

Switching From Morphine to Methadone to Improve Analgesia and Tolerability in Cancer Patients: A Prospective Study

By Sebastiano Mercadante, Alessandra Casuccio, Fabio Fulfaro, Liliana Groff, Roberto Boffi, Patrizia Villari, Vittorio Gebbia, and Carla Ripamonti

Purpose: To evaluate the clinical benefits of switching from morphine to oral methadone in patients who experience poor analgesia or adverse effects from morphine.

Patients and Methods: Fifty-two consecutive cancer patients receiving oral morphine but with uncontrolled pain and/or moderate to severe opioid adverse effects were switched to oral methadone administered every 8 hours using different dose ratios. Intensity of pain and adverse effects were assessed daily, and the symptom distress score (DS) was calculated before and after switching.

Results: Data were analyzed for 50 patients. Switching was considered effective in 80% of the patients; results were achieved in an average of 3.65 days. In the 10 patients who switched to methadone because of uncontrolled pain, a significant reduction in pain intensity ($P < .005$) and an average of a 33% increase in

methadone doses necessary ($P < .01$) were found after an average of 3.5 days. DS significantly decreased from an average of 8.4 to 4.5 ($P < .0005$). In the 32 patients switching because of uncontrolled pain and morphine-related adverse effects, significant improvement was found in pain intensity ($P < .0005$), nausea and vomiting ($P < .03$), constipation ($P < .001$), and drowsiness ($P < .01$), but a significant increase in the methadone dose of an average of 20% ($P < .004$) was required.

Conclusion: In most patients with cancer pain referred for poor pain control and/or adverse effects, switching to oral methadone is a valid therapeutic option. In the clinical setting of poor pain control, higher doses of methadone are necessary with respect to the equianalgesic calculated dose ratios previously published.

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ACCORDING TO WORLD Health Organization guidelines, opioid analgesics are the mainstay of cancer pain management.¹ Among analgesics, since 1977, oral morphine has been used by hospices and palliative care units as the opioid of choice for treating pain of moderate to severe intensity because it provides effective pain relief and is widely tolerated, simple to administer, and relatively inexpensive.²

In clinical practice, patients treated with oral morphine sometimes present with the following clinical situations: (1) pain is controlled but the patient experiences some intolerable adverse effects; (2) pain is not adequately controlled and it is impossible to increase the morphine dose because of adverse effects; (3) pain is not adequately controlled by

continuously increasing the dose of morphine but the morphine does not produce adverse effects.

Different therapeutic strategies may prevent or manage morphine-related adverse effects: (1) coadministering symptomatic drugs, (2) reducing morphine dose whenever possible, (3) administering an alternative opioid, or (4) administering morphine by an alternative route. No data in literature allow a comparison of the advantages and disadvantages of the different therapeutic strategies. Patients who obtain poor analgesic efficacy or tolerability with one opioid will frequently tolerate another opioid.³⁻¹⁰

Preclinical studies show that opioids can act on different receptors or subtype receptors, and individual receptor profiles may influence the analgesia as well as the adverse effects. Moreover, the genetic make-up of the individual person plays an important role.¹¹⁻¹⁴ The differences among the various opioids in response and tolerability may have to do with the active metabolites of the parent drug and different receptor affinities leading to incomplete cross-tolerance.^{8,15-22} However, the exact mechanisms that underlie this variability in the response to different opioids are unknown.

Methadone is an attractive alternative mu opioid analgesic because of its lack of neuroactive metabolites, clearance independent of renal function, good oral bioavailability, extremely low cost, long half-life with fewer doses needed

From the Pain Relief and Palliative Care Unit, La Maddalena Cancer Center; Home Care Program, Società per l'Assistenza al Malato Oncologico Terminale; Department of Hygiene and Microbiology, University of Palermo; and Department of Oncology, La Maddalena Cancer Center, Palermo; and Rehabilitation and Palliative Care Division, National Cancer Institute of Milan, Italy.

