mg

- **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"

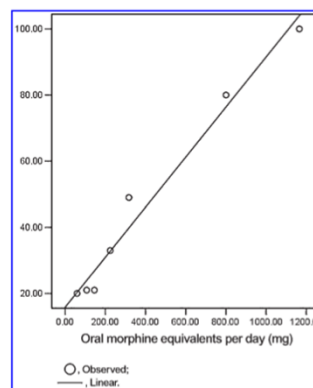
Simplified methadone conversion.
Plonk WM.
J Palliat Med.
2005
Jun;8(3):478-9.

With the rising popularity of methadone as an inexpensive and effective long-acting opioid, its use has become an important palliative care skill. Current dose conversion algorithms are inconsistent, complicated, and difficult to remember. To teach residents rotating through our palliative care unit how to dose methadone effectively, I derived from published empirical data a simple linear equation that accurately converts oral morphine equivalents to estimated oral methadone requirements within a common range.

Averaged data were extracted from five published articles (Lawlor, Cancer 1998, 82:1167-73; Ripamonte, J Clin Oncol 1998, 16:3216-21; Mercadante, J Clin Oncol 1999, 17:3307-12; Mercadante, J Clin Oncol 2001, 19:2898-904; Mercadante, Supp Care Cancer 2003, 11:326-31) and analyzed using linear regression.

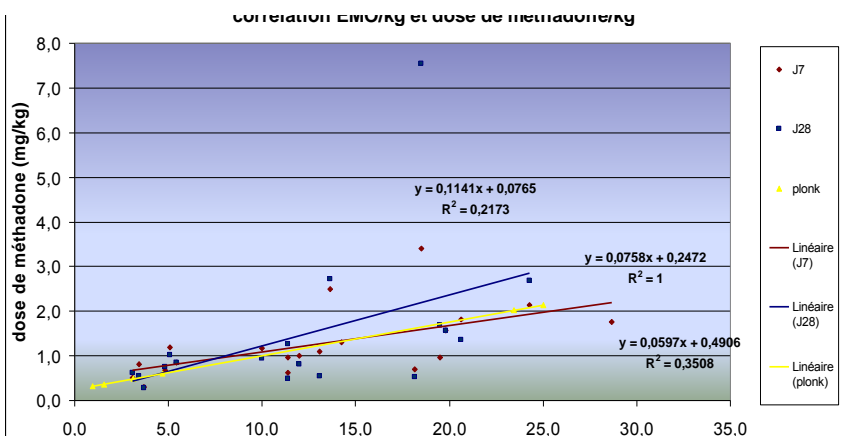
The best fit line ($R^2 = 0.975$, $p < .000$) is described by the following equation:

$$\text{oral methadone per day (mg)} = 0.0757 (\text{oral morphine equivalents per day, mg}) + 15.82$$



Simplified calculation: Daily dose of methadone= EDDM /15 + 15

Does this method works??



Dr erwan Treillet, 2011

The role of methadone

Findings

Methadone has often been viewed as an alternative to oral morphine but its specific pharmacokinetic characteristics and a very long and unpredictable half-life³¹ 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,³² which was updated by Cherny,³³ only three RCTs^{30,33,34} involving 277 patients addressed the comparison of methadone with another step III opioid (one study had a third group receiving transmucosal 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.³¹ In a previous study, four (15%) of 26 versus two (8%) of 26 patients in the methadone and diamorphine plus cocaine groups, respectively, withdrew because of sedation.³⁵

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.

R5

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 Faksvåg Haugen PhD, Gitte Juhl MD, Samuel King MRCP, Pål Klepstad MD, Eivør A Laugsand MD, Marco Maltoni MD, Sebastiano Mercadante 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 sparse
- Efficacy of methadone on postoperative pain
 - Berde CB. Beyer JE. Boumaki MC. Levin RC. Sethna NF. Comparison of morphine and methadone for prevention of postoperative pain in 3- to 7-year-old children. J Pediatr 1991;119:136-141
 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
 - Shir Y. Rosen G. Zeldin A. Davidson EM. Methadone is safe for treating hospitalized patients with severe pain. Can J Anaesth. 2001;48:1109-1113
 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
 - Shir Y. Shenkman Z. Shavelson V. Davidson EM. Rosen G. Oral Methadone for the Treatment of Severe Pain in Hospitalized Children: A Report of Five Cases. Clin J Pain. 1998;14(4):350-353
 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
 - Miser AW, Miser JS. The use of oral methadone to control moderate and severe pain in children and young adults with malignancy. Clin J Pain 1985;4:243-248

