Controlled Release of Oxycodone as an Opioid Titration for Cancer Pain Relief: A Retrospective Study

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Background: In 2014, a Chinese expert consensus was proposed regarding a titration protocol with controlled-release (CR) oxycodone as a background dose for relieving the moderate to severe cancer pain. This work aimed to summarize its efficacy and safety in our hospital.

Material/Methods: The Good Pain Management (GPM) protocol comprises a CR morphine or oxycodone given every 12-hours as a background dose and an immediate-release (IR) opioid as a rescue dose. Cancer patients with moderate to severe cancer pain were treated with this protocol, and the successful titration (numerical rating scale [NRS] ≤3 within 3 days) rate was analyzed. SPSS was used for statistical analysis. Differences of variables between opioid intolerant patients and opioid tolerant patients were analyzed using the Mann-Whitney U test. The chi square test was used for comparison of frequencies in different groups. A P-value <0.05 was set as the significance level.

Results: Among 257 enrolled patients, there were 179 opioid intolerant patients and 78 opioid tolerant patients. The successful titration rates were 91.1%, 94.4%, and 83.3% in the total population, in the opioid intolerant patients, and in the opioid tolerant patients, respectively. The successful titration rates and NRS were superior in the opioid intolerant patients compared to the opioid tolerant patients. The most common opioid adverse effects were constipation, somnolence, nausea, mouth dry, and vomiting; and no significant differences in side effects were found between groups.

Conclusions: Our study supports that the GPM titration protocol is effective for patients with moderate-severe cancer pain, and it is more effective for opioid intolerant patients.

MeSH Keywords: Management Audit • Oncology Service, Hospital • Therapy, Computer-Assisted

Abbreviations: **EAPC** – European Association of Palliative Care; **ECOG** – Eastern Cooperative Oncology Group; **CR** – controlled release; **GPM** – Good Pain Management; **IR** – immediate release; **NCCN** – National Comprehensive Cancer Network; **NRS** – numerical rating scale; **NSAIDs** – non-steroidal anti-inflammatory drugs; **PS** – performance status; **STR** – successful titration rate

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Background

Cancer pain is one of the most common symptoms in cancer patients, substantially affecting their life quality [1]. Strong opioid analgesics have been recommended as initial therapy for relieving moderate to severe cancer pain [2–7]. There is a great variation in the dose of opioids required by individuals, and titration is generally recommended to determine the optimal opioid dose, which helps reach an acceptable balance between analgesia and side effects. Previously, the European Association of Palliative Care (EAPC) recommended that titration with immediate-release (IR) opioids every 4-hours could be given for breakthrough pain [5,6]. The titration in the adult cancer pain guideline from the National Comprehensive Cancer Network (NCCN) is more aggressive in IR opioid usage [7]. To date, conversion of drug formulations from IR to controlled release (CR) is merited. In real-world clinical practice, the complicated procedures are major barriers in the effective management of cancer pain [8]. Recently, a new titration protocol using CR opioid as a background dose and IR opioid as a rescue dose has been developed. This protocol was thought to be more simple, practical, and easily mastered (by patients, caregivers, and clinicians) especially in the primary hospital setting [9–13]. Besides, it was theoretically efficient to reach the titration goal.

Good Pain Management (GPM) is a program to improve the management of cancer pain and life quality of cancer patients, which was launched in China in March 2011 [14]. At the fourth forum of the GPM Ward Program of heads of oncology departments in 2014, a Chinese expert consensus of a titration protocol (GPM titration protocol, Figure 1) with CR opioids for moderate to severe cancer pain was proposed. Afterwards, the GPM titration protocol had been incorporated in the Medicine Oncology Department in our hospital. In detail, The GPM titration protocol comprises a CR morphine or oxycodone given every 12-hours as a background dose and an IR opioid as a rescue dose. For opioid intolerant patients, the initial daily dose of CR opioid is 20 to 60 mg of CR morphine, or 20 to 40 mg of CR oxycodone. An equianalgesic to the total opioid doses is given in the past 24 hours for opioid tolerant patients. The rescue IR equianalgesic is 10% to 20% of total background doses in the past 24 hours. The following daily dose of CR opioid is increased according to different levels of pain: increasing by 50% to 100% when numerical rating scale (NRS) is from 7 to 10, 25% to 50% when NRS is from 4 to 6, and no increase when NRS is from 0 to 3. In our hospital, a built-in workflow was established, and then we trained the doctors and nurses in the medicine oncology department to comprehensively implement the workflow of the GPM titration protocol. Herein, we summarize the efficacy and safety of the GPM titration protocol in patients with moderate to severe cancer pain.

