ORIGINAL ARTICLE

Clinical effectiveness and safety of OROS® hydromorphone in breakthrough cancer pain treatment: A multicenter, prospective, open-label study in Korean patients

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ABSTRACT

Objective: *To evaluate the effectiveness of OROS® hydromorphone in reducing breakthrough pain (BTP) medication frequency in Korean patients with chronic cancer pain.*

Settings and Design: *Multicenter, prospective, open-label, phase IV study.*

Participants: *Patients with chronic malignant pain using immediate-release oxycodone more than two times per day for BTP.*

Interventions: *Patients were stabilized on their ongoing drug for 3 days immediately before baseline measurements (day 0). Medication was changed to OROS® hydromorphone at a dose equianalgesic to oxycodone using a 2.5:1 controlled-release oxycodone to hydromorphone hydrochloride conversion ratio; the patients were observed for 7 days. Dose was titrated, if required, and the patients were observed for another 7 days. Effectiveness and safety parameters were measured at baseline, day 7, and day 14.*

Main Outcomes: *BTP medication frequency on days 7 and 14, compared to baseline.*

Results: *Of the 141 patients screened, 114 received study drug and 98 completed the study. Compared to day 0, daily BTP medication frequency on day 14 decreased from 2.93 to 2.00 ($p < 0.0001$), daily BTP frequency decreased from 3.67 to 2.44 ($p < 0.0001$), and end-of-dose pain frequency decreased by 44 percent. Pain was controlled adequately during daytime and night-time. Pain intensity decreased by 11 percent as assessed using the Korean Brief Pain Inventory and by 17 percent as assessed using the numerical rating scale. About 61.2 percent patients and 60.2 percent physicians were satisfied with the treatment. Common adverse events, which occurred in 91.2 percent patients, were constipation, somnolence, and dizziness.*

Conclusion: *Once-daily OROS® hydromorphone is efficient in the reduction of cancer pain-related BTP episodes, including end-of-dose pain.*

INTRODUCTION

Pain is a prevalent yet undertreated symptom of cancer. According to a recent analysis, more than 50 percent cancer patients suffer from pain, mainly of moderate to severe intensity.[1] Apart from baseline chronic pain, some cancer patients suffer from short episodes of high-intensity pain known as episodic or breakthrough pain (BTP). BTP has been defined in various ways. According to the BTP Consensus Panel 2005 recommendations, the most widely accepted definition of BTP is "a transient exacerbation of pain that occurs in patients with an otherwise stable baseline pain."[2] This definition necessitates the presence

of persistent baseline pain in patients and emphasizes the transient nature and high intensity of BTP. Depending on the characteristics, BTP has been further subdivided into three main types: (1) incidental BTP occurs after a motor activity such as breathing, coughing, or micturition. Owing to its clear association with some form of motion, the occurrence of incidental BTP is usually predictable. (2) Idiopathic BTP has a sudden onset and is not associated with any particular cause. (3) End-of-dose BTP occurs when the effect of an ongoing analgesic drug has subsided. Usually, it occurs immediately before the scheduled dose of a round-the-clock pain medication. Neuropathic and nociceptive types of BTP have also been distinguished.[2]

The World Health Organization (WHO) has defined a three-step analgesic ladder for the treatment of cancer pain. Following the evaluation of patient's pain intensity, nonopioid drugs such as ibuprofen may be administered for mild pain (step 1), mild opioids such as codeine for mild to moderate pain (step 2), and strong opioids such as morphine for moderate to severe pain (step 3). According to the WHO general guideline for controlling BTP, an additional dose of 50-100 percent of the regular four hourly dose should be used as a "rescue drug" for BTP relief.[3]

Morphine and codeine are on the WHO-recommended list of essential drugs for the treatment of chronic as well as breakthrough cancer pain of moderate to severe intensity.[3] These drugs have successfully provided excellent pain relief to cancer patients, although prolonged use of opioids is said to result in increased drug tolerance.[4] Additionally, the genetic makeup of patients may affect the response to different opioids.[5] It has been reported that about 10-30 percent of cancer patients fail to respond to morphine treatment mainly because of (1) excessive adverse events, (2) inadequate analgesia, or (3) a combination of both.[6] In such cases, it has been suggested that opioid rotation, particularly with a pure opioid agonist such as oxycodone, methadone, hydromorphone, and fentanyl, may benefit nonresponding patients.[6] Furthermore, drug conversion may reduce side effects associated with the continuous use of a drug and may minimize the possibility of addiction, thereby enhancing pain relief.[7]

