Switching From Morphine to Oral Methadone in Treating Cancer Pain: What Is the Equianalgesic Dose Ratio?

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Purpose: To define the dose ratio between morphine and methadone in relation to the previous morphine dose and the number of days needed to achieve the same level of analgesia in a group of patients with advanced cancer with pain who switched from morphine to oral methadone.

Patients and Methods: A cross-sectional prospective study of 38 consecutive cancer patients who switched from morphine to oral methadone was performed. The intensity of pain before, during, and after the switching period was assessed through a four-point verbal Likert scale. The relationship between previous morphine dose and the final equianalgesic methadone dose, dose ratio between morphine and methadone, and the number of days required to achieve equianalgesia have been examined by means of Pearson's correlation coefficient, scatter plots, and Cuzick's test for trend respectively.

Results: Before the switch, the median oral equivalent daily dose of morphine was 145 mg/d; after the switch, the median equianalgesic oral methadone dose was 21 mg/d. A median time of 3 days (range, 1 to 7 days) was necessary to achieve the equianalgesia with oral methadone; the lower the preswitching morphine dose, the fewer days necessary to achieve equianalgesia with oral methadone ($P < .001$). Dose ratios ranged from 2.5:1 to 14.3:1 (median, 7.75:1), which indicated that, in most cases, the dose ratio was much higher than that suggested by the published equianalgesic tables. A strong linear positive relationship between morphine and methadone equianalgesic doses was obtained (Pearson's correlation coefficient, 0.91). The dose ratio increased with the increase of the previous morphine dose with a much higher increase at low morphine doses.

Conclusion: The results of our study confirm that methadone is a potent opioid, more potent than believed. Caution is recommended when switching from any opioid to methadone, especially in patients who are tolerant to high doses of opioids.

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OPIOIDS, of which morphine is the most commonly used, are the mainstay of moderate-to-severe cancer pain management.[1] In approximately 80% of the patients with advanced cancer-related pain, the type of opioid analgesic and/or the route of administration has to be changed one or more times[2-4] so the therapy is tailored to meet specific clinical circumstances, improve pain control,[5-7] and/or reduce opioid toxicity.[8] The individual responses to different opioids are extremely variable and when patients fail to obtain adequate pain relief at the maximum-tolerated doses of morphine, they may benefit from an alternative opioid drug.[7]

Among opioids, methadone is considered a good alternative to mu-opioid receptor agonist drugs because of its excellent oral[9] and rectal absorption.[10] analgesic efficacy,[11-13] higher potency, lower cost, longer administration intervals,[14] no active metabolites that can accumulate in patients with renal failure, and the potential to control pain no longer responsive to morphine, hydromorphone, and fentanyl.[6,8,15,16] Thus, methadone can have a major role in the treatment of cancer pain. Its use, however, is complicated by limited knowledge of the correct equianalgesic dose/ratio versus other opioids when switching in non–opioid-naive patients.

During the switch from one opioid to another, the dose of the new drug is titrated according to the indications of the published equianalgesic tables, in which dose ratios between oral morphine and oral methadone are 1:1,[17] 3:1 (ie, 3 mg of oral morphine:1 mg of oral methadone),[18] and 4:1 (ie, 4 mg of oral morphine:1 mg of oral methadone).[19] The dose equivalence reported in these tables is derived from equianalgesic studies conducted on opioid-naive subjects treated with single-drug doses, in which morphine and methadone show approximately the same analgesic potency,[20] whereas cancer patients are treated chronically and, during a switch, are already tolerant to opioids.

Because there is an incomplete cross-tolerance among these drugs, some investigators recommend the use of a lower equianalgesic dose during the switch and retitration according to response.[19] However, this is a rather vague indication and only partially applicable.

According to other investigators,[21] during the switch from morphine to methadone, a reduction in the calculated equi-

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analgesic dose of 75% or greater has been recommended in regard to the opioid previously administered. This indication is more definite than the former; however, it still does not consider the preswitching morphine dose level.

