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Symptom Management and Supportive Care

The Opioid Rotation Ratio of Hydrocodone to Strong Opioids in Cancer Patients

Akhila Reddy,[a] Sriram Yennurajalingam,[a] Hem Desai,[a] Suresh Reddy,[a] Maxine de la Cruz,[a] Jimin Wu,[b] Diane Liu,[b] Eden Mae Rodriguez,[a] Jessica Waletich,[a] Seong Hoon Shin,[a,c] Vicki Gayle,[a] Pritul Patel,[a] Shalini Dalal,[a] Marieberta Vidal,[a] Kimberson Tanco,[a] Joseph Arthur,[a] Kimmie Tallie,[a] Janet Williams,[a] Julio Silvestre,[a] Eduardo Bruera[a]

Departments of [a]Palliative Care and Rehabilitation Medicine and [b]Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA; [c]Department of Internal Medicine, College of Medicine, Kosin University, Busan, Republic of Korea

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Cancer • Opioid analgesics • Hydrocodone • Palliative care • Pain management • Opioid-related disorders

Abstract

Purpose. Cancer pain management guidelines recommend initial treatment with intermediate-strength analgesics such as hydrocodone and subsequent escalation to stronger opioids such as morphine. There are no published studies on the process of opioid rotation (OR) from hydrocodone to strong opioids in cancer patients. Our aim was to determine the opioid rotation ratio (ORR) of hydrocodone to morphine equivalent daily dose (MEDD) in cancer outpatients.

Patients and Methods. We reviewed the records of consecutive patient visits at our supportive care center in 2011–2012 for OR from hydrocodone to stronger opioids. Data regarding demographics, Edmonton Symptom Assessment Scale (ESAS), and MEDD were collected from patients who returned for follow-up within 6 weeks. Linear regression analysis was used to estimate the ORR between hydrocodone and MEDD. Successful OR was defined as 2-point or 30% reduction in the pain score and continuation of the new opioid at follow-up.

Results. Overall, 170 patients underwent OR from hydrocodone to stronger opioid. The median age was 59 years, and 81% had advanced cancer. The median time between OR and follow-up was 21 days. We found 53% had a successful OR with significant improvement in the ESAS pain and symptom distress scores. In 100 patients with complete OR and no worsening of pain at follow-up, the median ORR from hydrocodone to MEDD was 1.5 (quintiles 1–3: 0.9–2). The ORR was associated with hydrocodone dose ($r = -.52$; $p < .0001$) and was lower in patients receiving ≥40 mg of hydrocodone per day ($p < .0001$). The median ORR of hydrocodone to morphine was 1.5 ($n = 44$) and hydrocodone to oxycodone was 0.9 ($n = 24$).

Conclusion. The median ORR from hydrocodone to MEDD was 1.5 and varied according to hydrocodone dose. ***The Oncologist*** 2014;19:1186–1193

Implications for Practice: Opioid rotations from hydrocodone to other opioids such as morphine occur frequently in cancer patients to address uncontrolled pain; however, the opioid rotation ratio (ORR) from hydrocodone to morphine equivalent daily dose (MEDD) was unknown. Our findings suggest that an ORR of 1.5 may be used to calculate the MEDD of hydrocodone for doses <40 mg/day, and an ORR of 1 may be used for hydrocodone doses ≥40 mg/day. Because of the large variation in the MEDD-hydrocodone ratio, personalized titration and frequent monitoring are recommended.

Introduction

Pain affects 80%–90% of patients with advanced cancer [1]. Opioids are the preferred medications to treat cancer-related pain [2, 3]. The World Health Organization's (WHO's) pain ladder for cancer pain relief suggests prescribing pain medication in order of strength starting with nonopioids like acetaminophen and then, if needed, milder opioids like hydrocodone and then stronger opioids like morphine. Opioid therapy can result in side effects like nausea, constipation, and opioid-induced neurotoxicity (OIN). OIN presents with excessive sedation, delirium, hallucinations, myoclonus, and seizures, which are consequences of the accumulation of both the parent opioid and its metabolites [4]. Opioid rotation (OR), which is substituting one opioid by another, is recommended for intolerable side effects like OIN and for inadequate pain control despite dose escalation [5–12]. A recent study from our group showed that OR was conducted in 31% of cancer outpatients receiving strong opioids, with a 65% success rate. Uncontrolled pain (83%) was the most common reason for OR [13].