Hydromorphone, which is a hydrogenated, semisynthetic, ketone derivative of morphine, has been widely recommended as an alternative to morphine.[8] Like morphine, hydromorphone acts through the μ-opioid receptor of the central nervous system to exert its analgesic effect and does not show saturation in efficacy with increasing dose. The upward dose titration is, therefore, limited only by the side effects of the drug.[9] The physiologic half life of the immediate-release (IR) formulation of hydromorphone has been estimated to be 2.64 ± 0.88 hours, with a 1.22 L/kg distribution volume[10]; thus, the drug has to be administered every 4-6 hours to maintain a steady concentration in the body. To reduce the number of doses, a once-daily extended-release (ER) formulation of hydromorphone has been developed based on the OROS® (Alza Corporation, Mountain View, California, USA) push-pull™ osmotic release technology. The ER technology enables controlled delivery of the drug for up to 24 hours with negligible peak-trough variations.[11] The overall efficacy of OROS® hydromorphone has been found to be comparable to its IR counterpart.[11,12] Thus, owing to its favorable properties, OROS® hydromorphone has been effectively and safely used in the treatment of malignant and nonmalignant pain.[13]

With respect to opioid rotation, it is important to consider the dose conversion ratio between the drugs, as opioids show a wide variation in their potency. Studies have shown that hydromorphone is at least five times more potent than morphine, making the 5:1 morphine to hydromorphone ratio a standard conversion ratio between these two opioids.[14,15] An effective conversion ratio and dose titration protocol is one that allows a reduction in, or helps maintain, both BTP frequency and BTP medication frequency after drug conversion.

In the current study, we evaluated the effectiveness and safety of OROS® hydromorphone in reducing the BTP frequency and the BTP medication frequency in Korean cancer patients by using a 2.5:1 controlled-release oxycodone to hydromorphone hydrochloride conversion ratio.

METHODS

Study design

This prospective, multicenter, open-label trial was conducted at five sites across the Daegu and Kyung-Buk areas in Korea from October 2008 to September 2009. The study protocol was approved by the Institutional Review Board of each site, and the study was conducted in accordance with the Korean requirements for execution of clinical trials, International Conference on Harmonisation Good

Clinical Practices guidelines (2000), and the Declaration of Helsinki (1964). All patients provided written informed consent.

Study population

Enrolled patients were adults (>20 years) with chronic malignant pain caused by the underlying malignant disease for whom the frequency of IR opioid analgesic for BTP was more than two times per day for 3 days immediately prior to the baseline measurements. Patients were excluded from the trial if they required interventional procedures such as surgery; were pregnant or lactating; or had hypersensitivity to hydromorphone, gastrointestinal diseases likely to interfere with oral analgesic effects, colostomy, history of alcohol abuse within the last 6 months, or requirement for radiotherapy.

Interventions

The study was divided into three main phases: screening/stabilization, observation, and titration (Figure 1). The first phase included screening where eligible patients were enrolled in the trial and stabilized on their previous opioid analgesic (oxycodone). Stabilization was defined as at least 3 consecutive days of the screening phase during which the baseline daily oxycodone dose remained the same and more than two doses per day of rescue medication were required for BTP. Immediately after the third day of stabilization (day 0), baseline vital and demographic data, including pain intensity, pain frequency, and BTP subtype frequency, were collected; thereafter, patients underwent conversion to OROS® hydromorphone at a dose equivalent to oxycodone in effectiveness. Dose equivalence was calculated using the 2.5:1 controlled-release oxycodone to hydromorphone hydrochloride ratio, and the minimum starting dose of hydromorphone was 8 mg/d, as reported in literature.[15]

Patients were treated on an outpatient basis, and OROS® hydromorphone was provided in the form of 8, 16, and 32 mg tablets. There was no washout of or overlap with the previous opioid drug. The patients were specifically instructed to take hydromorphone at 8:00 AM each morning. The tablet was to be swallowed whole with water without chewing, dividing, or crushing. Patients were informed that the nonabsorbable shell of the tablet would pass off in stool. IR hydromorphone was used as the rescue medication, when needed, at a dose equaling 10-15 percent of OROS® hydromorphone. No other opioid medications were permitted after drug conversion. Patients were allowed to use nonopioid and adjuvant analgesics, if required.