According to Morley and Makin,[22] the previous opiate should be stopped and replaced by a fixed dose of methadone that is one tenth of the actual or calculated equivalent oral morphine dose when the 24-hour dose is less than 300 mg, or a fixed dose of 30 mg of methadone when the 24-hour dose is greater than 300 mg. This fixed dose should then be administered orally as required, but not more frequently than 3 hourly for 6 days. On day 6, the amount of methadone administered over the previous 2 days is noted and converted into a regular 12-hourly regimen. In this case, there is a wide range of doses, up to 300 mg of equivalent oral morphine dose, in which the equianalgesic dose between morphine and methadone is always 10:1.

At the Palliative Care Unit in Edmonton, Canada, the switch is performed over 3 days; the morphine dose is reduced daily and replaced with oral or rectal methadone every 8 hours, using a titration equianalgesic dose ratio of 10:1. The dose of methadone is increased only if the patient experiences moderate-to-severe pain, and transient episodes of pain are managed with the administration of short-acting opioids, if required.[23,24]

From all the different published indications regarding the modalities of the switch and the dose ratios to be used for the achievement of equianalgesia, it is obvious that there is no standardization in this practice.

Moreover, the switch is not easy in clinical practice because, for patients who are chronically treated for pain, there is a relationship between the preswitching morphine dose and the postswitching dose of methadone necessary to obtain at least the same analgesic effect. Interestingly, the dose of methadone required to achieve the equianalgesic effect is not only lower, but unexpectedly much lower in patients who previously received very high morphine doses.

The aims of this study were to define the dose ratio between morphine and methadone, the variation of the dose ratio in relation to the previous morphine dose, and the number of days needed to achieve at least the same level of analgesia in a group of advanced cancer patients with pain who switched from morphine to oral methadone.

PATIENTS AND METHODS

Patients

In a cross-sectional prospective study performed at the Pain Therapy and Palliative Care Division of the National Cancer Institute of Milan (Italy) from January to December 1997, we evaluated all consecutive cancer patients who switched from morphine administered by oral, subcutaneous, or intravenous routes to oral methadone in solution form. For the purpose of this study, only the patients who presented the following criteria were considered: nociceptive pain; collaboration; normal liver and kidney function; a stable dose of morphine during the week before the switch and a stable dose of methadone in the first week after the end of the switching period; no radiotherapy, chemotherapy, or any change in hormone therapy for at least 2 weeks before the switch, during the switching period, and for the first week after the end of the switching period.

Data Collection

The following data were collected for each patient: age; sex; primary tumor sites; intensity of pain before, during, and after the switch; the dosage (in milligrams daily) and route of morphine administration before the switch; the final equianalgesic dose of oral methadone (in milligrams daily); the number of days needed to achieve equianalgesia; and the reasons for the switch.

For comparative purposes, all morphine doses were calculated as the oral equivalent daily dosage. A conversion ratio of 3:1 was used for oral morphine doses versus subcutaneous and intravenous morphine (3 mg of oral morphine:1 mg of morphine administered subcutaneously or intravenously).[25,26]

Pain Assessment

The intensity of pain was reported weekly by the patient using a Therapy Impact Questionnaire (TIQ).[27,28] The TIQ is a validated tool used to evaluate quality of life. It includes 36 items to assess the degree of discomfort experienced and evaluated subjectively by the cancer patient through a verbal Likert scale, with four possible answers (not at all, 1; slight, 2; a lot, 3; or very much, 4). The period of reference is the previous week. Of the 36 items on the TIQ, answers with regard to pain were included in this study. In regard to symptoms other than pain, morphine or methadone-related adverse effects were considered when the patient reported a direct association of the symptoms with opioid administration.

During the switching period, the pain intensity and the opioid-related adverse effects were assessed daily. This evaluation was only performed for a continuous assessment of pain and other symptoms, with the aim of modifying the daily dose of methadone, and it was not included in data analysis.

Switching Modality

The switch was performed empirically; based on our clinical experience, we reduced the daily morphine dose by at least 30% over the first 24 hours and replaced it with oral methadone in solution form administered every 8 hours, using a dose ratio of 4:1 for patients who received 30 to 90 mg daily of morphine, a dose ratio of 6:1 for patients who received 90 to 300 mg daily, and a dose ratio of 8:1 for those who received 300 mg daily or more. During the second day, if pain control was good, the patient underwent a further decrease in the morphine dose. The methadone dose was only increased if the patient experienced moderate-to-severe pain. Transient episodes of pain were managed with intermittent rescue doses of short-acting opioids. During day 3, morphine was discontinued and the patient was maintained on methadone administered every 8 hours plus 10% of the daily methadone dose as an extra oral dose for breakthrough pain. The methadone dosage was titrated day by day until pain relief was achieved.