Material and Methods

Patients

The study was reviewed and approved by the Hospital Ethics Committee of Fujian Cancer Hospital and a waiver of informed consent was provided. All patients receiving CR oxycodone (Oxycontin®) from January 2015 to December 2015 in the Fujian Cancer Hospital Network were included. The primary inclusion criteria were as follow: patients with moderate to severe cancer pain (NRS 4–10) [7]; those given CR oxycodone titration for at least 3 days in line with the GPM titration protocol; age >18 years; with Eastern Cooperative Oncology Group (ECOG) performance status (PS) from 0 to 3; absence of cognitive impairment or psychiatric illness. The exclusion criteria were as follow: those without cancer pain; with unexplained pain, with post-operative pain, with neuropathic pain, with significant renal or hepatic disfunction, such as the creatinine ≥2×the upper limit of normal (ULN), ALT and AST ≥2.5×ULN.

For each included patient, we recorded the age, gender, cancer type, primary and secondary sites, ECOG PS score before starting titration, opioid tolerance or intolerance, daily oxycodone dose of the first 3 days, use of non-steroidal anti-inflammatory drugs (NSAIDs), opioid adverse effects, daily NRS scores before titration and in the first 3 days of titration, and times of daily breakthrough pain in the first 3 days.

The medical record system provided the information of age, sex, cancer type, primary and secondary sites, ECOG PS score, and NSAIDs usage. Daily oxycodone dose of the first 3 days was calculated by the physician. The NRS was recorded by the average score of cancer pain in the previous 24 hours. An NRS of 4–6 was defined as moderate pain and 7–10 as severe pain. The first day of titration was defined as day 1. Opioid intolerance refers to those were not chronically receiving opioid analgesic on a daily basis. The opioid tolerant patients mainly included those chronically receiving opioid analgesic on a daily basis. Tolerance was defined as receiving at least 60 mg of morphine daily, 30 mg of oral oxycodone daily, or 8 mg of oral hydromorphone daily, or an equianalgesic dose of other opioid medication for a week or longer.

The primary endpoint of this study focused on the successful titration rate (STR), namely NRS decreased to a level of ≤3 duration 3 days of titration [15,16]. We calculated the ratio of the increased upward dose using the difference between the following daily dose and previous daily dose divided by the previous daily dose.

