Rapid Switching From Morphine to Methadone in Cancer Patients With Poor Response to Morphine

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Purpose: **The aim of this study was to evidence the clinical effects of an abrupt substitution of morphine with methadone using a fixed ratio of 1:5 in patients for whom limiting adverse effects occurred before adequate analgesia was achieved with oral morphine.**

Patients and Methods: **A cross-sectional prospective study was carried out on 24 consecutive patients who were switched from oral morphine to oral methadone because they experienced substantial adverse effects that limited further increase in morphine dose. A fixed conversion morphine-to-methadone ratio of 5:1 was chosen. Subsequently, doses were changed according to clinical need, with frequent visits or phone contacts. Pain and symptom intensity, preswitching doses of morphine, initial and subsequent doses of methadone, and survival were recorded.**

Results: **A significant decrease in pain and symptom intensity was found within 24 hours after the substitution took place. The switching was effective in most patients (19 of 24), although five patients required alternative treatments. No significant changes in methadone dose were reported in the 3 days after switching. Methadone dose was significantly higher in patients who had lower preswitching doses of morphine and vice versa. No relevant complications were reported.**

Conclusion: **A rapid substitution of morphine with methadone using an initial fixed ratio of 5:1 is a safe and effective method for improving the balance between analgesia and adverse effects in cancer patients with poor morphine response. An appropriate system of patient monitoring is necessary, because further changes in dose may be required according to clinical needs.**

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OPIOIDS ARE THE MAINSTAY of moderate to severe cancer pain management. Morphine is usually considered the preferred drug for the treatment of severe cancer pain because of its wide availability, varied formulations, and well-characterized pharmacologic properties. However, morphine may produce adverse effects before adequate analgesia is achieved. Therapeutic response is a continuum phenomenon that can be affected by several factors and should not be based on one opioid.[1,2]

Previous experiences have shown that a failure to respond to one opioid does not mean failure to respond to all opioids, and opioid switching may allow pain control to be achieved without producing adverse disabling effects.[3-10] There are two important indications for choosing an alternative to morphine. One of these is when, during continuous use, intolerable CNS adverse effects develop and reducing the dose has no effect or leads to increased pain. The second is when dose-limiting adverse effects of morphine occur during opioid escalation, despite the use of adjuvants.

The keystone to the rationale behind opioid substitution is incomplete cross-tolerance, although the exact reason why opioid substitution is successful remains unclear. In some patients, pain that is poorly responsive to morphine may arise because of the development of analgesic tolerance to morphine, while tolerance to adverse effects does not develop to the same extent. As a consequence, the escalating dose of morphine may reach a level at which the adverse effects become predominant. Thus the benefit of a switch from one opioid to another could depend on the cross-tolerance to the analgesic effects being less than the cross-tolerance to the adverse effects. The disadvantage is that it is impossible to know in advance whether the balance between analgesia and adverse effects will be more acceptable after opioid substitution. In addition, the dose of the selected alternative opioid may be uncertain, as it will depend on a series of factors, including individual response, pain mechanism, and degree of cross-tolerance.[11]

There is no standardization in the substitution modalities and dose ratios to be used. A reduction in the calculated equianalgesic dose equal or superior to 75% has been recommended in respect to the opioid previously administered, to take account of the possible cross-tolerance among different drugs.[7,12] More recently, different protocols have been suggested with methadone. They include a fixed dose of methadone at one tenth of the previous morphine dose

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with a maximum dose of methadone of 30 mg administered as required, but not more frequently than every 3 hours. After 6 days, the amount of methadone taken in the last days is calculated and then converted on a daily basis with a regular 12- hour regimen.[13] A gradual switch-over has been suggested when switching to methadone. The switching is carried out over a period of 3 days, with the previous opioid being progressively stopped while introducing methadone (progressive substitution of one third of the previous opioid, using an equianalgesic dose ratio of 1:10).[10] However, these approaches may take time or allow a slow elimination of opioid metabolites, if they are considered to be responsible for some adverse effects. In a previous study evaluating the analgesic and adverse effects and the doses of methadone in comparison with morphine, patients reported an escalation ratio in milligrams between morphine and methadone of approximately 1:5.[14] The aim of this study was to find out whether a rapid substitution of morphine with methadone at 20% (ratio of 1:5) of the previous morphine dosage could improve the opioid response in terms of global effect (ie, balance between analgesia and adverse effects) in patients with poor pain control who experienced dose-limiting adverse effects with morphine.