Although OR is an established practice for treating cancer-related pain, the process has also been linked to fatal outcomes

Correspondence: Akhila Reddy, M.D., Department of Palliative Care and Rehabilitation Medicine, Unit 1414, The University of Texas MD Anderson Cancer, 1515 Holcombe Boulevard, Houston, Texas 77030, USA. Telephone: 713-792-7567; E-Mail: asreddy@mdanderson.org Received February 19, 2014; accepted for publication July 8, 2014; first published online in ***The Oncologist*** *Express* on October 23, 2014. http://dx.doi.org/10.1634/theoncologist.2014-0130

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[14, 15]. Limited evidence supporting the dose-conversion ratios across numerous published equianalgesic opioid tables calls the safety of OR into question [14]. Hydrocodone is one of the most commonly used opioids for the initial management of mild to moderate cancer pain if nonsteroidal anti-inflammatory drugs and acetaminophen are not effective or are contraindicated. Hydrocodone in the form of products combined with acetaminophen or ibuprofen is also the most widely prescribed opioid in the U.S. and has high abuse potential. Moreover, the U.S. Food and Drug Administration (FDA) recently approved extended-release hydrocodone products [16–18]. An FDA advisory committee also recommended that all hydrocodone-containing products be subject to tighter restrictions by reclassifying hydrocodone as a schedule II controlled substance [19]. ORs from hydrocodone to stronger opioids, following the WHO's cancer pain ladder, occur frequently in the palliative care setting [2]. Although several studies have focused on the conversion ratios of stronger opioids, no studies have focused on the opioid rotation ratio (ORR) of hydrocodone to other opioids in cancer patients. The lack of knowledge of the appropriate ORR of hydrocodone to strong opioids could result in uncontrolled pain or overdosing. The objective of this study was to determine the ORR or morphine equivalent daily dose (MEDD) of hydrocodone following an OR to stronger opioids.

Methods

This study was approved by the institutional review board at the University of Texas MD Anderson Cancer Center, which waived the requirement of informed patient consent.

We retrospectively reviewed medical records of consecutive patient visits to our outpatient supportive care center (SCC) from January 1, 2011, until December 31, 2012, to identify patients who received hydrocodone as the sole opioid and subsequently rotated to a stronger opioid. From that cohort, we then identified patients who returned for a follow-up visit within 6 weeks, as outlined in the study plan (Fig. 1).

Patient Assessments

Information regarding patient demographics; Eastern Cooperative Oncology Group (ECOG) performance status; scores on the Edmonton Symptom Assessment Scale (ESAS) [20], Symptom Distress Score (SDS), Memorial Delirium Assessment Scale (MDAS) [21], and the Cut Down, Annoyed, Guilty, Eye-Opener (CAGE) [22] questionnaire; pain characteristics (nociceptive, neuropathic, or both); tobacco and illicit substance use; constipation; opioid use; hydrocodone dosage; MEDD; and indications for OR was obtained from the chart review.

The ESAS is a valid and reliable tool used to assess 10 major symptoms (rated 0–10) that are common in cancer patients during the 24 hours preceding opioid administration; pain, fatigue, nausea, depression, anxiety, drowsiness, shortness of breath, appetite, insomnia, and well-being [20, 23]. The SDS is a composite score of all symptoms in the ESAS except insomnia. The MDAS is a reliable and validated tool used to measure the presence and severity of delirium. A score of ≥ 7 of 30 has been recommended as a cutoff for establishing a diagnosis of delirium [21]. The CAGE score was used to screen for alcoholism. In men, a score of ≥ 2 of 4 is considered positive, and in women, a score of ≥ 1 of 4 is considered positive [22]. The CAGE questionnaire is an important tool to detect history of alcoholism in advanced cancer patients. Patients who are CAGE positive are more likely to engage in recreational drug use and are also at risk for rapid opioid dose escalation and abuse [24–26].