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Address reprint requests to Sebastiano Mercadante, MD, Pain Relief and Palliative Care Unit, La Maddalena Cancer Center, Via S Lorenzo 312, 90146 Palermo, Italy; email: mercadsa@tin.it.

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per day, potential to control pain no longer responsive to other opioids, and other extraopioid analgesic effects caused by its noncompetitive antagonist activity at the *N*-methyl-D-aspartate receptors.²³⁻³⁷ Moreover, it also shares delta activity and potentially prevents monoamine reuptake in the brainstem, producing effects similar to tricyclic antidepressants.

The aim of this study was to prospectively evaluate the clinical benefits, in terms of improvement of analgesia and tolerability, of switching from morphine to oral methadone in patients treated with oral morphine who experience poor analgesia despite progressive increases in morphine dose or who have morphine-related adverse effects unresponsive to adjuvant medications.

PATIENTS AND METHODS

The criteria for inclusion in the study were uncontrolled pain (visual analog scale > 4) notwithstanding the titration and progressive increase of morphine doses, moderate to severe opioid adverse effects (level 3 and 4 by verbal scale) not controlled by symptomatic therapy, or both; life expectancy longer than 1 month; and informed consent. Pain intensity greater than 4 on a numerical scale from 0 to 10 is considered a valid cutoff to define a population with moderate to severe pain^{38,39} that also interferes with such functions as activity, mood, and sleep.³⁹

Exclusion criteria were brain metastases (documented by recent magnetic resonance imaging or computed tomography scan), cognitive failure (clinically evaluated), major alterations of biochemistry, poor liver and renal function, and anticancer treatment (radiotherapy, chemotherapy, or both) or pamidronate infusion 3 weeks before switching and carried on during the study period. Adjuvant analgesic drugs eventually administered with morphine (such as nonsteroidal anti-inflammatory drugs, anticonvulsants, and antidepressants) were maintained during the course of the study at the same doses and schedule.

Type of Switching and Dose Ratio Used

Switching from morphine to methadone was performed by stopping morphine and immediately substituting with methadone using a stop-and-go approach.²⁸ Also, in patients not having pain control, a switch to methadone was performed according to conversion guidelines published previously and referring to equianalgesia data.⁴⁰ The dosage of methadone was titrated for each patient.

A dose ratio of 1:4 (1 mg of oral methadone = 4 mg of oral morphine) was used for patients receiving less than 90 mg of morphine. Patients receiving 90 to 300 mg/d received methadone at a ratio of 1:8. Finally, a ratio of 1:12 was used for patients receiving morphine doses greater than 300 mg/d.

Methadone in solution form was administered every 8 hours. One sixth of the daily dose administered was used as rescue doses. Up to three extra doses per day were allowed. Subsequently, day by day, methadone doses were titrated according to the number of rescue doses administered to achieve the best balance between analgesia and adverse effects.

Data Collection and Statistical Analysis

For each patient, the primary tumor site, age, sex, and pain intensity and mechanism, as well as the type and intensity of morphine-related adverse effects, were collected. Pain intensity was measured daily

Table 1. Patient Characteristics

| | No. of Patients |
|------------------------------|-----------------|
| Age, years | |
| Mean | 60.7 |
| 95% confidence interval | 57-63 |
| Sex, male/female | 28/22 |
| Type of pain | |
| Somatic | 16 |
| Visceral | 4 |
| Neuropathic | 2 |
| Somatic-neuropathic | 14 |
| Somatic-visceral | 10 |
| Somatic-visceral-neuropathic | 4 |
| Primary tumor site | |
| Lung | 14 |
| Gastrointestinal | 8 |
| Breast | 6 |
| Gynecologic | 6 |
| Pancreas | 3 |
| Head and neck | 3 |
| Mesothelioma | 3 |
| Other | 7 |

using the patient's self-reported visual analog scale on a numerical scale of 0 to 10.

