Opioid Rotation in Patients with Cancer Pain

A Retrospective Comparison of Dose Ratios between Methadone, Hydromorphone, and Morphine

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BACKGROUND. When a change of opioid is considered, equianalgesic dose tables are used. These tables generally propose a dose ratio of 5:1 between morphine and hydromorphone. In the case of a change from subcutaneous hydromorphone to methadone, dose ratios ranging from 1:6 to 1:10 are proposed. The purpose of this study was to review the analgesic dose ratios for methadone compared with hydromorphone.

METHODS. In a retrospective study, 48 cases of medication changes from morphine to hydromorphone, and 65 changes between hydromorphone and methadone were identified. The reason for the change, the analgesic dose, and pain intensity were obtained.

RESULTS. The dose ratios between morphine and hydromorphone and vice versa were found to be 5.33 and 0.28, respectively (similar to expected results). However, the hydromorphone/methadone ratio was found to be 1.14:1 (5 to 10 times higher than expected). Although the dose ratios of hydromorphone/morphine and vice versa did not change according to a previous opioid dose, the hydromorphone/methadone ratio correlated with total opioid dose (correlation coefficient = 0.41 $P < 0.001$) and was 1.6 (range, 0.3–14.4) in patients receiving more than 330 mg of hydromorphone per day prior to the change, versus 0.95 (range, 0.2–12.3) in patients receiving æ330 mg of hydromorphone per day ($P = 0.023$).

CONCLUSIONS. These results suggest that only partial tolerance develops between methadone and hydromorphone. Methadone is much more potent than previously described and any change should start at a lower equivalent dose. ***Cancer* 1996; 78:852–7.** © *1996 American Cancer Society.*

KEYWORDS: equianalgesic dose tables, methadone, morphine, hydromorphone, opioid rotations, retrospective study.

Greater than 80% of cancer patients require opioid analgesics for pain before death.[1,2] In most cases, the type of opioid needs to be changed at least once because of the presence of side effects or escalating analgesic doses.[3,4] The recent finding of accumulations of active opioid metabolites in patients receiving common opioids such as morphine and hydromorphone has prompted authors to suggest that opioid rotation should be attempted in most patients who develop neuropsychiatric toxicity.[4,5] In these patients, methadone could be an attractive alternative because of its lack of known active metabolites, excellent oral bioavailability, and its extremely low cost compared with other opioids.[6,7] When a change in the type of opioid is considered, physicians and pharmacists follow equianalgesic dose tables for both oral and parenteral opioids such as those suggested by the U.S. Department of Health and Human Services,[8] Health and

Welfare Canada,[9] or other major textbooks or reviews.[10–12] These tables generally propose a dose ratio of 5:1 between morphine and hydromorphone (i.e., morphine 5 mg orally is equianalgesic to hydromorphone 1 mg orally). In the case of methadone, some tables propose a dose ratio of 1:1 between oral morphine and oral methadone (i.e., morphine 10 mg orally is equianalgesic to methadone 10 mg orally)[9–11] and others propose a morphine-methadone ratio of 4:1 for the oral route and 2.7:1 for the parenteral route.[8]

Our preliminary experience suggested that methadone was much more potent than as proposed by the aforementioned tables.[5] It was also our impression that the ratio of methadone might vary according to the previous opioid dose that patients were receiving. To test these two observations, we conducted a retrospective cohort study in consecutive patients admitted to the Palliative Care Unit, Edmonton General Hospital, Edmonton, Alberta, Canada.

PATIENTS AND METHODS

In this retrospective study, we reviewed the clinical charts of patients admitted to the Palliative Care Unit, Edmonton General Hospital between July 1989 and May 1995. All patients admitted to this tertiary Palliative Care Unit had advanced carcinoma and severe symptom complexes requiring medical interventions.

Of a total of 733 patients, 113 underwent a change of opioid from morphine to hydromorphone, hydromorphone to morphine, or hydromorphone to methadone. In the case of rotations between hydromorphone and morphine or vice versa, only those occurring between July 1989 and December 1991 were calculated. In the case of methadone, patients were included over the complete period of observation.