Data Analysis

Results are presented in medians, lower-upper quartiles (Q1 to Q3), and the ranges observed for the following data: age, previous morphine dose, final oral methadone dose at equianalgesia, pre- and postswitching

pain intensity, number of days to achieve equianalgesia with oral methadone, and dose ratio between morphine and methadone.

Scatterplots have been used to show the relationship between previous morphine dose and final equianalgesic methadone dose; in a the first plot, the values obtained were compared with those indicated in the literature at ratios of 1:1,[17] 3:1,[18] and 4:1.[19] A second scatterplot of the dose ratio of morphine/methadone versus the previous morphine dose was used to better describe the relationship between the equianalgesic doses of the two opioids, also evaluated by Pearson's correlation coefficient.

Cuzick's nonparametric test for trend[29] was performed to study the association between previous morphine doses and number of days required to reach equianalgesia.

RESULTS

From January to December 1997, 49 patients switched from morphine to methadone. Eleven of these patients were excluded from the study because they were not able to maintain a stable morphine dose in the week before the switch (six patients) or they were undergoing radiotherapy (three patients), chemotherapy (one patient), or a new hormone therapy (one patient) during the switching period.

Table 1 lists the age, sex, primary tumor sites, routes of morphine administration, and reasons for switching for the 38 patients on the study.

Table 1. Patient Characteristics

	No.	%
Sex		
Female	21	55.26
Male	17	44.74
Age, years		
Median	60.5	
Q1-Q3	55-66	
Primary tumor sites		
Head and neck	4	10.5
Lung	9	23.7
Breast	12	31.9
Female genitourinary	2	5.2
Sarcoma	2	5.2
Colon, rectum	4	10.5
Pancreas	2	5.2
Bladder	1	2.6
Prostate	1	2.6
Lymphoma	1	2.63
Morphine administration routes before the switch		
Oral slow-release formulation	28	
Continuous subcutaneous infusion	9	
Continuous intravenous infusion	1	
Reasons for the switch		
Poor pain control at dose-limiting toxicity of morphine	6	
Difficulty swallowing tablets	7*	
Placement of an NGT for feeding	5*	
Mild confusion or drowsiness	10	
Change from parenteral morphine	10	

Abbreviation: NGT, nasogastric tube.
*Methadone is the only opioid available in solution form in Italy.

Before the switch, 28 patients were receiving oral morphine and 10 patients were receiving parenteral morphine. All the patients who received parenteral morphine could be treated again by oral route and methadone was chosen to reduce the opioid dose. Because of difficulty swallowing tablets or because they had a nasogastric tube for feeding, 12 patients had to receive an opioid in solution form, and methadone is the only one available in Italy. Ten patients switched to methadone because they presented mild but uncomfortable morphine-related adverse effects, such as confusion and drowsiness. Six patients switched because of poor pain control at dose-limiting toxicity of morphine (Table 1).

Median pain intensity during the week before the switch was equal to the median of the first postswitching week (Table 2). Before the switch, the oral equivalent daily dose of morphine ranged from 30 to 800 mg daily (median, 145 mg daily). After the switch, the equianalgesic oral methadone dose ranged from 9 to 60 mg daily (median, 21 mg daily). A median time of 3 days (range, 1 to 7 days) was necessary to achieve equianalgesia with oral methadone. The median dose ratio between morphine and methadone was 7.75 (range, 2.5 to 14.3).

No patients discontinued methadone treatment because of unwanted adverse effects. The patients with constipation during morphine treatment continued to report this symptom during methadone treatment. The patients who presented uncomfortable confusion or drowsiness during morphine treatment had a downward trend of symptoms during methadone treatment. This improvement may have been caused by an appropriate hydration therapy.