Opioid-related adverse effects such as nausea, vomiting, constipation, drowsiness, confusion, xerostomia, sweating, and myoclonus were assessed daily by a verbal Likert-type scale with four possible answers (0 = none, 1 = mild, 2 = moderate, 3 = severe). The sum of symptom intensity, called the symptom distress score (DS), was calculated before and after switching.

Switching to methadone was considered effective when the visual analog scale for pain decreased to 4 or less, and the intensity of other symptoms was reduced to a clinically acceptable level. When it was observed that opioid switching was not offering any specific clinical benefit, other therapeutic options were offered. Statistical analysis was performed using the Wilcoxon signed ranks test and the paired sample *t* test. The minimum level of significance was established at *P* < .05.

RESULTS

Fifty-two consecutive patients referred to Palliative Care Units in Palermo and Milan from July 1998 to May 2000 met the previously described criteria of eligibility on the study. Two patients were excluded from analysis because the data collected were incomplete in one patient and compliance was poor in the other.

Table 1 shows the patients' characteristics. The mean age was 60.7 years (95% confidence interval, 57 to 63 years). Twenty-eight patients were male and most of the patients had lung cancer. The patients presented different pain mechanisms. Seventeen patients were taking less than 90 mg of morphine, 30 patients were taking 90 to 300 mg of morphine, and three patients were taking more than 300 mg of morphine daily.

Ten patients were switched because of uncontrolled pain, with a visual analog scale ranging from 5 to 9. In these patients, the median dose of oral morphine taken before switching was 180 mg/d. Eight patients were switched because of moderate or severe adverse effects in the presence of acceptable pain control, and 32 patients were switched because of uncontrolled pain in addition to morphine-related adverse effects.

Switching was successful in 80% of the patients when comparing analgesic response with opioid-adverse effects, and benefit was achieved within an average of 3.65 days. With respect to the preswitching period, significant differences in pain and symptom relief were reported (Table 2). Drowsiness, nausea and vomiting, and, above all, constipation significantly decreased after opioid switching, whereas no significant changes in myoclonus, xerostomia, confusion, and sweating were reported. Eight patients did not improve their pain level sufficiently to achieve a pain intensity of at least 4 (on visual analog scale 0 to 10). In two patients, adverse effects worsened rather than improving. One of these patients refused to increase the methadone dose. Interestingly, to improve the analgesia, methadone doses had to be significantly increased after switching with respect to the calculated morphine-methadone ratio. In particular, 50% of the patients needed an increase in their methadone dose to reach an acceptable balance between analgesia and adverse effects within the average 3.65 days. The increase in the methadone dose was approximately 20% from the starting dose used.

Significant improvements in pain intensity and some symptoms were reported in patients receiving less than 90 mg/d of morphine. Confusion, constipation, and analgesia improved significantly, as well as the DS (Table 2). In patients receiving middle ranges of morphine (90 to 300 mg/d), significant reductions in pain intensity, constipation, and DS were observed. To reach this benefit, both groups required higher methadone dose than anticipated by basal calculated dose ratios.⁴⁰

A statistical approach was not attempted for the three patients who were receiving more than 300 mg/d of morphine. The first of these patients was taking 480 mg/d of morphine. Seven days after switching to methadone, pain intensity did not change and drowsiness worsened, but the patient experienced a significant improvement in constipation. The second patient was taking 800 mg/d of morphine and was switched to 66 mg/d of methadone. Doses of methadone were increased up to 80 mg/d, and acceptable pain relief was achieved in 5 days while maintaining the same level of myoclonus and drowsiness. The third patient was taking 600 mg/d of morphine with good pain control but presented with vertigo of severe intensity attributed

to the opioid. After switching to methadone, the same level of pain control was maintained without any change in the other symptoms. Thus in two instances switching was unsuccessful.