Supportive Care Center

Our SCC provides interdisciplinary palliative care through physicians, fellows, midlevel providers, nurses, social workers, chaplains, pharmacists, nutritionists, and counselors. A standardized model of care is practiced, as published previously [27, 28]. The patients and families are first assessed by the palliative care-trained registered nurses using validated tools like ESAS, MDAS, and CAGE. The nurses then present their detailed assessments to a board-certified palliative care physician who then sees the patient and involves other members of the interdisciplinary team according to the needs of the patient and the family. Detailed attention is paid to assessment and management of cancer-related symptoms, along with counseling, discussions of goals of care, and assistance with advance care planning.

Opioids

Hydrocodone is considered a weak opioid, according to the WHO cancer pain ladder [2]. Hydrocodone exists in various combinations with acetaminophen or ibuprofen. The most common forms of hydrocodone-acetaminophen preparations are 5/500 mg, 5/325 mg, 7.5/500 mg, 7.5/325 mg, 10/500 mg, 10/325 mg, and 7.5/750 mg. The common hydrocodone-ibuprofen preparations are 2.5/200 mg, 5/200 mg, 7.5/200 mg, and 10/200 mg. Other opioids like morphine, hydromorphone, oxycodone, fentanyl, methadone, and oxymorphone were defined as strong opioids.

Morphine Equivalent Daily Dose

The MEDD is the total daily dose of the opioid administered in a 24-hour period, converted to an equivalent dose of oral morphine. The MEDD was calculated using the standard OR-conversion ratios [28], and a conversion factor of 5 was used for calculating the MEDD for methadone [29].

Successful OR

As previously used by our team [13, 30], the following criteria at the time of follow-up were used to define a successful OR: Improvement of pain, which is 30% or 2 point reduction in the ESAS pain score (0–10) for those patients who underwent OR in the setting of uncontrolled pain [31]; or evidence of disappearance of side effects at the follow-up visit in cases in which the reason for OR was the development of side effects, such as OIN with hydrocodone; or no worsening of pain score in situations in which OR was performed for other reasons such as need to change the route of drug administration or attempt to cut down on acetaminophen consumption related to hydrocodone-acetaminophen combination products; and continued use of the new opioid at the follow-up visit.

Successful partial OR was defined as continuation of hydrocodone and the new opioid with the criteria listed above. A patient receiving hydrocodone, for example, gets rotated to

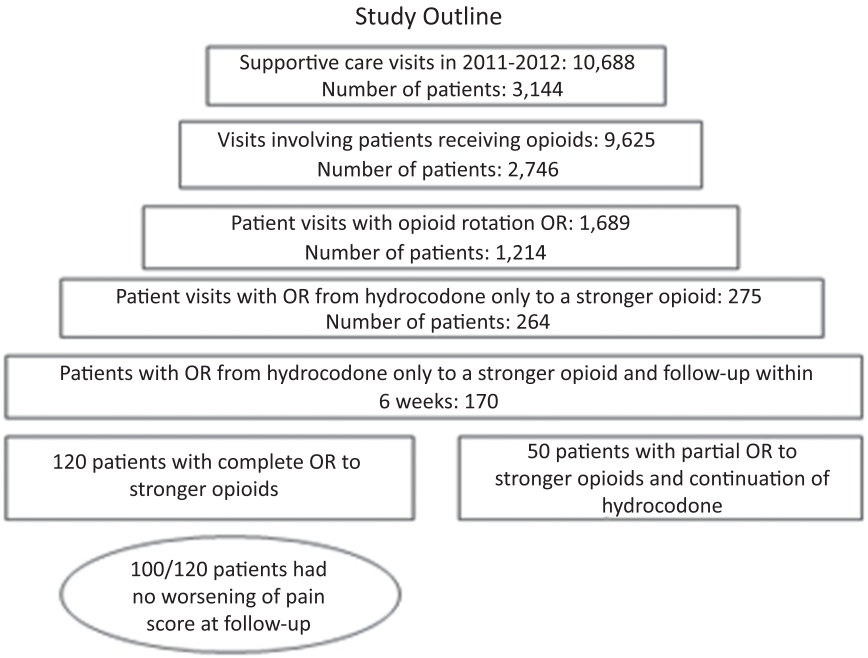

Figure 1. Study outline.
Abbreviation: OR, opioid rotation.

extended-release morphine around the clock with the continuation of hydrocodone for breakthrough pain.