Figure 1 shows the final methadone doses required to achieve equianalgesia versus the morphine doses previously administered, in comparison with the three equianalgesic dose ratios reported in the literature: 1:1,[14] 3:1,[15] and 4:1 ratio,[16] represented by three straight lines. Note that no patient on the study underwent a dose ratio of 1:1, and that the dose ratio ranged from 2.5:1 to 14.3:1 (14.3 mg of morphine:1 mg of methadone), with a median of 7.75:1,

Table 2. Pre- and Postswitching Clinical Results

	Median	Q1-Q3	Range
Previous morphine dose, mg/d (oral equivalent daily dose)	145	80-240	30-800
Final oral methadone dose, mg/d (at the equianalgesia)	21	15-30	9-60
Preswitching pain intensity	2	2-2	1-3
Postswitching pain intensity	2	2-2	1-3
No. of days to achieve equianalgesia with oral methadone dose	3	2-4	1-7
Equianalgesic dose ratio between morphine and methadone	7.75	5-10	2.5-14.3

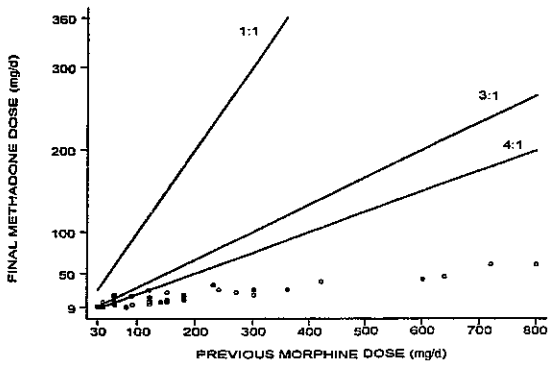

Fig 1. Final doses of methadone required to achieve equianalgesia versus the morphine dose administered before the switch compared with the three equianalgesic dose ratios reported in the literature (1:1, 3:1, and 4:1), represented by three straight lines.

which indicated that, in most cases, the dose ratio was much higher than that suggested by the published equianalgesic tables. The strong linear positive relationship between morphine and methadone equianalgesic doses seen in Fig 1 and also confirmed by a Pearson's correlation coefficient of 0.91 can be examined more deeply in Fig 2. In this figure, the plot shows that the dose ratio increases at the increase of the previous morphine dose and that the increase is much higher at low morphine dosages (30 to 300 mg), whereas the dose ratio increases more slowly with doses of morphine greater than 300 mg. This finding is not compatible with the hypothesis of a constant dose ratio in relation to the previous morphine dose.

Table 3 shows that in respect to the dose ratio between morphine and methadone empirically used during the switching phase, the final median dose ratio of methadone obtained was 3.7:1 for patients who received 30 to 90 mg daily of morphine (our dose ratio was 4:1), 7.75:1 for those who

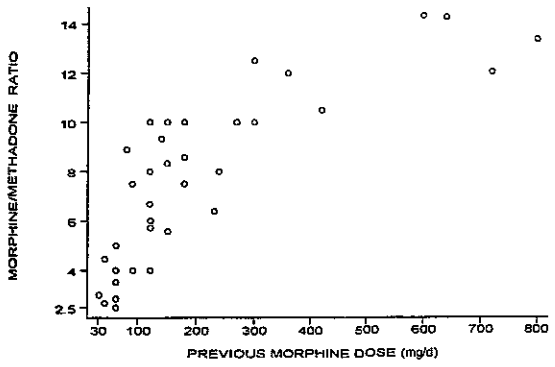

Fig 2. Equianalgesic dose ratio between morphine and methadone versus previous morphine dose (in milligrams daily).

Table 3. Equianalgesic Dose Ratios at Different Previous Morphine Doses

Preswitching Morphine Dose (mg/d)	30-90	90-300	≥ 300
No. of patients	10	20	8
Dose ratio used during the switch	4:1	6:1	8:1
Dose ratio achieved after the switch			
Median	3.7	7.75	12.25
Range	2.5-8.8	4-10	10-14.3
No. of days to achieve equianalgesia			
Median	2	3	5.5
Range	1-3	1-7	2-7

received 90 to 300 mg daily (our dose ratio was 6:1), and 12.25:1 for patients who received greater than 300 mg daily (our dose ratio was 8:1). The last row shows that the lower the morphine dose previously administered, the fewer days it took to achieve equianalgesia with methadone, also confirmed by Cuzick's test for trend ($P < .001$).