Statistical analysis

All categorical data were expressed in percentages with 95% confidence intervals (CI); continuous data were expressed in
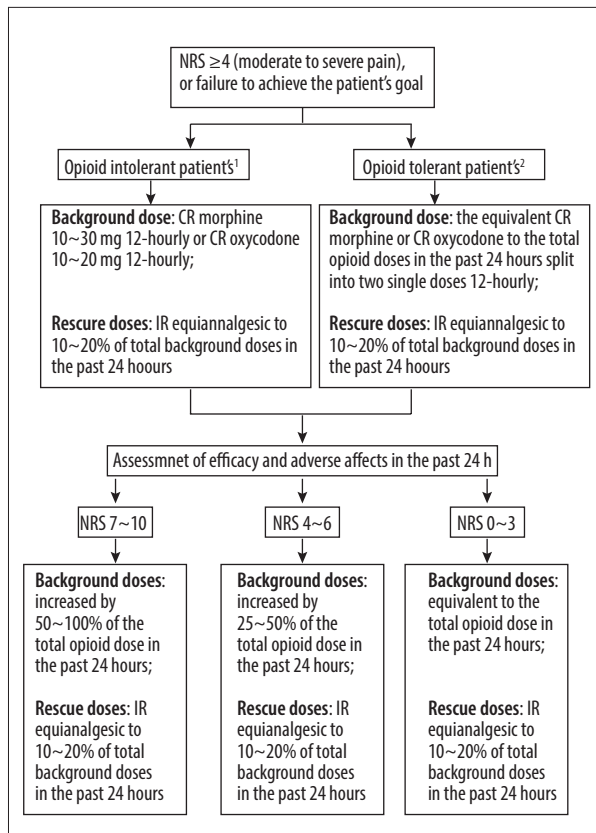
Figure 1. Flowchart of the Good Pain Management (GPM) titration protocol for opioid titration in moderate to severe cancer pain. (1) Opioid intolerant includes patients who are not chronically receiving opioid analgesic on a daily basis; (2) Opioid tolerant includes patients who are chronically receiving opioid analgesic on a daily basis; (3) Tolerance was defined as receiving at least 60 mg of morphine daily, at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid for a week or longer.

medium with ranges or mean±standard deviation (SD). SPSS software was used for statistical analysis. Differences of variables between opioid intolerant patients and opioid tolerant patients were analyzed using the Mann-Whitney U test for the counts of breakthrough pain, the mean dose of CR oxycodone, and the median upward increased dose (in patients with dose adjustment). The chi square test was used for comparison of frequencies in different groups. A P value <0.05 was set as the significance level.

Results

Overall, 339 patients were excluded, and 257 included patients were analyzed (Figure 2). Twenty patients (7.8%) received NSAIDs during the study period. There were 179
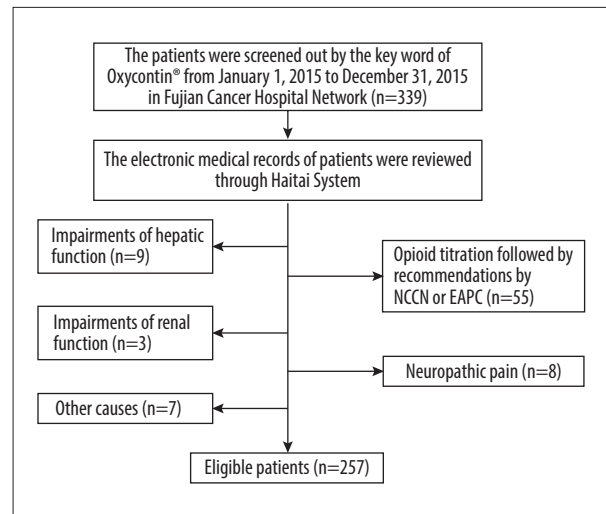
Figure 2. The inclusion and exclusion process of this study.

opioid-intolerant patients (69.6%) and 78 opioid-tolerant patients (30.4%). The basal clinical characteristics are shown in Table 1. Among all cancer types, colorectal cancer patients showed a high proportion of the opioid tolerant patients than opioid-intolerant patients (19.2% versus 4.5%, $P<0.001$). The ECOG PS of the opioid intolerant patients was better than the opioid tolerant patients ($P=0.01$).