Eligible Patients for Determination of MEDD of Hydrocodone

Patients undergoing complete OR from hydrocodone to strong opioids with discontinuation of hydrocodone and no worsening of pain at the time of follow-up were included in the analysis to determine the ORR or MEDD of hydrocodone.

Statistical Analysis

The primary objective was to evaluate the relationship between hydrocodone dose and the MEDD of the stronger opioid after complete OR. The variables included were demographic and clinical characteristics, such as age, sex, ECOG performance status, and CAGE. Data were summarized using standard descriptive statistics and contingency tables. Association between categorical variables was examined by the chi-square test or Fisher's exact test. The Wilcoxon-Mann-Whitney test was used to examine the difference of continuous variables between groups. Correlation was assessed between hydrocodone dose and MEDD using the Spearman correlation coefficient. A linear regression model was applied to estimate the linear association between MEDD and hydrocodone and between the MEDD-hydrocodone ratio and hydrocodone. A univariate logistic regression model was used to measure the effects of variables on successful OR. A p value of <0.05 was considered statistically significant. All computations were carried out in SAS 9.3 (SAS Institute Inc., Cary, NC, http://www.sas.com) and R 3.0.2.

Results

A total of 3,144 patients attended 10,688 SCC visits in 2011 and 2012. Of those, 2,746 patients (87%) received opioid therapy, and 1,214 of 2,746 (44%) underwent OR. Of the patients who underwent OR, 264 patients switched from hydrocodone only to stronger opioids, and 173 patients had a follow-up visit within 6 weeks. Three patients were missing data such as MEDD, ESAS, and hydrocodone dose and were excluded from the analysis. A total of 170 patients who had an OR from hydrocodone to stronger opioids and attended a follow-up visit within 6 weeks were available for analysis (Fig. 1). Only two patients received a hydrocodone-ibuprofen combination; the rest received hydrocodone-acetaminophen combination products. Overall, 120 patients underwent a complete OR from hydrocodone to strong opioids. Of those, 100 patients did not have a worsening of pain score at the follow-up visit.

Table 1 summarizes the patient characteristics: 72% (123 of 170) were white, 43.5% were female, and the median age was 59 years. Head and neck cancer (25%) and lung cancer (23.5%) were the most common cancer types, and 81% had advanced cancer. CAGE was positive in 22%, and 15.5% had a history of illicit drug use. *Mixed* (42%) was the most common pain mechanism, followed by nociceptive pain (38%) and neuropathic pain (20%). A majority of the patients (94%) underwent OR for uncontrolled pain. None of the 170 patients had a diagnosis of delirium (all exhibited a MDAS score of <7). There were no significant differences between the groups of complete and partial OR. The median time to follow-up was 21 days (quintiles 1–3: 14–28 days), and the median PS was 2. In addition, 53% had a successful OR, with morphine (75 of 170, 45%) and oxycodone (36 of 170, 21%) being the most commonly used opioids for rotation. There were no clinically significant independent predictors for successful OR in the univariate logistic regression model of baseline factors.

Compared with the baseline scores, the scores for pain ($p <$ .0001), anxiety ($p = .02$), well-being ($p = .0006$), insomnia ($p <$ .0001), and SDS ($p = .0018$) were significantly improved at follow-up. There was also a trend toward improvement in depression ($p = .0545$).