DISCUSSION

The results of our prospective study of 38 patients chronically treated with various morphine dosages confirm that the equianalgesic dose ratio between morphine and methadone is significantly higher (ie, methadone is much more potent) in patients tolerant to higher morphine doses.

These results agree with those of Lawlor et al,[23] who retrospectively evaluated 14 patients with advanced cancer who switched from morphine to oral methadone and were treated with a median morphine daily dose eight times greater than that used in our study. The investigators reported that the median dose ratio obtained was 11.36, which shows that methadone is much more potent than expected and the dose ratio correlates with the previous administered morphine dose.

In respect to the equianalgesic tables, no patient in our study presented an equianalgesic dose ratio of 1:1, whereas the dose ratios of 3:1 and 4:1 approached those obtained in patients previously treated with low daily doses of morphine that ranged from 30 to 90 mg.

Recent data in the literature show that although the dose ratio between morphine and hydromorphone is equal to that expected,[24,30] the hydromorphone/methadone ratio is 5 to 10 times greater and varies significantly according to the previously administered dose of hydromorphone.[24,31]

It is not clearly understood why this occurs during the switch from morphine or hydromorphone to methadone. These findings can be partially explained by the incomplete cross-tolerance of methadone in respect to the other opioid analgesics. Methadone is a mu-delta opioid agonist and morphine is a mu-agonist and, therefore, the doses of methadone would be smaller than expected in patients who were at least partly tolerant to morphine by escalation of the dose to very high levels.

Moreover, in the rat, methadone has been shown to differ from morphine and hydromorphone because it has noncompetitive antagonist activity at the N-methyl-D-aspartate (NMDA) receptors.[32,33] Because NMDA receptors have been associated with the development of opioid tolerance in animals[34-38] and humans,[39] the nonopioid NMDA receptor antagonism of methadone may reduce the development of tolerance in patients who switch from morphine or hydromorphone to methadone.

According to Lawlor et al,[23] the median period of 5 days to reach equianalgesia during the switch from morphine to methadone could allow the elimination of morphine-3-glucuronide, which is a metabolite of morphine with proalgesic activity in rodents and, possibly, in humans.[40,41] The eventual elimination of this metabolite could reduce pain intensity and therefore require a lower postswitching dose of methadone to achieve analgesia.

From the pharmacokinetic aspect, differently from morphine, methadone is characterized by a slow elimination phase (beta half-life of 15 to 60 hours) that causes an accumulation of the drug.[14] However, similar to morphine, the plasmatic level of methadone does not correlate with the analgesic level.[42,43] Because of one or more of the previously mentioned reasons, methadone is more potent than believed and even more potent in patients tolerant to high morphine doses and should be investigated further.

Whatever the reason for this major potency of methadone, a clinical problem remains for the doctors who treat patients with cancer pain and who find it necessary to switch from morphine to methadone for various reasons. The first question concerns the best switching modality and the second concerns the dose ratio to be used during the switch.

Our experience shows that a switch over a period of 3 days, with a daily reduction of the morphine and replacement with oral methadone every 8 hours, as described previously,[23,24] is a simple and safe modality. Furthermore, we believe the different median dose ratios and the relative ranges obtained in respect to the preswitching morphine dose could be used as an indication in clinical practice for methadone dose titration, instead of the use of a constant dose ratio of 10:1. In fact, not all patients who require opioid switching take high doses of morphine. For example, many of the outpatients of our Palliative Care Unit are opioid naive at the first visit. They begin morphine treatment and, therefore, if they require a switch, the morphine dose is very low, even less than 90 mg daily. For these patients, a dose ratio of 10:1 is not indicated, as our results show.

Moreover, our findings have very important clinical implications because they confirm that the published equianalgesic dose ratios of 3:1 and 4:1[18,19] can only be relied on for patients who are treated with low morphine doses and, at the same time, show that the dose ratio of 1:1[17] is not applicable, even in patients tolerant to very low oral morphine dosages, such as 30 mg daily.

We stress that caution is recommended during a switch from any opioid to methadone, especially in patients tolerant to high doses of opioids. These patients may be at risk for toxicity and, therefore, the switch to methadone must be performed gradually and personalized. In fact, because of the high potency of methadone and its long elimination half-life, its inappropriate administration could be life-threatening.