Only changes of opioids between these three drugs were recorded. Both morphine and hydromorphone are well known strong and recommended opioid agonists with recognized equianalgesic dose ratios.[8,9] These drugs were administered orally (20 patients) or subcutaneously (28 patients), respectively every 4 hours. Methadone was used mostly in patients receiving higher doses of opioids or in patients who had already undergone one change of opioid. All patients who were switched to methadone were already receiving hydromorphone. This is because of the higher potency and solubility of hydromorphone compared with morphine, thereby allowing for the administration of a decreased number of pills and decreased volume of infusions.

The following information was collected from the charts:

1) age, sex, and primary diagnosis.
2) reason for switching to the alternate opioid (escalating dose, side effects, or both).
3) Previous final dose of morphine or hydromorphone before the rotation.
4) Stabilization dose of the new alternate opioid. This dose was calculated to be the one in which the patient was able to remain for more than 48 hours without requiring a dose change or more than 2 extra doses of rescue analgesic. Each dose of rescue analgesic was approximately 10% of the daily opioid dose. In patients receiving morphine or hydromorphone, this stabilization dose was usually reached within 24 to 48 hours of the opioid rotation. Conversion from oral to parenteral routes of opioids was done using the ratio guidelines suggested by Health & Welfare Canada,[8] i.e., 100 mg of oral hydromorphone per day was equivalent to 50 mg of subcutaneous hydromorphone per day and 100 mg of oral morphine per day was equivalent to 50 mg of subcutaneous morphine per day. In patients receiving methadone, because the change usually took place over 3 days, this stabilization was reached between 3 to 6 days after the opioid rotation. Based on our previous experience, the switch from subcutaneous hydromorphone to oral and rectal methadone was done using a ratio of 1:1 (1 mg subcutaneous hydromorphone was equivalent to 1 mg oral or rectal methadone). Because of the excellent oral bioavailability of methadone, no dose adjustments were made between the oral and rectal route.[6]
5) Severe sedation (defined as communication with the patient being impossible and the need to withhold opioids or administer naloxone), or respiratory depression requiring opioid discontinuation or administration of naloxone.

Data were analyzed using the chi-square test for the comparison of proportions. The Wilcoxon's test and Spearman correlation coefficients were used for the comparison of continuous variables such as opioid dose and dose ratios. Data was analyzed according to the SAS system for personal computers.[13] These variables were analyzed in this manner and expressed as medians (range) because of the absence of a normal distribution of the data.

RESULTS

A total of 113 patients were evaluable for this study. These patients were divided into three groups. Group 1

TABLE 1
Patients Characteristics

	Group 1 (HM-ME)	Group 2 (M-HM)	Group 3 (HM-M)	*P* value
Mean Age (± S.D.) (Yrs)	59.3 (12.4)	66.1 (13.1)	71.6 (11.1)	>0.2
Female/male (%)	32/33	17/19	8/4	>0.2
Primary tumor				>0.2
Genitourinary	20	7	3	
Lung	15	8	1	
Gastrointestinal	10	5	1	
Breast	6	7	4	
Head and neck	5	4	1	
Unknown	3	1	—	
Other	3	2	1	
Hematologic	2	1	—	
Sarcoma	1	1	1	
Total	65	36	12	
Reason for opioid change				<0.001
Escalating opioid dose	24	4	—	
Toxicity	8	23	9	
Both	15	4	1	
Other	2	4	2	
Days on unit (SD)	64.2 (56.8)	59 (48.1)	72.6 (37.2)	>0.2
Median total equivalent morphine dose "before the opioid change (mg/d) (range)"	1185 (65–10,380)	145 (30–1350)	165 (30–1035)	<0.001

HM-ME: hydromorphone to methadone switch; M-HM: morphine to hydromorphone switch; HM-M: hydromorphone to morphine switch; SD: standard deviation.

included 65 patients who changed from subcutaneous hydromorphone to oral (n = 37) or rectal (n = 28) methadone. Group 2 included 36 patients who changed from oral (n = 16) or subcutaneous (n = 20) morphine to oral (n = 13) or subcutaneous (n = 23) hydromorphone. Group 3 included 12 patients who changed from oral (n = 4) or subcutaneous (n = 8) hydromorphone to oral (n = 4) or subcutaneous (n = 8) morphine.