Drug conversion was followed by a 7-day observation phase (days 0-7). On day 7, interim effectiveness and safety parameters were recorded, and dose adjustments were made for patients who required rescue medication more than four times per day on average for BTP. During the titration phase (days 7-14), depending on whether the dose of OROS® hydromorphone during the observation phase was <32 mg or >32 mg, the dose was increased by increments of 8 mg or 16 mg, respectively. If the dose was 32 mg, titration was performed based on physician's discretion, and the patients received either 8 mg or 16 mg dose increments. At the end of the titration phase (day 14), the effectiveness and safety data were collected, and the trial was closed.

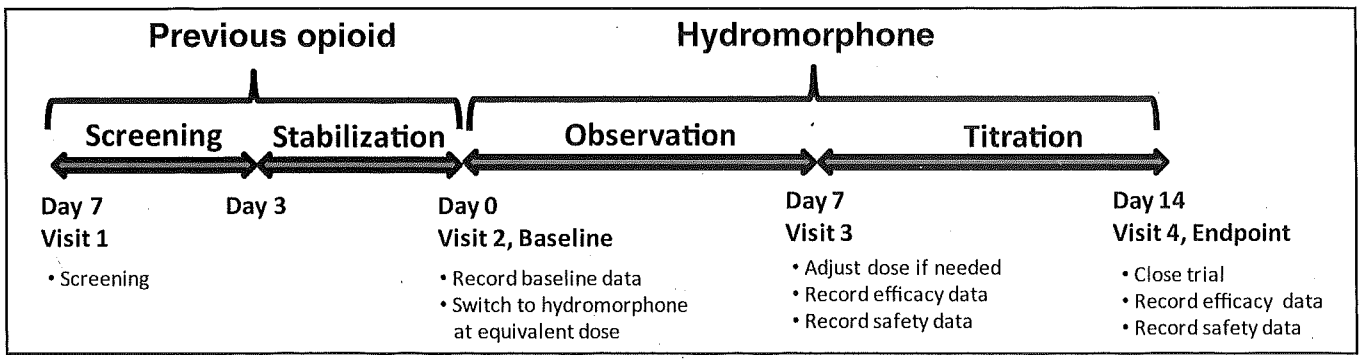

Figure 1. Study design. The study was divided into screening/stabilization, observation, and titration phases. Screening was performed at visit 1 and was followed by stabilization. Baseline data were recorded on day 0 after at least 3 days of stabilization, and the drug was changed to OROS® hydromorphone. After 7 days of observation, the dose was titrated as needed, and the patients were observed for another 7 days. The study was closed on day 14 from the baseline.

Primary outcomes

The medication frequency of IR opioid analgesics for BTP treatment was measured at baseline, day 7, and day 14. Medication frequency at each time point was a mean of the medication frequency recorded in the patient's pain diary for the 3 days immediately prior to the respective visit. Data were considered for calculating the mean if both 8:00 AM and 8:00 PM values were available for 3 days; however, the calculation was omitted if only one value was available for any of the 3 days. The frequency of BTP and its subtypes was evaluated by using the data recorded in the patient's pain diary. The typology of the BTP subtypes was based on the definition provided by Bennet et al.[2] The primary effectiveness endpoint was the change from baseline in frequency of BTP medication at day 14.

Secondary outcomes

Secondary endpoints included evaluation of analgesic effectiveness, pain intensity, pain severity, pain relief, pain interference, quality of life, global effectiveness of the study drug, and patient's and physician's medication preference. Analgesic effectiveness was assessed two times per day at 8:00 AM and 8:00 PM by using the previously validated[16] short form of the Korean-Brief Pain Inventory (K-BPI), which the patients completed on day 0, day 7, and day 14. Pain intensity was rated on a scale ranging from 0 (no pain) to 10 (pain as bad as you can imagine). Intensity was evaluated for least pain, pain at its worst, current pain, and average pain during the last 24 hours; an average of the four scores was termed as pain severity. In addition to the K-BPI, pain severity was also assessed using a numerical rating scale (NRS) of 0 (no pain) to 10 (most severe pain). Pain relief was rated on a scale of 0 percent (no relief) to 100 percent (complete relief). Interference of pain in general activities, mood, ability to walk, normal work activities, relationships with others, sleep, and enjoyment of life was rated on a scale of 0 (no interference) to 10 (complete interference). Patients were also asked to fill out the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30; available on the EORTC Web site) comprising 30 questions at the time of screening and at the end of the trial or upon withdrawal/unscheduled visit.