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Table 1. Patient profile

Characteristics	Total, *n* (%)	Opioid rotation *n* (%)		*p* value
		Complete	Partial	
All patients	170 (100)	120 (70)	50 (30)	
Race				
Asian	4 (2)	2 (50)	2 (50)	.40
Black	20 (12)	17 (85)	3 (15)	
Hispanic	22 (13)	14 (64)	8 (36)	
White	123 (72)	86 (70)	37 (30)	
Sex, female	74 (43.5)	54 (73)	20 (27)	.54
Cancer type				
Breast	14 (8)	8 (57)	6 (43)	.41
Gastrointestinal	30 (18)	24 (80)	6 (20)	
Genitourinary	12 (7)	8 (67)	4 (33)	
Gynecologic	15 (9)	13 (87)	2 (13)	
Head and neck	43 (25)	26 (60.5)	17 (39.5)	
Lung	40 (23.5)	29 (72.5)	11 (27.5)	
Other	15 (9)	11 (73)	4 (27)	
Cancer stage, advanced	137 (81)	99 (72)	38 (28)	.32
CAGE, positive	37 (22)	23 (62)	14 (38)	.20
History of drug abuse, yes	26 (15.5)	15 (58)	11 (42)	.10
History of smoking, yes	113 (66.5)	76 (67)	37 (33)	.17
ECOG PS				
0	1 (0.6)	1 (100)	0 (0)	.86
1	35 (21)	24 (69)	11 (31)	
2	82 (48)	56 (68)	26 (32)	
3	51 (30)	38 (74.5)	13 (25.5)	
Characteristics of pain				
Mixed	70 (42)	51 (73)	19 (27)	.22
Neuropathic	33 (20)	19 (58)	14 (42)	
Nociceptive	63 (38)	46 (73)	17 (27)	
Reason for opioid rotation, uncontrolled pain	160 (94)	111 (70)	49 (30)	.48
Change of route	2 (1)	2 (100)	0 (0)	
Decrease consumption of acetaminophen	8 (5)	7 (87.5)	1 (12.5)	

Abbreviations: CAGE, Cut Down, Annoyed, Guilty, Eye-Opener questionnaire; ECOG PS, Eastern Cooperative Oncology Group performance status.

Compared with patients with unsuccessful OR, patients with successful OR had significant improvements in ESAS scores for pain ($p < .0001$), fatigue ($p = .006$), dyspnea ($p = .046$), and insomnia ($p = .008$) and in SDS ($p < .0002$). There was a trend toward improvement in drowsiness ($p = .058$).

In linear regression, MEDD and hydrocodone dose were significantly correlated, and the Spearman correlation coefficient was 0.52 ($p < .0001$). The median ORR of hydrocodone to MEDD was 1.5 (Table 2; Fig. 2). Hydrocodone dose and MEDD-hydrocodone ratio were significantly correlated, and the Spearman correlation coefficient was -0.52 ($p < .0001$), as shown in Table 2 and Figure 2.

The median MEDD-hydrocodone ratio or ORR of hydrocodone to MEDD decreased with increasing dose of hydrocodone. There was a significant difference between the median MEDD-hydrocodone ratio in those with hydrocodone dose <40 mg (2.00) and ≥ 40 mg (1.10; $p < .0001$) (Table 2).

On further breakdown, the median MEDD-hydrocodone ratio was 2.25 for hydrocodone dose <20 mg in 20 patients and 1.7 for hydrocodone dose 20–39 mg in 27 patients.

Table 3 shows that the median ORR of hydrocodone to morphine was 1.5 in 44 patients, and the median ORR of hydrocodone to oxycodone was 0.9 in 24 patients.

Discussion

In this preliminary study of consecutive cancer outpatients undergoing OR from hydrocodone to stronger opioids, the median ORR of hydrocodone to MEDD was 1.5, indicating that hydrocodone is 1.5-fold stronger than morphine. This information must be considered when prescribing hydrocodone to cancer patients so as to obtain optimal pain control with minimal side effects. This study is the first, to our knowledge, conducted in cancer patients to determine the ORR of hydrocodone to stronger opioids.

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Table 2. Comparison of MEDD/hydrocodone ratio and hydrocodone dose

Groups	*n*	Median (range)	Correlation coefficient	*p* value
HDC (mg)	100	40 (5–140)		
MEDD	100	60 (9–200)	0.52	<.0001
MEDD-HDC ratio	100	1.5 (0.38–6.0)	−0.52	<.0001
MEDD-HDC ratio when HDC <40 mg	47	2 (0.50–6.0)		<.0001
MEDD-HDC ratio when HDC ≥40mg	53	1.1 (0.38–2.5)		

Abbreviations: HDC, hydrocodone; MEDD, morphine equivalent daily dose.