Of all the included patients, the overall STR was 91.1% (95% CI: 86.9% to 94.0%), it was significantly higher ($P=0.004$) in the opioid intolerant patients (94.4%, 95% CI: 90.0% to 96.9%) than tolerant (83.3%, 95% CI: 73.5% to 90.0%) (Table 2). The mean daily NRS score at the baseline was not significantly difference between the opioid intolerant and opioid tolerant patients and mean daily NRS scores in the following 3 days were significantly lower in the opioid intolerant group (Table 3). Subsequently, breakthrough pain in the first 3 days of titration was analyzed (Table 4). There were 195 patients (75.9%, 95% CI: 70.3% to 80.7%) experienced ≤2 episodes of breakthrough pain, and 235 patients experienced ≤4 episodes of breakthrough pain (91.4%, 95% CI: 87.4% to 94.3%). The number of patients who experienced ≥2 episodes of breakthrough pain on day 1, day 2, and day 3 was 58, 37, and 17, respectively. The frequency of breakthrough pain in the first 3 days of titration was significantly lower in the opioid intolerant patients compared to the opioid tolerant patients (1.08±1.79 versus 2.50±2.45, $P<0.001$). Moreover, besides opioid tolerance (r=0.376, $P<0.001$), breakthrough pain counts had a significantly positive correlation with the basal ECOG score (r=0.185, $P=0.003$). This finding suggests that using the GPM protocol with CR oxycodone is highly recommendable for opioid intolerant patients with a low ECOG score.

Table 5 shows the daily doses of CR oxycodone and ratios of the upward increased dose on day 1 to day 3. The daily dose of

Table 1. Patient characteristics.

Characteristic	Total (n, %) n=257		Opioid tolerant n=78		Opioid intolerant n=179	
Gender						
Male	192	(74.7%)	69	(88.5%)	123	(68.7%)
Female	65	(25.3%)	9	(11.5%)	56	(31.3%)
Age, Years						
Median (range)	58	(18-81)	57	(24-77)	58	(18-81)
Cancer type						
Lung cancer	126	(49.0%)	37	(47.4%)	89	(49.7%)
Gastric cancer	27	(10.5%)	9	(11.5%)	18	(10.1%)
Colorectal cancer	23	(8.9%)	15	(19.2%)	8	(4.5%)
Esophageal cancer	21	(8.2%)	7	(9.0%)	14	(7.8%)
Others	60	(23.3%)	10	(12.8%)	50	(27.9%)
ECOG PS						
0–1	225	(87.5%)	62	(79.5%)	163	(91.1%)
2–3	32	(12.5%)	16	(20.5%)	16	(8.9%)
Pain intensity (NRS)						
4	149	(58.0%)	44	(56.4%)	105	(58.7%)
5	81	(31.5%)	26	(33.3%)	55	(30.7%)
6	24	(9.3%)	6	(7.7%)	18	(10.1%)
7	3	(1.2%)	2	(2.6%)	1	(0.6%)

ECOG – Eastern Cooperative Oncology Group; PS – performance status; NRS – numerical rating scale.

Table 2. Successful titration rates.

	No. of patients with NRS of pain ≤3 (%, 95% CI)		
	Total patients	Opioid tolerant	Opioid intolerant
Day 1	126 (49.0%, 43.0% to 55.1%)	20 (25.6%, 17.3% to 36.3%)	106 (59.2%, 51.9% to 66.2%)
Day 2	184 (71.6%, 65.8% to 76.8%)	48 (61.5%, 50.4% to 71.6%)	136 (76.0%, 69.2% to 81.7%)
Day 3	234 (91.1%, 86.9% to 94.0%)	65 (83.3%, 73.5% to 90.0%)	169 (94.4%, 90.0% to 96.9%)

NRS – numerical rating scale; CI – confidence interval.

Table 3. Mean NRS score in first 3 days.

	Total	Opioid tolerant	Opioid intolerant	P
Day 0	4.54 (±0.71)	4.56 (±0.75)	4.53 (±0.70)	0.69
Day 1	2.89 (±1.23)	3.45 (±1.06)	2.65 (±1.22)	<0.001
Day 2	2.39 (±1.14)	2.73 (±1.19)	2.25 (±1.09)	0.003
Day 3	1.88 (±1.03)	2.13 (±1.32)	1.78 (±0.85)	0.03

Table 4. Breakthrough pain frequencies in first 3 days.

	Opioid tolerant	Opioid intolerant	P
Day 1	1.26±1.06	0.57±0.86	<0.001
Day 2	0.79±1.02	0.31±0.67	<0.001
Day 3	0.37±0.79	0.19±0.56	0.068
Total	2.50±2.45	1.08±1.79	<0.001

Table 5. Mean daily dose of controlled-release oxycodone (mean±SD) and ratio of upward dose.