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
 - Davies D, DeVlaming D, Haines C. Methadone analgesia for children with advanced cancer. Pediatr Blood Cancer 2008;51:393-397 :

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
 - Angheliescu DL, Faughnan LG, Hankins GM, Ward DA, Oakes LL. Methadone use in children and young adults at a cancer center: a retrospective study. J Opioid Manag. 2011;7(5):353-61

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
- Sirkia K, Hovi L, Pouttu J, Saarinen-Pihkala UM. Pain medication during terminal care of children with cancer. J Pain Symptom Manage 1998;15:220-226:
 - 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

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- 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

PATIENTS	SEX	AGE (years)	WEIGHT (Kg)	TUMOR	TYPOLGY OF PAIN
1	M	19	49	Pelvic Schwannoma	neuropathic
2	F	17	50	Ewing Sarcoma	mixte
3	M	16	71	Leukemia	mixte
4	M	21	48	Rabdoid cancer	neuropathic
5	M	13	34	Hepatocarcinoma	mixte
6	M	10	39	Pineal Germinoma	neuropathic
7	F	14	56	Leukemia	mixte
8	F	11	33	Ewing Sarcoma	mixte
9	F	16	58	Lumbar Schwannoma	neuropathic
10	F	10	30	High grade Glioblastoma	mixte
11	M	14	32	Pelvic Schwannoma	neuropathic

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VT	Age (years)	Opioid used before methadone	OME (Oral Morphine Equivalent) mg/Kg/day	OME mg/Kg/day	Methadone D1 (mg/day)	Methadone D1 (mg/kg/day)	Methadone D7 (mg/day)	Methadone D7 (mg/kg/day)	RATIO D1	RATIO D7	Duration (days)	Delay to pain control (day)
	19	fentanyl	480	9.8	90	1,8	50	1.0	5.3	9.6	15	3
	17	morphine	684	13,7	300	6.0	300	6.0	2,3	2,3	21	5
	16	sufentanyl	700	9.9	60	0,8	60	0,8	11,7	11,7	7	6
	21	fentanyl	360	7.5	60	1,3	25	0,5	6.0	14.4	12	0
	13	sufentanyl	300	8.8	60	1,8	70	2.1	5,0	4,3	180	7
	10	fentanyl	55	1,4	12	0,3	8	0,2	4.6	6.9	105	3
	14	sufentanyl	1000	17.9	90	1,6	60	1.1	11,1	16,7	9	3
	11	fentanyl	20	0,6	15	0,5	27	0,8	1,3	0,7	ongoing	3
	16	morphine	180	3.1	90	1,6	120	2.1	2,0	1,5	134	30
	10	morphine	120	4.0	7.5	0,3	15	0,5	16,0	8,0	9	2
	14	fentanyl	210	6.6	25	0,8	31	1.0	8.4	6.8	ongoing	2
N	14		300	5	60	1.3	50	1.0	5.3	6.9		3
	14.6		374	6.8	74	1,5	70	1,5	6.7	7.5		5.8

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 de ME/kg D1: mean = 1,5 mg/kg/day med = 1,3 mg/kg/day (0,3 – 6)

Dose de ME/kg D7: mean = 1,5 mg/kg/day med = 1 mg/kg/day (0,2 – 6)

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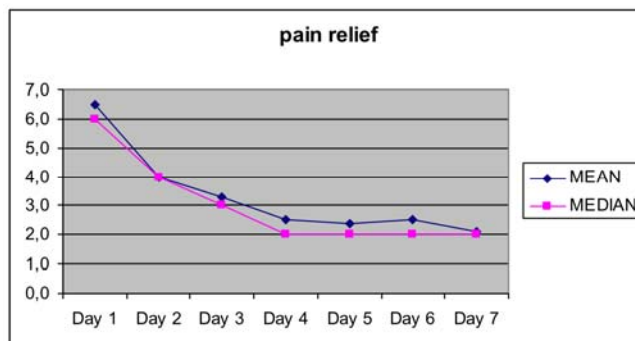
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10 patients out of 11 obtained a relief > 30% on D4

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

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

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 peditry
- 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?
 - Efficacy: “**Assessment of methadone efficacy in refractory pain management in patients with advanced cancer: a prospective, randomized, open study – METHADOUL**” : written, looking for funding
 - 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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Wellcome in Paris!