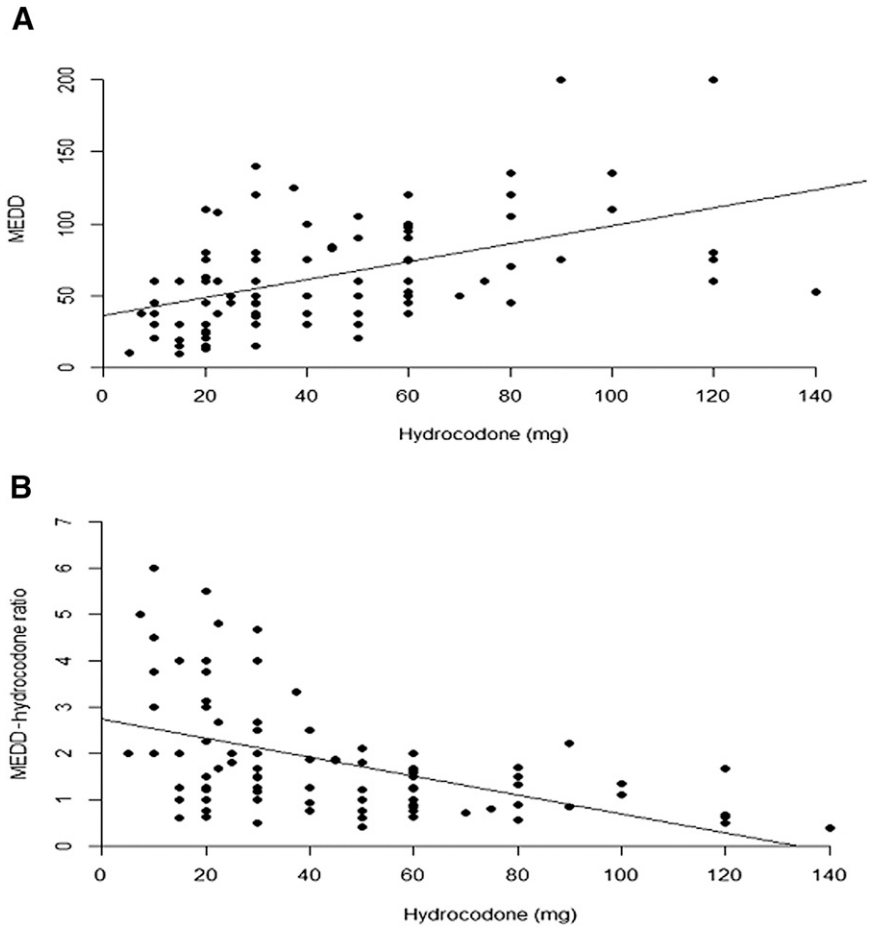

Figure 2. Linear regression. **(A):** Hydrocodone to MEDD. **(B):** Hydrocodone to MEDD-hydrocodone ratio.
Abbreviation: MEDD, morphine equivalent daily dose.

The median ORR from hydrocodone to MEDD varied between 1.1 and 2.25 depending on the dose of hydrocodone. This finding suggests that hydrocodone at higher doses (≥40 mg/day) is just as strong as morphine and at lower doses (<40 mg/day) may be twice as strong as morphine and just as strong as oxycodone. This finding is similar to findings of other abuse-potential studies of hydrocodone in noncancer patients. Zacny et al. conducted a series of studies in healthy volunteers and in volunteers with a history of recreational drug use and concluded that hydrocodone produced dose-related effects similar to those produced by morphine and oxycodone, such as opioid-induced pleasant and unpleasant feelings, indicating that hydrocodone is equipotent to, if not more potent than, morphine [32–35]. Relative potency studies to determine the abuse potential of various opioids, conducted in both healthy volunteers and volunteers with a history of drug abuse, indicated that hydrocodone may be equipotent to morphine and oxycodone and only slightly less potent than hydromorphone [35–37]. Hydrocodone was compared with methadone for maintenance therapy in 40 heroin addicts, and there was no significant difference between the groups in rates of employment, criminality, and prostitution, which are measures of therapeutic success [38]. In single-dose studies, hydrocodone was equipotent to oxycodone [39] following a fracture and slighter less potent than oxycodone but equipotent to morphine following dental surgery [40].