	Total		Opioid tolerant		Opioid intolerant	
	Mean dose	Ratio of upward dose	Mean dose	Ratio of upward dose	Mean dose	Ratio of upward dose
Day 1	35.6 mg (±56.2)		72.9 mg (±91.2)		19.2 mg (±7.9)	
Day 2	47.0 mg (±63.8)	32.0%	95.0 mg (±99.2)	30.1%	26.0 mg (±12.6)	35.4%
Day 3	55.2 mg (±76.6)	17.4%	112.0 mg (±118.8)	17.9%	30.4 mg (±17.6)	16.9%

SD – standard deviation.

CR oxycodone in the opioid tolerant patients was significantly higher than in the opioid intolerant patients in the first 3 days (*P*<0.001). There were 160 patients receiving a dose adjustment, including 67 opioid tolerant and 99 opioid intolerant cases. The median upward dose was 20 mg (range 5 mg to 120 mg) in the opioid tolerant group and 10 mg (range 5 mg to 30 mg) in the opioid intolerant group, respectively (*P*<0.001). The median ratios of the upward dose were 100% (range 33.3% to 300%) and 35.7% (range 7.2% to 188%) in the opioid tolerant and opioid intolerant patients, respectively (*P*<0.001). The initial daily titration dose in opioid intolerant patients with moderate pain was 10 mg, among whom 19 patients (45.2%) achieved successful titration without dose adjustment.

Finally, the most common opioid adverse effects were constipation (n=83, 32.3%), somnolence (n=65, 25.3%), nausea (n=46, 17.9%), dry mouth (n=36, 14.0%), vomiting (n=32, 12.5%), dizziness (n=25, 9.7%), and pruritus (n=19, 7.4%). However, these adverse effects were well tolerated after symptom treatment. There were no significant differences in type and incidence of side effects between groups.

Discussion

To date, titration with an IR opioid for cancer pain has been commonly recommended by various guidelines [5–7]. However, many clinicians simply use a CR opioid titration without individualized treatment. Meanwhile, they usually do not know how to teach patients opioid titration. Therefore, an opioid titration protocol with simplicity and effectiveness can largely benefit patients with cancer pain. Recently, increasing evidences have shown that CR formulations have good effectiveness and safety for opioid titration. Prospective studies suggested that use of once-daily CR opioids does not delay the time of pain control and is as effective and well tolerated as the 4-hourly IR opioid titration [9,10]. Protocols have also been developed for the standard of CR oxycodone titration in clinical practice [13].

STR of the GPM titration protocol in our study was 91.1% after 3 days of titration, with a 58.6% reduction in NRS score from baseline to day 3. Similarly, Silvestri et al. reported a reduction by 47.2% in the NRS score from baseline to day 3 in 390 patients with controlled oxycodone [12]. Klepstad et al. reported a reduction by 40.0% in a 7-point verbal-rating-scale score [10]. Salzman et al. reported a reduction by 38.9% in a 3-point pain intensity score [9]. A retrospective study using continuous and on demand opioids (CoDem) in 73 patients reported more than 50% of individuals acquired NRS score reduction of at least 2 points [13]. Although it is difficult to directly compare our results with these studies because of different assessment methods, we strongly support that the GPM titration protocol has a satisfactory efficacy.

