Original Article

A retrospective review of the use of oxymorphone immediate release for long term pain control in cancer patients with gastrostomy tubes

Akhila Reddy[#], Marieberta Vidal[#], Ali Haider, Joseph Arthur, David Hui, Jimin Wu, Diane Liu, Carolyn Holmes, Michelle Carrol, Shalini Dalal, Rony Dev, Kimberson Tanco, Eduardo Bruera

Department of Palliative, Rehabilitation, and Integrative Medicine, UT MD Anderson Cancer Center, Houston, TX, USA

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[#]These authors contributed equally to this work.

Correspondence to: Akhila Reddy, MD. Associate Professor, Department of Palliative, Rehabilitation, and Integrative Medicine, Unit 1414, The University of Texas MD Anderson Cancer, 1515 Holcombe Boulevard, Houston, TX 77030, USA. Email: ASReddy@mdanderson.org.

Background: Cancer patients often require feeding or venting gastrostomy-tubes (G-tubes) for enteral nutrition or symptom palliation. The administration of most extended-release (ER) opioids via the G-tube or orally followed by clamping of the venting G-tube is contraindicated. Oxymorphone immediate release (IR) may be useful because of its longer half-life compared to other IR opioids. We examined the use of oxymorphone IR administered every 8 hours in patients with G-tubes.

Methods: This was a retrospective chart review of 40 consecutive cancer patients with G-tubes who underwent opioid rotation (OR) to oxymorphone. Demographics, symptoms, morphine equivalent daily dose (MEDD), and oxymorphone dose were collected. Successful OR was defined as a 2-point or 30% reduction in pain score and continued use of oxymorphone at follow-up in outpatient setting, or discharge in inpatient setting. Opioid rotation ration (ORR) between MEDD and oxymorphone in patients with successful OR was calculated as MEDD before the OR divided by total oxymorphone dose/day at follow-up or discharge.

Results: The median age was 56 years, 57.5% were white, 68% male, 47.5% (n=19) had head and neck cancer, 90% had advanced disease, 67.5% (n=27) were inpatient, and 15% (n=6) had venting G-tubes. 25/40 (62.5%) patients had successful OR to oxymorphone. The median ORR from MEDD to oxymorphone was 3.5 (IQR, 3.1–4). There were no independent predictors for successful OR, and ORR did not significantly differ among various groups.

Conclusions: Oxymorphone IR can be used successfully in cancer patients with G-tubes using an ORR of 3.5 to calculate dose from MEDD.

Keywords: Opioid rotation (OR); cancer; oxymorphone; gastrostomy tubes; bowel obstruction; pain

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Introduction

More than 80% of advanced cancer patients experience pain and require opioids (1-4). Up-titration of opioid doses to achieve sufficient analgesia may cause accumulation of opioid metabolites leading to the development of opioid-induced neurotoxicity (OIN) (5). Opioid rotation (OR), the substitution of one opioid by another, is recommended in situations such as OIN and uncontrolled pain despite opioid up-titration (6). Approximately 30–50% of cancer patients treated by palliative care teams will require an OR (6,7). OR is also performed when a change in the route of

administration is required, such as in cases of oral mucositis, dysphagia, and bowel obstruction (8-16).

The placement of a percutaneous endoscopic gastrostomy-tube (G-tube) in patients with dysphagia allows for the administration of opioids per-tube. Only methadone and immediate-release (IR) preparations of opioids can be administered per-tube, except for newer extended-release (ER) preparations of morphine and oxycodone which can be opened and the contents administered via G-tubes (8-10). However, these preparations are expensive and contraindicated in patients with bowel obstruction, ileus, and venting G-tubes (8-11). Venting G-tubes are frequently placed in patients with bowel obstruction and allows for orally administered IR opioids to be absorbed higher up in the gastrointestinal (GI) tract when the G-tube is temporarily clamped after administration. In patients with dysphagia or bowel obstruction, long-acting formulations of opioids are restricted to fentanyl patch due to its transdermal delivery, and methadone due to its pharmacokinetic properties (11-16), while conventional ER formulations of morphine, oxycodone, and hydromorphone are contraindicated (11). Transmucosal rapid-acting fentanyl products are useful only for breakthrough pain (12).

Oxymorphone is a potent semi-synthetic mu-opioid agonist initially approved in the 1950s. It is available in both IR and ER formulations.

In contrast to other IR oral opioids, oxymorphone IR has a longer half-life and takes a shorter time to attain peak concentration allowing for dosing every 8 hours. Oxymorphone does not utilize the cytochrome P-450 system and has minimal drug interactions. Adverse effects observed are no different than any other opioids, such as morphine, oxycodone, and hydromorphone (17-20). Oxymorphone IR tablet's unique features of a long half-life, rapid absorption from the upper GI tract, and ability to be crushed and administered via G-tubes, makes for an attractive alternative to fentanyl and methadone for long-acting pain control in patients with G-tubes. Our goal was to determine the proportion of successful OR to oxymorphone in cancer patients with G-tubes and to determine the OR ratio (ORR) from morphine equivalent daily dose (MEDD) to oxymorphone. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/apm-20-969).