In a subgroup of 10 patients who switched to methadone because of uncontrolled pain, a significant reduction in pain intensity ($P < .005$) and a significant increase in methadone doses of an average of 33% ($P < .012$) were found after an average of 3.5 days. DS significantly decreased from 8.4 to 4.5 ($P < .0005$). One patient was able to reduce the methadone dose from the calculated 15 mg daily to 12 mg within 4 days.

Although no relevant improvements were reported in the patients who switched for a specific adverse effect, a highly significant reduction in DS—from a mean of 7.2 (range, 6.2 to 8.3) to 4 (range, 2 to 5.9)—was found ($P < .021$).

Finally, in the larger group of 32 patients, in which switching took place for both uncontrolled pain and morphine-related adverse effects, significant improvements were found in pain intensity ($P < .0005$), nausea and vomiting ($P < .031$), constipation ($P < .001$), and drowsiness ($P < .018$), but a significant increase in methadone dose of an average of 20% ($P < .004$) in an average of 3.6 days was necessary. DS significantly decreased ($P < .0005$) from a mean of 11.8 (range, 10.7 to 12.9) to 5.9 (range, 4.6 to 7.3). In one patient, the methadone dose was decreased from 22 mg to 15 mg because pain relief had been maintained at even lower doses, but no improvement was obtained with regard to constipation. No significant differences in the results were found based on pain mechanism, age, or sex.

DISCUSSION

In the last few years, data from the literature show that in advanced cancer patients with pain, the type of opioid analgesic, the route of administration, or both must be changed once or more^{3,41} so that the therapy can be tailored to the specific circumstances to improve pain control,^{4,30,42,43} reduce opioid toxicity, or both.²² However, there are very few controlled clinical trials showing what happens when switching the opioid or the route of its administration occurs.⁴⁴

It is important to underline the need for escalating doses of an opioid in the presence of inadequate analgesia. The absence of adverse effects is not an indication to switch to another opioid, as increasing the doses of the first opioid may still produce analgesia. However, the need to rapidly increase the doses may mean risking adverse effects^{22,45} or developing rapid tolerance.

For these reasons, in some patients, opioid switching may provide some therapeutic advantages. Previously reported