Global effectiveness of the study medication was assessed by the patients and the physicians at baseline and at the end of the trial (or an early withdrawal/unscheduled visit) using a five-point scale (1, ineffective; 2, average; 3, effective, 4, very effective, 5, highly effective). Patients' preference between their previous drug and the study drug was also evaluated.

Safety outcomes

Safety and tolerability were assessed based on the adverse events (AEs) and serious adverse events (SAEs) that were reported by the patients or identified by the investigator during the follow-up visits and in terms of the number of patients who discontinued the treatment because of AEs. Patient discontinuation was considered if an inadequate analgesic response occurred following OROS® hydromorphone and IR medications, patient's condition became unstable, or an SAE occurred.

Statistical analysis

The required sample size was estimated to be 96 patients and target sample size as 120 patients based on the following assumptions: 95 percent certainty, 50 percent response rate (decrease in pain intensity in the last 24 hours), and 20 percent drop rate.[17] The intent-to-treat (ITT) set included all patients who received at least one dose of the study medication and provided data for BTP frequency on day 7 (end of the observation phase). This set was used to calculate the parameters indicative of effectiveness and safety. Demographic and baseline characteristics were summarized using descriptive analysis. Quantitative data were represented as mean (SD) and qualitative data, as frequency and percentages. The primary effectiveness endpoint and quantitative secondary effectiveness endpoints, including some safety data, were analyzed using the paired t-test and Wilcoxon signed-rank test depending on whether or not the data followed a normal distribution. Repeated one-factor analysis was used for assessing the change in pain intensity with time. A χ^2 test was used for qualitative variables, and 95% confidence interval was determined, where applicable. The statistical software used was SPSS (version 14.0; SPSS Inc., Chicago, IL, USA), and the results were considered statistically significant if p was <0.05.

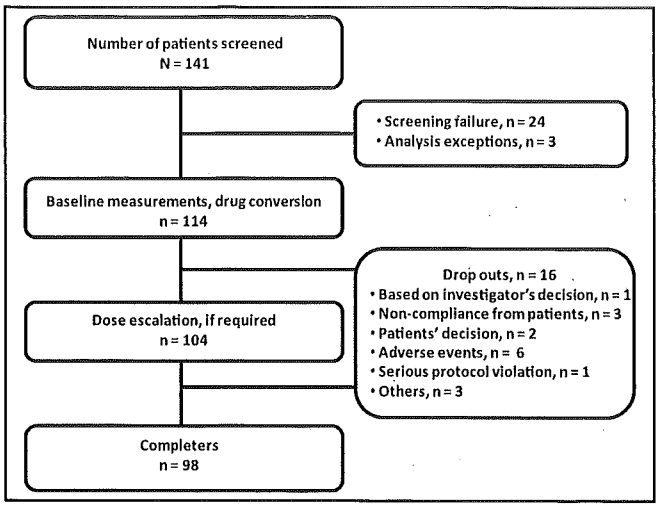

Figure 2. Patient disposition. A total of 141 patients were screened, of which 114 received the study drug, 104 underwent dose titration, and 98 completed the study.

RESULTS

Patient disposition

Of the 141 patients screened, 114 were found eligible for the study and were stabilized on their ongoing opioid. A total of 10 patients withdrew from the trial during the observation phase, and six patients withdrew during the titration phase. At the end of the trial, 98 (86 percent) patients completed the study and 16 (14 percent) withdrew from the trial (Figure 2). The reasons for withdrawal in these 16 patients were as follows: AEs, six (38 percent); noncompliance, three (19 percent); patient's choice, two (13 percent); serious protocol violation, one (6 percent); investigator's decision, one (6 percent); and other causes, three (19 percent).

Demographics

The demographic data of the study population are shown in Table 1. The mean (SD) age was 58.2 (11) years and 67 percent were males. Metastatic lesions were present in 84.2 percent of the patients in the screening period, with the most common site being the lung (20.8 percent). All patients had cancer-related pain and were receiving oxycodone (mean dose 61.8 mg) as their prestudy opioid for pain control.