Methods

This retrospective study was approved by the Institutional Review Board at The University of Texas MD Anderson Cancer Center (PA17-0385) and conformed to the provisions of the Declaration of Helsinki (as revised in 2013). Individual consent for this retrospective analysis was waived. We reviewed the charts of cancer patients with G-tubes between the years 2014 and 2017 to identify patients that underwent OR to oxymorphone IR. All cases from this time window were included in the data analysis to maximize the sample size and avoid selection bias. Data regarding patient characteristics, opioid use, MEDD, and scores on the Edmonton Symptom Assessment Scale (ESAS) (21), Memorial Delirium Assessment Scale (MDAS) (22), and Cut-down, Annoyed, Guilty, Eye-opener (CAGE) (23) questionnaire were obtained. Criteria previously reported by our team defining successful OR were used in our study (6,24-27). These criteria include: (I) a 30% or 2-point reduction in the ESAS pain [0–10] score, for OR due to uncontrolled pain; or (II) evidence of the disappearance of side effects at the follow-up visit for OR due to OIN; or (III) no worsening of pain score for OR performed due to change in route of administration or drug interaction; and (IV) continued use of oxymorphone at the time of follow-up in outpatients and discharge in inpatients.

ORR was calculated as the baseline pre-rotation MEDD mg/oxymorphone mg/day at the time of follow-up (outpatients) or discharge (inpatients) in patients who underwent a successful OR (6,24-27). The MEDD calculated based on the MEDD table used by our team (28).

Statistical analysis

Data were summarized using standard descriptive statistics such as mean, standard deviation, median, interquartile range (IQR), and range for continuous variables; frequency and proportion for categorical variables. Association between categorical variables was examined by the Chi-Squared test or Fisher's exact test when appropriate. Wilcoxon rank-sum test or Kruskal-Wallis test was used to examine the difference in continuous variables. Univariate logistic regression models were applied to assess the effect of variables of interest on the success of OR. All computations were carried out in SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Forty patients with G-tubes underwent OR from other strong opioids to oxymorphone. The median age was 56

Table 1 Summary of demographics & clinical characteristics

Covariate	Levels	Total	Success of opioid rotation		P value
			Yes	No	
All patients		40 (100%)	25 (62.5%)	15 (37.5%)	
Race	Asian	6 (15%)	4 (67%)	2 (33%)	0.9543
	Black	5 (12.5%)	3 (60%)	2 (40%)	
	Hispanic	6 (15%)	3 (50%)	3 (50%)	
	White	23 (57.5%)	15 (65%)	8 (35%)	
Gender	Female	13 (32.5%)	8 (61.5%)	5 (38.5%)	1.0000
Cancer type	Breast	2 (5%)	2 (100%)	0 (0%)	0.8020
	Gastrointestinal	14 (35%)	8 (57%)	6 (43%)	
	Genitourinary	1 (2.5%)	0 (0%)	1 (100%)	
	Gynecologic oncology	3 (7.5%)	2 (67%)	1 (33%)	
	Head/neck	19 (47.5%)	12 (63%)	7 (37%)	
	Lung	1 (2.5%)	1 (100%)	0 (0%)	
Advanced disease	Yes	36 (90%)	23 (64%)	13 (36%)	0.6225
CAGE score	Positive	12 (30%)	8 (67%)	4 (33%)	1.0000
History of substance use disorder	Yes	8 (20%)	5 (62.5%)	3 (37.5%)	1.0000
Smoking status	Yes	27 (67.5%)	16 (59%)	11 (41%)	0.7301
Inpatient or outpatient opioid rotation	Inpatient	27 (67.5%)	19 (70%)	8 (30%)	0.1384
	Outpatient	13 (32.5%)	6 (46%)	7 (54%)	
G-Tube type	Feeding	34 (85%)	20 (59%)	14 (41%)	0.3813
	Venting	6 (15%)	5 (83%)	1 (17%)	
ECOG performance status	1	2 (5%)	1 (50%)	1 (50%)	1.0000
	2	10 (25%)	6 (60%)	4 (40%)	
	3	26 (65%)	17 (65%)	9 (35%)	
	4	2 (5%)	1 (50%)	1 (50%)	
Characteristics of pain	Nociceptive and neuropathic	13 (32.5%)	10 (77%)	3 (23%)	0.2984
	Nociceptive	27 (67.5%)	15 (56%)	12 (44%)	
Reason for opioid rotation	OIN	2 (5%)	0 (0%)	2 (100%)	0.1346
	Pain	38 (95%)	25 (66%)	13 (34%)	

CAGE, cut down-annoyed-guilty-eye-opener questionnaire to screen for alcoholism; G-Tube, gastrostomy tube; OIN, opioid-induced neurotoxicity.

years, 27 (67.5%) were male, 23 (57.5%) were white, and 36 (90%) had advanced-stage cancer (*Table 1*). Twenty-seven (67.5%) were inpatients and 13 (32.5%) outpatients. Only 6/40 patients had venting G-tubes and received the medications orally with clamping of the G-tube, and the remainder had feeding tubes and received medications per-tube. Uncontrolled pain was the most common (95%) reason for OR.