PATIENTS AND METHODS

From June 1996 to June 1998, a prospective study was carried out in a sample of 24 consecutive advanced cancer patients (3% of the total admitted for home palliative care or to an outpatient pain clinic who were on morphine therapy for the management of cancer pain) for whom it was necessary to switch opioid therapy due to an unacceptable balance between analgesia and adverse effects. Patients with known coexisting liver or renal disease or a low performance score ($<$ 40 on the Karnofsky scale) at referral were excluded. Patients had been treated with a slow-release morphine preparation administered two to three times a day at different dosages. Further escalation, progressively increasing the dose every 2 to 3 days by 30%, had been limited by the occurrence of adverse effects, such as drowsiness, nausea and vomiting, confusion, and dry mouth. Adjuvant drugs had been administered unsuccessfully. The patients were switched to oral methadone at 20% of the previous dose of morphine, while morphine was discontinued. The methadone daily dose was divided into three doses daily and a further dose as needed. At that point, the patient and relatives were instructed to manage pain with a rescue dose taken as needed or to contact the medical team in case of any problem. Daily telephone contacts and two to three visits per week for home care patients (once a week for ambulatory patients) were maintained. Adjuvant drugs, previously administered to control symptoms caused by illness or treatment, were continued at the same doses during the substitution process. Nonopioid analgesics were also continued, if previously administered, at the same doses. The dose of the drug was subsequently kept as low as possible according to the clinical needs or titrated to achieve an acceptable analgesia with minimal adverse effects. No patient received anticancer therapy during the course of the study.

Age, sex, primary cancer and known metastases, performance status, and morphine dose at time of substitution were recorded. The following data were also recorded before switching (T0) and then for 3 days after the substitution was complete (T1, T2, T3):

- Methadone dose
- Adjuvant medications previously used to improve analgesia or reduce adverse effects
- Symptoms associated with opioid therapy or commonly present in advanced cancer patients, such as nausea and vomiting, drowsiness, confusion, xerostomia, and so on, using a scale from 0 to 3 (0 = ''not at all,'' 1 = ''slight,'' 2 = ''a lot,'' and 3 = ''awful'') and assessed by the patient (a distress score was calculated from the sum of symptom intensity)
- Pain intensity, measured using the patient's self-reported Visual Analog Scale (VAS) on a numerical scale of 0 to 10 Pain syndromes, as considered on the basis of clinical history, anatomical site of primary tumor and known metastases, physical examination, and investigations when available

Data were analyzed using the Kruskal-Wallis one-way analysis of variance and the Wilcoxon signed rank test when required to compare differences in groups. χ^2 test was used to compare frequencies. Multivariate analysis of variance was also used for trend comparisons. Differences resulting in *P* values of less than .05 were considered to be statistically significant.

RESULTS

The characteristics of patients are reported in Table 1. Drowsiness was the main symptom that limited further opioid escalation, with a severity graded as 2 (''a lot'') in 21 patients. Most patients (n = 14) were on a relatively low dose of daily oral morphine ($\leq$ 90 mg). A significant decrease in pain intensity was observed at the different times of study. At T1, 13 patients achieved a substantial benefit in pain relief, with the VAS being reduced by two points, and 11 patients achieved a VAS of 4 or less. The switching was considered effective within 3 days in 19 patients, when the global effect on the balance between analgesia and adverse effects was taken into consideration. Most of these patients achieved an improvement in adverse effects, as demonstrated by the significant reduction in symptom intensity (Table 2). Specifically, relevant improvements were obtained in central adverse effects, such as drowsiness and confusion. Also, gastrointestinal symptom intensity substantially improved, although no differences in dry mouth were observed. The mean distress symptom score significantly decreased after opioid substitution (Table 2). Five patients,

Table 1. Patient Characteristics

Age, mean ± SE (years)	67 ± 2
Sex, male/female	11/13
Karnofsky performance status, median	50
Survival, mean ± SE (days)	48 ± 6
Preswitching morphine dose, mean (mg)	125
Maximum methadone dose, mean (mg)	32

Table 2. Symptoms and Methadone Dose at the Time Intervals Studied

	T0	T1	T2	T3
Pain intensity	5.7	4.4‡	3.9‡§	3.8‡§
Drowsiness	1.9	1.3‡	1.2‡	1.1‡
Confusion	0.7	0.4‡	0.4‡	0.3‡
Nausea and vomiting	1.1	0.8*	0.8*	0.7*
Dry mouth	1.4	1.4	1.5	1.5
Distress score	5.1	3.9†	3.9†	3.6†§
Methadone dose, mg	25.6	27.8	25.7	25.7

Abbreviations: T0, before switching; T1, after 1 day; T2, after 2 days; T3, after 3 days.

*$P < .05$ versus T0.

†$P < .01$ versus T0.

‡$P < .0005$ versus T0.