Application of this protocol in opioid intolerant patients had better performance in STR, mean daily pain scores, and incidence of breakthrough pain. One possibility was that the types of cancer in the tolerant group were associated with more intractable pain, for example, colorectal cancer patients with bowel obstructions are difficult to treat. Besides, the pain type was significantly associated with the opioid tolerant classification (not shown), which potentially impact the titration

outcomes. Another possibility was that clinicians were more reluctant to increase the dose towards the opioid tolerant patients. The basal dose had been higher for the opioid tolerant patients compared with intolerant, accordingly, the dose increase would be much greater in the tolerant group than the intolerant group (40 mg versus 20 mg). However, when excluding patients who did not have a dose adjustment, the ratio of dose increase was much lower in the opioid tolerant patients than the opioid intolerant ones (35.7% versus 100%). This is reasonable considering that it would be easier to accept a high ratio of dose increase when the dose at baseline was low. Another reason is that the minimal dosage in the market is 5 mg and an initial daily dose of ≤20 mg (10 mg every 12 hours) was used more often in opioid intolerant patients than opioid tolerant patients (63 patients versus 12 patients). This caused a high ratio relatively. As aforementioned, the CoDem study proposed by Samolsky et al. demonstrated that the absolute value and ratio of the upward dose in opioid tolerant patients is higher than in opioid intolerant patients, while the pain control in opioid tolerant patients is not inferior to that in opioid intolerant patients [13]. Therefore, clinicians need to be encouraged to be more aggressive in increasing the dose when the baseline dose is high.

In our study, the minimal effective opioid dose varied widely among individuals. A small proportion of patients may archive cancer pain control with a small daily dose of CR oxycodone (10 mg) [13,17]. The CoDem titration protocol with an initial daily dose of 10 mg in opioid naïve patients and 20 mg in weak-opioids tolerant patients were shown effectiveness [13]. Therefore, the initial daily dose in a GPM titration protocol is crucial. Nevertheless, an initial daily dose reduced to 10 mg may compromise the efficacy of pain control for many patients. Further exploration of the optimal initial dose for opioid intolerant patients is warranted. Especially in Asian patients whose average body weights are much lower than Western patients, a lower initial dose may be better tolerated [17]. Moreover, genotype testing can be applied for selecting different initial opioid dose [18,19].

In the GPM titration protocol, whether the dose of CR oxycodone on subsequent days needs to be increased depends on a 10-point NRS score ≥4, while in the CoDem titration protocol it depends on the number of rescue doses consumed ≥2 [13]. In our study, the daily number of patients with an NRS ≥4 was higher than the number of patients with 2 or more incidence of breakthrough pain, the cause of which may be that the patients with breakthrough pain were reluctant to disturb the caregivers in our study. Subsequently, the need for a dose increase seemed greatly reduced based on incidences of breakthrough pain. Therefore, it is more reasonable to increase the dose depending on the NRS score rather than the incidence of breakthrough pain for Chinese population.

In the GPM titration protocol, the increased dose of CR oxycodone included different percentage of the total equivalent opioid dose used in the past 24 hours as well as the rescue dose according to the different pain levels. However, in the CoDem titration protocol, the increased dose of CR oxycodone for the following day is equivalent to the rescue dose consumed in the past 24 hours. The GPM protocol has a more aggressive strategy for increasing the dose. However, it does not significantly increase the incidence of opioid adverse effects.

Still, there are some limitations in our study. First, this retrospective study has a relatively short observation duration and lack of comparator, and future prospective studies are needed to address the existing obscures. Second, most patients in our study had moderate cancer pain. However, NCCN titration protocols were usually applied for patients with severe pain in order to rapidly achieve pain relief. Further evidences are to be accumulated to reveal more reflective efficacy of the GPM titration protocol for severe cancer pain. Third, our study excluded neuropathic pain which has a low incidence in our hospital. Lack of use of antidepressants and anticonvulsants in our hospital may negatively impact the effectiveness for neuropathic pain. Therefore, our study did not approve the effectiveness of the GPM titration protocol for neuropathic pain.

Conclusions

Together, as the GPM titration protocol advised, using CR opioid as a background dose and IR opioid as a rescue dose is effective and reasonably tolerated for patients with moderate/severe cancer pain, especially those without opioid tolerance and a low ECOG score. Our study revealed that this protocol not only increases patient compliance, but also reduces the workload of caregivers, for it avoids the step of converting the drug formulation and prolongs the overall titration time.

Acknowledgements

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