Table 2. Pain and Symptom Relief

| | All Patients* (N = 50) | | < 90 mg† (n = 17) | | 90-300 mg‡ (n = 30) | |
|----------------------|--------------------------|----------------------------|--------------------------|----------------------------|--------------------------|----------------------------|
| | Time of Opioid Switching | Time of Stable Opioid Dose | Time of Opioid Switching | Time of Stable Opioid Dose | Time of Opioid Switching | Time of Stable Opioid Dose |
| VAS | | | | | | |
| Mean | 6.15 | 3.06 | 5.23 | 2.76 | 6.83 | 3.2 |
| 95% CI | 5.5-6.7 | 2.5-3.6 | 3.8-6.6 | 1.6-3.8 | 6.1-7.4 | 2.5-3.9 |
| P | | .0005 | | .003 | | .0005 |
| Nausea and vomiting | | | | | | |
| Mean | 0.47 | 0.27 | 0.76 | 0.41 | 0.36 | 0.23 |
| 95% CI | 0.2-0.7 | 0.1-0.4 | 0.2-1.32 | 0.04-0.77 | 0.03-0.7 | 0.02-0.44 |
| P | | .030 | | .109 | | .157 |
| Drowsiness | | | | | | |
| Mean | 0.96 | 0.56 | 0.76 | 0.35 | 1.1 | 0.58 |
| 95% CI | 0.6-1.2 | 0.3-0.7 | 0.3-1.2 | 0.04-0.6 | 0.7-1.5 | 0.3-0.86 |
| P | | .020 | | .053 | | .052 |
| Confusion | | | | | | |
| Mean | 0.31 | 0.13 | 0.47 | 0.05 | 0.26 | 0.2 |
| 95% CI | 0.1-0.5 | 0-0.2 | 0.05-0.8 | 0-0.18 | 0-0.5 | 0-0.42 |
| P | | .067 | | .038 | | .492 |
| Constipation | | | | | | |
| Mean | 1.41 | 0.62 | 1.7 | 0.64 | 1.3 | 0.66 |
| 95% CI | 1.0-1.7 | 0.3-0.8 | 1-2.4 | 0.2-1.1 | 0.8-1.7 | 0.3-1 |
| P | | .0005 | | .009 | | .004 |
| Xerostomia | | | | | | |
| Mean | 0.45 | 0.37 | 0.58 | 0.41 | 0.4 | 0.36 |
| 95% CI | 0.2-0.7 | 0.1-0.6 | 0.07-1.1 | 0-0.8 | 0.1-0.7 | 0.06-0.6 |
| P | | .102 | | .180 | | .317 |
| Sweating | | | | | | |
| Mean | 0.19 | 0.07 | 0.47 | 0.17 | 0.06 | 0.03 |
| 95% CI | 0-0.4 | 0-0.03 | 0-1 | 0-0.37 | 0-0.2 | 0-0.1 |
| P | | .063 | | .102 | | .317 |
| Myoclonus | | | | | | |
| Mean | 0.17 | 0.11 | 0.05 | 0.17 | 0.2 | 0.03 |
| 95% CI | 0-0.3 | 0-0.2 | 0-0.18 | 0-0.44 | 0-0.4 | 0-0.1 |
| P | | .45 | | .317 | | .102 |
| Methadone dose, mg/d | | | | | | |
| Mean | 20.1 | 25.7 | 14.5 | 17 | 20.7 | 27.5 |
| 95% CI | 17.6-22.6 | 21.7-29.7 | 12.8-16.3 | 14-21.7 | 19.3-22.1 | 23.1-32 |
| P | | .0005 | | .025 | | .002 |
| DS | | | | | | |
| Mean | 10.3 | 5.3 | 10.4 | 5.1 | 10.6 | 5.3 |
| 95% CI | 9.4-11.2 | 4.4-6.3 | 8.4-12.4 | 3.3-6.8 | 9.5-11.7 | 4-6.5 |
| P | | .0005 | | .0005 | | .0005 |

NOTE. Table shows mean values, 95% confidence intervals (CI), and P values at the time of opioid switching and at the time when the objective of switching was considered to have been reached (ie, pain relief improvement and/or reduction of morphine-related adverse effects). Three patients were receiving more than 300 mg/d of morphine.

Abbreviation: VAS, visual analog scale (pain intensity).

*For all patients, a stable opioid dose was achieved at a mean of 3.6 days (range, 2.7 to 4.5 days).

†For patients receiving less than 90 mg of morphine before switching, a stable opioid dose was achieved at a mean of 2.8 days (range, 2.1 to 3.4 days).

‡For patients receiving 90 to 300 mg of morphine before switching, a stable opioid dose was achieved at a mean of 4 days (range, 2.6 to 5.3 days).

results on opioid switching from morphine to methadone have indicated dose ratios between such opioids.^{28,40,43,46,47} According to both prospective and retrospective studies, the doses of methadone to be administered are inversely correlated with the morphine dose previously administered. In

other words, the ratio between morphine and methadone is higher in patients receiving higher doses of morphine.⁴⁰

In clinical practice, the most common indication for opioid switching is related to an imbalance between analgesia and adverse effects. In our study, significant improve-

ments were found in pain intensity and in some morphine-related adverse effects—including nausea and vomiting, constipation, and drowsiness—although a significant increase in the methadone dose was necessary in most cases. In approximately 20% of the patients, opioid switching failed despite increasing the dose of methadone. The causes of this failure are difficult to define and may be related to the patients' characteristics or the alternative opioid used, as well as the pain mechanism. Despite a rapid switching, stop-and-go, the period needed to achieve better analgesia using the ratios suggested from the previous equianalgesic study⁴⁰ was relatively prolonged, taking 3 to 4 days, and this result was obtained by increasing the doses of methadone in 50% of the patients.