Our study provided safety data and preliminary clinical indications that can be used in daily practice. However, future prospective, properly designed studies should be performed to evaluate the equianalgesia between morphine and methadone and to review the current equianalgesic tables.

REFERENCES

1. World Health Organization: Cancer Pain Relief (ed 2) Geneva, Switzerland, World Health Organization, 1996

2. Cherny NJ, Chang V, Frager G, et al: Opioid pharmacotherapy in the management of cancer pain: A survey of strategies used by pain physicians for the selection of analgesic drugs and routes of administration. Cancer 76:1283-1293, 1995

3. Bruera E, MacMillan K, Hanson J: Palliative care in a cancer center: Results in 1984 versus 1987. J Pain Symptom Manage 5:1-5, 1990

4. Coyle N, Adelhart J, Foley KM, et al: Character of terminal illness in the advanced cancer patient: Pain and other symptoms during the last four weeks of life. J Pain Symptom Manage 5:83-93, 1990

5. Kalso E, Heiskanen T, Rantio M, et al: Epidural and subcutaneous morphine in the management of cancer pain: A double-blind cross-over study. Pain 67:443-449, 1996

6. Morley JS, Watt JWG, Wells JC, et al: Methadone in pain uncontrolled by morphine. Lancet 342:1243-1244, 1993

7. Galer BS, Coyle N, Pasternak GW, et al: Individual variability in the response to different opioids: Report of five cases. Pain 49:87-91, 1992

8. Ripamonti C, Bruera E: CNS adverse effects of opioids in cancer patients: Guidelines for drug treatment. CNS Drugs 8:21-37, 1997

9. Gourlay GK, Cherry DA, Cousin MJ: A comparative study of the efficacy and pharmacokinetics of oral methadone and morphine in the treatment of severe pain in patients with cancer. Pain 25:297-312, 1986

10. Ripamonti C, Zecca E, Brunelli C, et al: Rectal methadone in cancer patients with pain. A preliminary clinical and pharmacokinetic study. Ann Oncol 6:841-843, 1995

11. Ventafridda V, Ripamonti C, Bianchi M, et al: A randomized study on oral administration of morphine and methadone in the treatment of cancer pain. J Pain Symptom Manage 1:203-207, 1986

12. Bruera E, Watanabe S, Fainsinger RL, et al: Custom-made capsules and suppositories of methadone for patients on high-dose opioids for cancer pain. Pain 62:141-146, 1995

13. De Conno F, Groff L, Brunelli C, et al: Clinical experience with

oral methadone administration in the treatment of pain in 196 advanced cancer patients. J Clin Oncol 14:2836-2842, 1996

14. Ripamonti C, Zecca E, Bruera E: An update on the clinical use of methadone for cancer pain. Pain 70:109-115, 1997

15. Crews JC, Sweeney NJ, Denson DD: Clinical efficacy of methadone in patients refractory to other mu-opioid receptor agonist analgesics for management of terminal cancer pain. Cancer 72:2266-2272, 1993

16. Manfredi PL, Borsook D, Chandler SW, et al: Intravenous methadone for cancer pain unrelieved by morphine and hydromorphone: Clinical observations. Pain 70:99-101, 1997

17. Health and Welfare Canada: Cancer Pain: A Monograph on the Management of Cancer Pain. Ottawa, Canada, Health & Welfare Canada, Minister of Supply and Services, H42-2/5, 1984E

18. Levy MH: Pharmacological treatment of cancer pain. N Engl J Med 335:1124-1132, 1996

19. Agency for Health Care Policy Research: Management of Cancer Pain. Clinical Practice Guidelines. Rockville, MD, US Department of Health and Human Services. AHCPR Publications no. 94-0592, March 1994, p 52

20. Houde RE: Misinformation: Side effects and drug interactions, in Hill CS, Fields WS (eds): Advances in Pain Research and Therapy. New York, NY, Raven, 1989, pp 145-161

21. Portenoy RK, Coyle N: Controversies in the long-term management of analgesic therapy in patients with advanced cancer. J Pain Symptom Manage 5:307-319, 1990