§$P < .05$ versus T1.

however, required further alternative treatment (subcutaneous morphine in four patients and spinal treatment with local anesthetics, morphine, and clonidine in one patient), because pain intensity and distress scores were unchanged or worse after 3 days, despite receiving escalating doses of methadone. Of these, one patient started subcutaneous morphine at T2.

No significant variation in mean methadone dose was reported after switching. Specifically, doses of methadone were reduced, remained stable, or were increased in six, seven and 11 patients, respectively, in the 3 days of the study. Patients who needed a reduction in methadone dose had received higher preswitching doses of morphine (median, 256 mg; range, 120 to 400 mg), whereas patients who had received lower preswitching doses of morphine (median, 67 mg; range, 30 to 90 mg) required increased methadone doses (Table 3). However, one patient who was treated with 200 mg of morphine daily required increasing doses of methadone. This means that doses also could be increased in patients who had received higher doses of morphine. The trend in methadone dose 3 days after switching was significantly different between patients who had received preswitching doses of morphine that were greater than or less than 90 mg ($P < .001$, multivariate analysis of variance repeated measures analysis). Patients who achieved immediate pain relief and did not require changes in methadone dose had received a mean preswitching morphine dose of 107 mg (range, 30 to 180 mg).

Table 3. Survival, Morphine Dose, and Methadone Dose

	Preswitching Morphine Dose	
	< 90 mg	> 90 mg
No. of patients	14	9
Age, mean (years)	65	69
Survival, mean (days)	51	44
Morphine dose, mean (mg)	59	224
Methadone dose at T0, mean (mg)	14	45
Methadone at T3, mean (mg)	20	33

The mean maximum methadone dose until death was 32 mg for a mean survival of 48 days. Therefore, the calculated escalation index (ie, the mean increase of methadone dosage in milligrams, using the formula of maximum dose minus the starting dose divided by days) of methadone was quite low (0.1 mg/d) when compared with that reported with morphine in previous studies.[14] Regarding the influence of the pain mechanism, patients who had neuropathic pain had a higher pain intensity at T0 and received a significantly higher methadone dose at T1 in comparison with patients with nociceptive pain ($P < .05$). No other significant differences were found. Drugs used as adjuvants before switching are listed in Table 4.

DISCUSSION

The high variability of frequency and the different indications for opioid substitution that have been reported in the literature probably depend on the setting of the study.[15,16] After an unsuccessful attempt with adjuvant drugs to reduce opioid-induced adverse effects, opioid substitution or a change in the route of administration are commonly indicated. Severe drowsiness was the most frequent indication for opioid substitution. However, no stimulants were used as adjuvant drugs because they are relatively unavailable in our country. In this study in an unselected (home care) and more selected (outpatient pain clinic) population, opioid substitution took place in approximately 3% of patients because of difficult situations in which further opioid escalation was limited by the occurrence of adverse effects, despite the use of adjuvant drugs. Patients with advanced disease or short life expectancy were excluded from the study.

Problems arise when switching from one opioid to another, with the dose of the new drug being titrated according to the indication of the published equianalgesic tables. Such tables report different dose ratios between oral morphine and oral methadone and often come from single-

Table 4. Adjuvant Drugs Used Before Switching

Drug	No. of Patients
Nonsteroidal anti-inflammatory drugs	17
Prostaglandins	10
Ranitidine	4
Omeprazole	1
Senna	15
Lactulose	10
Cisapride	1
Metoclopramide	10
Haloperidol	6
Ondansetron	2
Corticosteroids	3
Amitriptyline	4
Carbamazepine	2

dose studies.[17] However, the setting of cancer pain management is different because most patients are commonly on chronic opioid treatment and require administration of multiple drugs. Our results show that switching abruptly from morphine to methadone is an effective, simple, and safe modality. This method can be used even at home with a relatively small amount of risk, if continuous monitoring is performed by an experienced team. No serious complications were found among patients in this study.

A different adverse effect profile may exist among different opioids. Rapid switching allows patients to benefit from the asymmetric tolerance that exists between different classes of opioids and also may allow for a faster elimination of toxic metabolites, which are often believed to be responsible for the unfavorable clinical picture.[1,18] The ratio that was selected to find the initial dose of methadone is derived from a previous experience in which different requirements in time of these two different opioids were found, with a ratio of approximately 1:5.[14] The extra value required for uncontrolled pain was attributed to other potential factors, including extra-opioid effects, such as the NMDA-antagonist activity, higher efficacy, and pharmacokinetic properties of methadone. The possible improvement in adverse effects was attributed to a drug-selective effect as well as a rapid morphine metabolite elimination. No attempts to induce diuresis with hydration were made.