In all patients, except for 5 who went from oral to subcutaneous routes and vice versa, patients from Groups 2 and 3 received the new opioid by the same route as the previous opioid. In the 5 exceptions, the equivalent dose was used as described in equianalgesic tables.[8–11] Patient characteristics are summarized in Table 1. The main difference between the patients in Group 1 (hydromorphone to methadone) and the other two groups is that these patients were receiving overall higher doses of opioids before the change occurred and that the reason for the switch was more frequently escalating doses.

Table 2 summarizes the previous dose, new stable dose, and dose ratio for the three different patient groups. Doses of morphine and hydromorphone are expressed in subcutaneous equivalents. The dose ratio for Groups 2 and 3 were 5.33 (range, 1.33–16.67) and 0.28 (range, 0.2–0.7), respectively. These values are consistent with ratios of 5 and 0.2, respectively, as reported in equianalgesic tables.[8,9] However, the value for Group 1 was 1.14 (range, 0.15–4.2). This is approximately 6 to 10 times higher than that suggested by equianalgesic tables.[8,9] The subcutaneous hydromorphone/methadone ratio in 37 patients who received oral methadone was 2.2 ± 2.9, versus 1.2 ± 1.4 in 28 patients who changed from subcutaneous hydromorphone to rectal methadone ($P < 0.01$). Table 3 summarizes the dose ratio for the 25% of patients receiving the highest opioid dose versus the 75% of patients receiving the lowest opioid dose for each of the 3 patient groups. Patients in the top 25th percentile were receiving 330 mg or more of hydromorphone for Group 1 (hydromorphone to methadone switch), 265 mg or more of morphine for Group 2 (morphine to hydromorphone switch), and 105 mg or more of hy-

TABLE 2
Summary of Previous Dose, New Stable Dose, and Dose Ratio for The Three Different Patient Groups

	Group 1 (HM-ME)	Group 2 (M-HM)	Group 3 (HM-M)
Final previous opioid dose (mg)[a]	237 (13–2076) sc HM	145 (30–1350) sc M	33 (6–187) sc HM
Stable dose of new opioid (mg)[a]	180 (20–1350) po.pr ME	23 (6–240) sc HM	120 (18–600) sc M
Dose ratio (previous opioid/new opioid)[b]	1.14 HM/ME (0.52–2.04)	5.33 M/HM (4.9–6.4)	0.28 HM/M (0.22–0.33)
Pain intensity (VAS 0-100) before switch[c]	51 ± 23	37 ± 24	27 ± 19
Pain intensity after switch[c]	41 ± 2	28 ± 18	24 ± 15

HM-ME: hydromorphone to methadone switch; M-HM: morphine to hydromorphone switch; HM-M: hydromorphone to morphine switch; SC: subcutaneous; po.pr: oral and rectal; VAS: Visual Analogue Scale.
[a] Data expressed as median (range).
[b] Expressed as median (lower upper quartiles).
[c] Data expressed as mean ± standard deviation.

TABLE 3
Dose Ratio Summary for 25% of Patients Receiving Higher Opioid Dose versus 75% of Patients Receiving Lower Opioid Dose for Each Group

		Highest 25%	Lowest 75%	*P* value
Group 1	Overall (n = 65)	1.6 (0.3–14.4)	0.95 (0.2–12.3)	0.023
	Oral route (n = 37)	1.65 (0.3–14.4)	1.2 (0.2–12.3)	0.02
	Rectal route (n = 28)	1 (0.6–6.9)	0.45 (0.2–2.4)	0.04
Group 2		5 (2.76–8)	5.42 (1.33–16.69)	0.61
Group 3		0.31 (0.23–0.73)	0.24 (0.2–0.4)	0.23

Group 1: hydromorphone to methadone switch; Group 2: morphine to hydromorphone switch; Group 3: hydromorphone to morphine switch.

dromorphone for Group 3 (hydromorphone to morphine switch). Although the dose ratios were not significantly different between the lowest 75% and the highest 25% for Groups 2 and 3, the dose ratio between hydromorphone and methadone was significantly higher when patients were receiving higher opioid doses before the switch.