22. Morley JS, Makin MK: Letter to the Editor. Pain 70:109-115, 1997

23. Lawlor PG, Turner K, Hanson J, et al: Dose ratio between morphine and methadone in patients with cancer pain: A retrospective study. Cancer 82:1167-1173, 1998

24. Bruera E, Pereira J, Watanabe S, et al: Opioid rotation in patients with cancer pain. A retrospective comparison of dose ratios between methadone, hydromorphone, and morphine. Cancer 78:852-857, 1996

25. Hanks GW, De Conno F, Ripamonti C, et al: Morphine in cancer pain: Modes of administration. BMJ 312:823-826, 1996

26. Kalso E, Vainio A: Morphine and oxycodone hydrochloride in the management of cancer pain. Clin Pharmacol Ther 47:639-646, 1990

27. Ventafridda V, De Conno F, Ripamonti C, et al: Quality-of-life assessment during a palliative care program. Ann Oncol 1:415-420, 1990

28. Tamburini M, Rosso S, Gamba A, et al: A therapy impact questionnaire for quality-of-life assessment in advanced cancer research. Ann Oncol 3:565-570, 1992

29. Cuzick J: A Wilcoxon-type test for trend. Stat Med 4:87-90, 1985

30. Lawlor PG, Turner K, Hanson J, et al: Dose ratio between morphine and hydromorphone in patients with cancer pain: A retrospective study. Pain 72:79-85, 1997

31. Ripamonti C, De Conno F, Groff L, et al: Equianalgesic dose/ratio between methadone and other opioid agonists in cancer pain: Comparison of two clinical experiences. Ann Oncol 9:79-83, 1998

32. Ebert B, Andersen S, Krogsgaard-Larsen P: Ketobemidone, methadone and pethidine are noncompetitive N-methyl-D-aspartate (NMDA) antagonists in the rat cortex and spinal cord. Neurosci Lett 187:165-168, 1995

33. Gorman AL, Elliott KJ, Inturrisi CE: The d- and l-isomers of methadone bind to the noncompetitive site on the N-methyl-D-aspartate (NMDA) receptor in rat forebrain and spinal cord. Neurosci Lett 223:5-8, 1997

34. Elliot K, Kest B, Man A, et al: N-methyl-d-aspartate (NMDA) receptors, mu and kappa opioid tolerance and perspectives on new analgesic drug development. Neuropsychopharmacology 13:347-356, 1995

35. Trujillo K: Effects of noncompetitive N-methyl-d-aspartate receptor antagonists on opiate tolerance and physical dependence. Neuropsychopharmacology 13:301-307, 1995

36. Yamamoto T, Yaksh TL: Studies on the spinal interaction of morphine and the NMDA antagonist Mk-801 on the hyperaesthesia observed in a rat model of sciatic mononeuropathy. Neurosci Lett 135:67-70, 1992

37. Tiseo PJ, Inturrisi CE: Attenuation and reversal of morphine tolerance by competitive N-methyl-D-aspartate receptor antagonist LY 274614. J Pharmacol Exp Ther 264:1090-1096, 1993

38. Elliott K, Minami N, Kohesnidov Y, et al: The NMDA receptor antagonist LY 274614 and Mk-801 and the nitric oxide synthase inhibitor NG-nitro-L-arginine attenuate analgesic tolerance to the mu-opioid morphine. Pain 56:69-75, 1994

39. Clark JK, Kalen GE: Effective treatment of severe cancer pain of the head using low-dose ketamine in an opioid-tolerant patient. J Pain Symptom Manage 10:310-314; 1995

40. Smith MJ, Watt JA, Cramond T: Morphine-3-glucuronide: A potent antagonist of morphine analgesia. Life Sci 47:579-585, 1990

41. Morley J, Miles JB, Wells JC, et al: Paradoxical pain. Lancet 340:1045, 1992

42. Nilsson MI, Meresaar U, Anggard E, et al: Clinical pharmacokinetics of methadone. Acta Anaesth Scand 74:66-69, 1982

43. Jaffe JH, Martin WR: Opioid analgesics and antagonists, in Goodman Gilman A, Goodman LS (eds): Goodman and Gilman's The Pharmacological Basis of Therapeutics. New York, NY, Pergamon, 1990, p 508