The use of a fixed equianalgesic ratio between morphine and methadone may be questionable, because it is now well recognized that the equianalgesic dose ratio is correlated with the previous dose of morphine, methadone being more potent than expected in patients who had been receiving high doses of morphine.[17-21] Unlike previous studies of patients with controlled pain in which several days were required before achieving equianalgesia when switching from morphine to methadone,[18-21] the approach used in this study was intended to shorten the time required to achieve a steady state in a very simple way, with better analgesia and fewer adverse effects. Indeed, the reason for switching was not to find equianalgesia but to remedy poor pain control in the presence of distressing symptoms that limited further escalation in morphine dose, so that potential extra doses would need to achieve an extra-analgesia in a short time to avoid inconvenient and prolonged suffering on the part of patients. Thus the intention was to find a simple protocol to resolve difficult problems encountered in clinical practice. The feasibility of this method was confirmed by the finding that approximately 30% of patients did not require changes in methadone dose, and no significant variations in mean methadone dose have been found after switching. A clear improvement of the clinical condition was observed in most patients within 1 day. However, the trend of methadone requirements was higher among patients who had previously received lower doses of morphine with respect to the methadone doses that were initially chosen using a fixed ratio of 1 to 5. A continuous contact with patients and their families was maintained to monitor the balance between analgesia and adverse effects, which eventually allowed the dose to be changed as appropriate. In patients who had received higher doses of morphine, doses of methadone were more frequently reduced, without causing subsequent complications. Patients who receive higher opioid doses might potentially present with more serious sedation or even respiratory depression.[22] However, methadone toxicity caused by accumulation is more likely to occur after several days of administration at high doses rather than in the first days of treatment, according to conversion ratios calculated with previous equipotency tables and based on single-dose studies, recently reported.[23-25] Methadone should be administered frequently during the first days of treatment, because approximately 48 hours may be required to approach steady-state blood levels due to the large initial volume of distribution.[26] After achieving an adequate level of analgesia, the long elimination half-life of methadone greatly reduces the need to increase the doses of methadone that are required to maintain analgesia.[27] This observation also explains why long periods are required before achieving analgesia using a patient-controlled method. Although previous studies suggest that a patient-controlled analgesia with methadone should be useful in titrating methadone or switching from morphine to methadone,[13,28] the major drawback of this approach is the waiting period before pain control is achieved, which can be overcome with an appropriate priming using fixed doses, as reported previously.[29]

However, five patients (approximately 20%) did not benefit from switching to methadone and required alternative and more intensive treatments. Of interest, these patients did not have a neuropathic component in their pain. The mechanism of pain had almost no influence, although the low number of patients prevents us from drawing any definite conclusions.

The broad spectrum of activity makes methadone unique in reversing opioid tolerance and suppressing the effect of central sensitization, such as in cases of difficult pain syndromes, namely neuropathic pain.[27] Moreover, opioid response may also be drug-selective. It has been suggested that the degree of tolerance is inversely related to the reserve of spare receptors. The larger the receptor reserve, the greatest the intrinsic efficacy. Methadone has been shown to

have much higher efficacy than morphine, due to a higher receptor reserve, and to not be influenced by renal disease.[13] Methadone has been safely used in a way similar to that of morphine, without increased difficulties.[14,29,30] The administration of oral methadone every 8 hours, both in the titration phase and during the treatment of chronic pain, was effective, with no signs of accumulation or severe adverse effects. Methadone, if titrated against the pain according to the need in an individualized manner, may also be effective in older populations, with a low potential for adverse effects. This would allow for a reduction in the use of other analgesics that have high potential for adverse effects in older patients, who are recognized as a population at risk.[31] Fears regarding methadone administration may reflect an unbalanced focus on risks associated with inappropriate use as opposed to benefits and should not deter clinicians from the appropriate use of this agent.

We recognize that morphine is often prescribed inappropriately in the hospital setting, and there may be the risk of further difficulties when inexperienced staff prescribe new drugs with which they are unfamiliar.[14] However, it would be more hazardous to introduce other treatment measures in complicated situations, such as neurologic impairment accompanied by uncontrolled pain. As with any treatment for any other disease (hypertension, cancer, and so on), we should have an alternative for providing a better balance between analgesia and adverse effects, without the fear that accompanies a new situation. This should be managed with more attention until the new treatment becomes familiar. A limitation of this study could be a lack of blinding. This requires a more complex approach that is difficult to attempt in advanced cancer patients in which the principal goal is the improvement of pain. Pain intensity measurements in this study should be interpreted with extreme caution. The findings of this study should not be generalized to patients who receive extremely high doses of morphine, such as those reported in North American studies.[19,20,22,32]

Further controlled studies are necessary to establish the role of opioid substitution in comparison with adjuvant treatment or changing the route of opioid administration and to explore the possible advantages of methadone over morphine in the treatment of neuropathic pain.

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