Of the 40 patients, 27 continued to use oxymorphone at the time of discharge from the inpatient setting or at the

Table 2 ORR from MEDD to oxymorphone in patients with successful opioid rotation

Covariate	N	Median	Inter quartile range	Mean	Standard deviation
Oxymorphone total dose	25	30	[20, 40]	35.3	18.25
MEDD	25	102.5	[80, 150]	125.3	69.03
ORR	25	3.5	(3.11, 4)	3.6	0.74

ORR, opioid rotation ratio; MEDD, morphine equivalent daily dose.

time of follow-up in the outpatient setting, and 25 (62.5%) met the criteria for successful OR. Among the 15 patients with unsuccessful OR, five did not return for a follow-up, seven had insufficient improvement in pain requiring OR to another opioid, and three passed away in the palliative care unit and did not meet the criteria of successful discharge.

There were no independent predictors for successful OR. The median ORR from MEDD to oxymorphone was 3.5 (IQR, 3.1–4) in the 25 patients with successful OR (*Table 2*). The median ORR did not vary according to gender, cancer type, history of substance use, CAGE status, G-tube (feeding or venting), setting of OR (inpatient or outpatient), or baseline MEDD. The median ORR was 3.5 in patients with MEDD of <100 mg (11 patients) and ≥100 mg (14 patients).

There were no reports of any unusual side effects or discontinuation of oxymorphone related to G-tube administration or clamping of the venting G-tube.

Discussion

ORs in cancer patients have a success rate of ≥50% (29). ORs from MEDD to oxymorphone IR in cancer patients with G-tubes had a success rate of 62.5% in our study. Due to its long half-life, oxymorphone IR was successfully used in cancer patients with feeding tubes and conferred long term analgesia when administered every 8 hours around the clock. In contrast, other IR opioids have a half-life of ≤4 hours and require administration every 4 hours for efficient pain management. The need for six doses of IR opioids timed 4 hours apart may subject patients to uncontrolled pain associated with missed or delayed doses, and are cumbersome to administer at night interfering with sleep.

Oxymorphone is more lipophilic than morphine, hydromorphone, or oxycodone, resulting in quick absorption through the GI tract, faster penetration of the blood-brain barrier, and attainment of peak concentration in only 30 minutes. Due to its rapid absorption and long half-life, oxymorphone IR can be successfully used orally in patients with venting G-tubes for bowel obstruction. In these patients, oral administration of oxymorphone IR should be followed by clamping of the G-tube for 30 minutes.

The recommended ORR from oral morphine to oxymorphone is 3 (30 mg of morphine =10 mg of oxymorphone) (30). In our study, the median ORR from MEDD to oxymorphone in 25 cancer patients with G-tubes who underwent a successful OR was 3.5. Due to our small sample size, our group recommends that an ORR of 3 continue to be used for OR from MEDD to oxymorphone in patients with G-tubes. As always, close patient monitoring after OR is required. Unlike our previous OR studies involving hydrocodone, hydromorphone, and transdermal fentanyl, the ORR in this study did not differ according to the pre-rotation opioid dose (24-27).

Oxymorphone may have specific benefits when compared to other opioids. It has less potential for drug interactions since it does not involve the cytochrome P450 enzymes. Oxymorphone is metabolized by uridine diphosphate glucuronosyltransferase (UGT) to form oxymorphone 3-glucuronide (inactive metabolite), and 6-hydroxy-oxymorphone which can accumulate in renal failure (31). Oxymorphone must be prescribed with caution in patients with renal insufficiency and avoided in renal failure, similar to morphine, oxycodone, and hydromorphone. Oxymorphone is not highly protein bound and does not promote histamine release and hence may be helpful in patients with hypoalbuminemia and opioid-related pruritis. It is recommended that oxymorphone be taken on an empty stomach—at least 1 hour before or 2 hours after a meal. However, in clinical studies, oxymorphone did not demonstrate any clinically meaningful difference in absorption when taken with meals (18). Caution must be exercised with avoidance of oxymorphone administration closer to the timing of G-tube feeds.

Our study has some limitations, including its retrospective design, small sample size, and enrollment of

both inpatient and outpatient populations. Well-designed prospective studies in defined outpatient or inpatient populations must be conducted in the future to investigate the use of oxymorphone in patients with G-tubes, and to determine the ORR for OR from MEDD to oxymorphone.

In summary, oxymorphone IR offers another alternative to methadone, transdermal fentanyl, and newer ER opioid capsule preparations for long term pain control in cancer patients with feeding tubes and is an attractive option in patients with venting G-tubes where all ER oral opioid preparations are contraindicated.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/apm-20-969

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This retrospective study was approved by the Institutional Review Board at The University of Texas MD Anderson Cancer Center (PA17-0385) and conformed to the provisions of the Declaration of Helsinki (as revised in 2013). Individual consent for this retrospective analysis was waived.

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