Table 4 shows the univariate correlation between the opioid dose ratio and the previous opioid dose for each of the three groups. Although there was a highly significant correlation between the previous opioid dose and the dose ratio for methadone, there was no significant correlation when patients were rotated into hydromorphone (Group 2) or morphine (Group 3).

Figure 1 shows the correlation between the final hydromorphone dose and the hydromorphone/methadone ratio in 65 patients from Group 1.

Severe sedation or respiratory depression occurred in 8 of 65 patients who were rotated into methadone (12%) versus in none of 48 patients who changed from morphine to hydromorphone and vice versa ($P < 0.01$). Naloxone was required in three patients. All patients who presented with severe sedation or respiratory depression as a result of methadone administration experienced complete recovery and were able to continue treatment at a total lower dose.

DISCUSSION

In this retrospective study, we reviewed the results of opioid rotation in 113 in-patients with cancer pain. All patients had a reason for changing opioids. In all cases, patients who switched from any of the three opioids did so for clinical reasons (either toxicity or insufficient analgesia). This may be considered a limitation for accurately estimating dose ratios. However, in the clinical setting, most patients are switched from one opioid to another because of side effects and insufficient analgesia. Therefore, our observations are applicable. Moreover, similar reasons existed for the changes between morphine and hydromorphone. Therefore, the presence of a cause for change is not likely to be an explanation for the observed difference between methadone and the other two opioids. Patients who switched to methadone were receiving a higher equivalent morphine dose before rotation and escalating opioid dose was, more frequently, the reason for opioid change (Table 1). These patient characteristics are consistent with our use of methadone in patients with

TABLE 4
Univariate Correlation between the Opioid Dose Ratio and the Previous Opioid Dose for Each Group

		Spearman correlation coefficient	*P* value
Group 1	Total (n = 65)	0.48	<0.001
	Oral route (n = 37)	0.43	<0.001
	Rectal route (n = 28)	0.59	<0.001
Group 2	(n = 36)	0.05	>0.2
Group 3	(n = 12)	0.18	>0.2

Group 1: hydromorphone to methadone switch; Group 2: morphine to hydromorphone switch; Group 3: hydromorphone to morphine switch.

more difficult pain syndromes in whom opioid dose escalation had already occurred.[14] It could be expected that, in these patients, the dose of the new opioid would need to be proportionately higher than in those patients in whom the main reason for opioid change was opioid toxicity. Our findings suggest that methadone was able to achieve equal or superior analgesia compared with hydromorphone (as demonstrated by pain intensity scales, Table 2) at doses approximately 10 times lower than expected. It confirms a previous observation by our group[7] suggesting that methadone is almost 10 times more potent than as suggested in equianalgesic tables.[8–12] Our results are supported by some recent case reports from the literature[15–18] and suggest that, if currently recommended ratios are used when switching to methadone, severe toxicity or death may occur.