The results of these prior studies are similar to our results, which show the ORR from hydrocodone to morphine was 1.5, and the ORR from hydrocodone to oxycodone was 0.9.

One possible explanation for the varying MEDD-hydrocodone ratio could be hyperalgesia or increased sensitivity to pain as a result of hydrocodone being administered at higher doses. In

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Table 3. Opioid rotation ratios from hydrocodone to other opioids

Opioid used for rotation from HDC	*n*	HDC dose before OR, mg, median (range)	Opioid dose after OR, mg, median (range)	OR ratio, opioid dose to HDC dose, (range)
Morphine	44	50 (5–140)	60 (9–200)	1.5 (0.3–4.5)
Oxycodone	24	35 (10–60)	25 (10–80)	0.9 (0.3–2.5)[a]
Others[b]	32	30 (8–120)	66 (12–200)[c]	1.7 (0.5–6)
Overall	100	40 (5–140)	60 (9–200)[c]	1.5 (0.4–6.0)

[a]OR ratio to MEDD in these 24 patients is 1.35 (0.9 × 1.5; oxycodone is 1.5-fold stronger than morphine).
[b]Methadone (6), hydromorphone (8), fentanyl (4), and combination of multiple opioids (14).
[c]The opioid dose represented as MEDD.
Abbreviations: HDC, hydrocodone; MEDD, morphine equivalent daily dose; OR, opioid rotation.

situations related to hyperalgesia, OR can significantly improve pain at much lower doses of the new opioid [12, 41]. More research is needed to explore this finding because extended-release formulations of hydrocodone could result in the consumption of higher doses of hydrocodone than the currently available combination products.

In a study conducted in advanced cancer patients receiving a stable dose of opioids, the addition of 5 g of acetaminophen daily resulted in significant improvement in pain compared with placebo [42]. Combination opioid products confer better pain control than do individual components given at the same doses, owing to the concept of additive synergistic analgesia [43–45]. However, whether acetaminophen exhibits a ceiling effect at higher doses is unknown [46–48], and such an effect could explain the lower MEDD-hydrocodone ratio for higher doses of hydrocodone. More research is needed to clarify this finding.

Although the rate of successful OR was lower in this study than in our previous study of OR from one strong opioid to another, the results were consistent with our previous finding that OR for OIN is more successful (100%) than OR for uncontrolled pain [13]. In our study, 94% of the patients underwent OR for uncontrolled pain and none underwent OR for OIN, which could account for the lower rate of successful OR; however, OR resulted in improvement of pain, several nonpain symptoms, and SDS along the lines of previous studies on OR in cancer patients [11, 13, 49]. This could be explained as an outcome of a complete palliative care intervention, which, compared with symptom management alone, also focuses on psychosocial, emotional, and spiritual support. The improvement of pain after OR may also be explained by concepts such as hyperalgesia, tolerance, or OIN due to the previous opioid [8, 11, 12, 50, 51]. Consequently, our data reflect the dose required for OR from hydrocodone to another strong opioid and may not be a true equianalgesic ratio [39, 40].

Understanding higher strength of hydrocodone compared with morphine in cancer patients underscores the need for evaluating the safety of its prescription and may justify the FDA's proposed reclassification of hydrocodone combination products as schedule II controlled substances. Although the upscheduling of hydrocodone to schedule II could have a major impact on our patients' access to adequate pain management, it will ensure that only handwritten, nonrefillable prescriptions can result in the dispensing of hydrocodone and may help minimize abuse and diversion. In 2011, 131 million prescriptions for hydrocodone were dispensed to 47 million patients in the U.S. Moreover, 99% of the world's hydrocodone is consumed in the U.S. and comprises 66% of all opioid sales, rendering it one of the most widely used and abused opioids [19]. Cancer patients are initially prescribed hydrocodone and later switched to stronger opioids if their pain is uncontrolled. This common practice, without knowing the potency of hydrocodone, poses a risk of both undertreatment of pain and overdosing.