Therefore, in the presence of uncontrolled pain, the morphine to methadone conversion as described by equianalgesic tables may be inadequate or unreliable in predicting pain relief. Many of these patients will not be able to obtain adequate analgesia within 4 days without increased doses. Although these ratios can be useful, patients with uncontrolled pain and opioid adverse effects require higher than anticipated doses based on previously published data.⁴⁰ According to the results of the present study, starting doses of methadone should be increased by approximately 20% to 30% with respect to the equianalgesic calculated dose ratios. Considering the pharmacokinetics of methadone, the time to reach an effective plasma concentration requires an immediate priming dose, which can possibly be reduced once a steady state is obtained.⁴⁸

No relevant changes were observed in eight patients who switched because of specific adverse effects. However, this was probably due to the presence of different specific symptoms, so it was impossible to reach a significant value because of the low number of patients in this group. However, DS was significantly reduced, confirming improvement in the symptom pattern intensity after opioid switching. For the patients with good pain control with morphine, the morphine/methadone dose ratio used in this study can be considered adequate according to the results obtained in the equianalgesic study of Ripamonti et al.⁴⁰

Constipation seems to be the symptom most frequently improved after the opioid switch. This may be due to different opioid affinities for gastrointestinal mu receptors or the lipophilic nature of methadone. Different reports have shown that methadone causes less constipation than morphine^{49,50} and reduces the use of laxatives.⁵¹

All subjective results regarding pain and adverse effects should be interpreted with caution because of the unblinded nature of this study. Unlike other reported series of patients,⁷ refractory pain with adverse effects can occur at relatively low doses of morphine. This observation was also reported in another study.⁹ Therefore, opioid switching is indicated even in patients receiving low doses of morphine

if there are excessive adverse effects for the degree of analgesia. The advantages reported after opioid switching were observed in patients taking less than 90 mg/d of morphine and also in those taking between 90 and 300 mg/d. In patients with uncontrolled pain and adverse effects, a 20% increase in the equianalgesic dose of methadone should be used as the initial dose to achieve rapid pain control.

With respect to the dose ratio used, only two patients were able to reduce their methadone dose during the study. It has also been suggested that methadone, known to have the *N*-methyl-D-aspartate antagonist activity, may be effective in controlling neuropathic pain where other opioids sometimes fail. However, we were not able to find any specific improvement in patients with neuropathic pain with respect to patients with other pain mechanisms, although the limited number of patients does not allow us to draw conclusive information. Previous experience failed to show a difference in pain control between methadone and morphine in patients with neuropathic or nonneuropathic pain syndromes.⁵²

For most patients with cancer who have poorly controlled pain, are experiencing adverse side effects with morphine administration, or both, a switch to methadone is a valid therapeutic option. The results of our study confirm that the starting dose of methadone still remains difficult to calculate in the clinical setting of poor pain control. However, caution in switching to methadone is always necessary for clinical purposes. Higher doses of methadone in the first days of treatment are required with respect to published equianalgesic dose ratios to reach an acceptable analgesia in a short time. Initial higher doses of methadone are not dangerous, because the pharmacokinetics of methadone require priming before achieving a pharmacologic effect. However, appropriate monitoring of methadone dosing is necessary in the days that follow, when methadone accumulation could occur. Caution in switching to methadone is particularly necessary for North American physicians who use higher doses of opioids than European physicians. In fact, high-dose methadone may be dramatically more potent than observed in this study. Future double-blind studies are necessary to better define the dose ratio between morphine and methadone in patients with poor pain control. Moreover, the efficacy as well as the duration of such efficacy of opioid switching with respect to route switching and the benefit of symptomatic drugs should be compared in patients who present poor pain control, opioid-related adverse effects, or both. Possible interaction between methadone and the adjuvant medications used for treating neuropathic pain, which potentially may interfere with the pharmacokinetics and pharmacodynamics of methadone, should also be explored.

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