The ratio of morphine to hydromorphone and vice versa were very similar to those recommended by some guidelines[8] and consistent with our regular practice, but lower than the ratio recommended by other authors.[9,19] However, for all three drugs, a wide range in ratio was observed, suggesting that the process of reaching an optimal dose should be highly individualized. A previous controlled, double blind study suggested that there is some degree of reciprocal incomplete cross-tolerance between intramuscular morphine and metopon (a close analogue of hydromorphone).[20]

The dose ratio for both morphine and hydromorphone did not change significantly over a wide range of dosages, suggesting that complete or almost complete cross-tolerance develops to both opioids. In the case of methadone, however, the hydromorphone/methadone ratio was 60% higher in patients receiving higher opioid doses (Table 3) and the ratio showed a significant correlation with the previous opioid dose (Table 4). These results are consistent with only a partial development of cross-tolerance between hydromorphone and methadone and are probably also valid for morphine/methadone. The varying methadone ratio according to opioid dose is unique among opioid analgesics and is particularly important for two reasons: 1) placing patients on high doses of opioids may give the physician a false sense of security because of the development of tolerance to severe sedation and respiratory depression (even when prescribed by a group of cancer pain experts, this drug resulted in 8 of 65 patients [12%] with severe sedation or respiratory depression, and 2) patients receiving high doses are more likely to develop opioid toxicity or incur higher costs and therefore are more likely to be switched over to methadone.

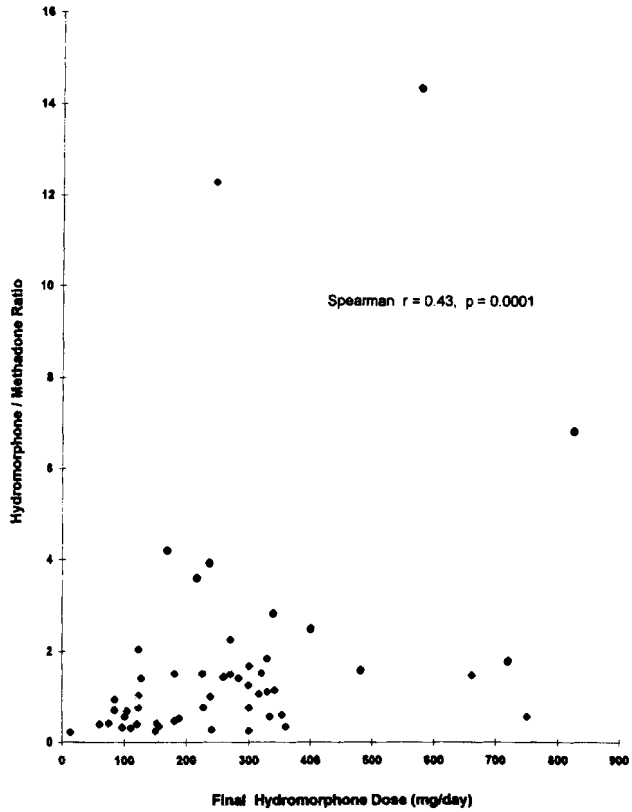

FIGURE 1. Correlation between the final hydromorphone dose and the hydromorphone/methadone ratio.

The dose ratios of hydromorphone to methadone via the oral route were also found to be higher than those via the rectal route (Table 3). This is likely due to the increased bioavailability of oral methadone in comparison with the rectal route.

The use of methadone to control pain in certain well selected cases of advanced cancer-related pain holds potential advantages. During recent years, opioid agonists such as morphine or hydromorphone or

their active glucoronides and their metabolites have been associated with delirium, organic hallucinosis, generalized myoclonus, grand mal seizures, and hyperalgesia.[5,15,20–25] One of the potential significant advantages of methadone is its lack of known active metabolites. Another is its low cost, a potential benefit for patients receiving high doses of opioids or patients in developing countries. A third advantage relates to methadone's long half-life. It can be given 2 to 3 times a day, a schedule most patients find more convenient than every 4 hours as in other opioid formulations.

Our results only apply to the special situation of patients receiving chronic opioid therapy around the clock for the prevention of cancer pain, and need to be confirmed in prospective, randomized trials, ideally with blind titration in patients who have achieved good pain control.[26,27] Until these studies are available, patients should be switched over to methadone at much higher hydromorphone to methadone equianalgesic ratios, and the ratios should be at least 60% higher in patients receiving more than 300 mg of parenteral hydromorphone per day. Because of the potential toxicity, the use of methadone for advanced cancer-related pain should be restricted to experienced physicians until more evidence is generated.

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