Our study had some weaknesses. It was a retrospective study of prospectively collected data, and we included data from only one follow-up visit. Although the median time from OR to follow-up was 3 weeks, which is the typical time between outpatient follow-up visits, changes such as disease progression and cancer treatment could potentially have altered the pain mechanism and thereby influenced the consumption of opioids. Moreover, the dosage of acetaminophen was not accounted for in our analysis. Although the calculation of MEDD in our study was based on published opioid-conversion tables, there are several such opioid-conversion tables with varying conversion ratios. Hence our finding an ORR of 1.5 from hydrocodone to MEDD needs to be validated in larger studies in which hydrocodone is rotated to a defined opioid such as morphine or oxycodone. Further prospective studies are needed to validate our findings using both combination hydrocodone products and the new extended-release formulations and to investigate the role of acetaminophen in the final dose-conversion ratio for OR from hydrocodone. Studies to validate our findings in populations other than cancer patients are also warranted.

Conclusion

The ORR from hydrocodone to MEDD suggests that hydrocodone is stronger than morphine and could be just as strong as oxycodone at lower doses. An ORR of 1.5 is suggested to calculate the MEDD of hydrocodone for doses $<$40 mg/day, and an ORR of 1 is suggested for doses $\geq$40 mg/day. Because of the large variation in the MEDD-hydrocodone ratio, personalized titration and frequent monitoring are recommended.

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Author Contributions

Conception/Design: Akhila Reddy, Sriram Yennurajalingam, Suresh Reddy, Maxine de la Cruz, Jimin Wu, Diane Liu, Eduardo Bruera
Provision of study material or patients: Akhila Reddy
Collection and/or assembly of data: Akhila Reddy, Sriram Yennurajalingam, Hem Desai, Maxine de la Cruz, Eden Mae Rodriguez, Jessica Waletich, Seong Hoon Shin, Vicki Gayle, Pritul Patel, Shalini Dalal, Marieberta Vidal, Kimberson Tanco, Joseph Arthur, Kimmie Tallie, Janet Williams, Julio Silvestre, Eduardo Bruera
Data analysis and interpretation: Akhila Reddy, Sriram Yennurajalingam, Jimin Wu, Diane Liu, Eduardo Bruera
Manuscript writing: Akhila Reddy, Sriram Yennurajalingam, Hem Desai, Suresh Reddy, Maxine de la Cruz, Jimin Wu, Diane Liu, Eden Mae Rodriguez, Jessica Waletich, Seong Hoon Shin, Vicki Gayle, Pritul Patel, Shalini Dalal, Marieberta Vidal, Kimberson Tanco, Joseph Arthur, Kimmie Tallie, Janet Williams, Julio Silvestre, Eduardo Bruera
Final approval of manuscript: Akhila Reddy, Sriram Yennurajalingam, Hem Desai, Suresh Reddy, Maxine de la Cruz, Jimin Wu, Diane Liu, Eden Mae Rodriguez, Jessica Waletich, Seong Hoon Shin, Vicki Gayle, Pritul Patel, Shalini Dalal, Marieberta Vidal, Kimberson Tanco, Joseph Arthur, Kimmie Tallie, Janet Williams, Julio Silvestre, Eduardo Bruera

Disclosures

The authors indicated no financial relationships.

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For Further Reading:
Akhila Reddy, Sriram Yennurajalingam, Kalyan Pulivarthi et al. Frequency, Outcome, and Predictors of Success Within 6 Weeks of an Opioid Rotation Among Outpatients with Cancer Receiving Strong Opioids. ***The Oncologist*** 2013;18:212–220.

Implications for Practice:
Opioid rotation (OR) is the replacement of one opioid by another using an equianalgesic dose. The strategy is used to treat uncontrolled pain and intolerable opioid-related side effects like opioid-induced neurotoxicity (OIN). In this study, OR was administered in about one third of cancer outpatients receiving strong opioids. The rate of success with OR was 65%, which parallels findings of previous studies in the inpatient setting. OR was associated with improvements in pain, symptom distress score, depression, well-being, and insomnia in addition to the resolution of symptoms associated with OIN. OR can effectively manage uncontrolled pain and OIN in cancer outpatients. Further prospective studies should aim at determining the predictors of successful OR.