Primary outcomes

The mean of all the average BTP frequencies assessed using the patient pain diary decreased significantly ($p < 0.001$) on day 7 and day 14 as compared to that at the baseline (Figure 3A). The mean (SD) frequency of the IR rescue drug required for BTP relief decreased from 2.93 (0.99) times per day at baseline to 2.11 (1.56) times per day on Day 7 and to 2.00 (1.14) times per day on day 14 (Figure 3B). Analysis of BTP incidence by subtypes showed that the frequency of all the three subtypes decreased on day 7 and day 14, as shown in Figure 3A. Compared to baseline, the incidental BTP frequency decreased by 30 percent on day 7 and 33 percent on day 14, whereas the idiopathic BTP frequency decreased by 25 percent on day 7 and 29 percent on day 14. More importantly, the end-of-dose BTP frequency showed a 33 percent decrease on day 7 and 41 percent decrease on day 14 as compared to that at the baseline. As end-of-dose BTP usually occurs when the effect of a round-the-clock analgesic subsides, a decrease in end-of-dose BTP indicates a consistent pain-controlling ability of the drug. Upward adjustment of doses was needed in 53 (54 percent) patients, whereas the dose had to be titrated downward in three (3 percent) patients because of the occurrence of AEs. The mean dose of OROS® hydromorphone at the start and end of the titration phase was 27.93 and 41.14 mg, respectively.

Secondary outcomes

Pain intensity at its worst, at its least, current pain intensity, and average pain intensity over the last 24 hours all showed a decrease on day 14 compared to the baseline, as measured by the K-BPI. In particular, differences were found to be statistically significant for pain at its worst (5.93 vs 5.13, $p < 0.001$) and average pain intensity over the last 24 hours (3.75 vs 3.26, $p < 0.005$). Subgroup analysis was carried out to determine the number of patients who had >50 percent decrease in pain intensity in the last 24 hours, following drug conversion. A total of 15 of 98 (15.3 percent) showed a >50 percent decrease in pain intensity at the end of the trial as compared to the baseline. As seen in Figure 4, the BTP frequency and BTP medication frequency of these patients decreased dramatically ($p < 0.001$). These results suggest that there is a subset of cancer patients who respond better to OROS® hydromorphone and may greatly benefit from opioid conversion.

The mean (SD) pain severity measured using the K-BPI showed a decrease from 3.60 (1.25) at the baseline to 3.20 (1.36) on day 7 and to 3.08 (0.003)

Table 1. Demographic data	
Variable	**ITT set, n = 114**
Age, years; mean (SD)	58.15 (11.04)
Height, cm; mean (SD)	162.20 (8.36)
Weight, kg; mean (SD)	58.59 (8.34)
Gender, n (percent)	
Male	76 (66.7)
Female	38 (33.3)
Diagnosis, n (percent)	
Lung cancer	25 (20.8)
Stomach cancer	20 (35.7)
Pancreatic cancer	10 (8.3)
Breast cancer	7 (5.8)
Esophageal cancer	7 (5.8)
Colorectal cancer	5 (4.2)
Liver cancer	4 (3.3)
Multiple myeloma	3 (5.4)
Lymphoma	3 (2.5)
Endometrial cancer	2 (1.7)
Cervical cancer	1 (0.8)
Others	17 (15)
Metastasis, n (percent)	
Yes	96 (84.2)
No	18 (15.8)
ECOG performance status*, n (percent)	
0	1 (0.9)
1	76 (66.7)
2	34 (29.8)
3	2 (1.8)
4	1 (0.9)
Stage,† n (percent)	
4	90 (78.9)
3	7 (6.1)
2	4 (3.5)
1	3 (2.6)
Others	10 (8.8)
Previous treatment for cancer, n (percent)	
Yes	70 (61.4)
No	44 (38.6)
Type of treatment received for cancer, n (percent)	
Chemotherapy	62 (73.8)
Radiotherapy	12 (14.3)
Surgery	9 (10.7)
Others	1 (1.2)

*Eastern Cooperative Oncology Group (ECOG) performance status was adjudged using the following scale[18]: 0, fully active, able to carry on all predisease performance without restriction; 1, restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; 2, ambulatory and capable of self-care but unable to carry out any work activities. Up and about more than 50 percent waking hours; 3, capable of only limited self-care, confined to bed or chair more than 50 percent of waking hours; 4, completely disabled, cannot carry on any self-care. Totally confined to bed or chair; 5, dead.
†Staging was based on the TNM classification.

on day 14. A similar trend was observed in the mean (SD) pain severity measured by the NRS, which showed a decrease from 3.91 (1.64) at baseline to 3.30 (1.73) on day 7 and to 3.24 (1.82) on day 14. Interference of pain in general activities, mood, ability to walk, normal work activities, relationships with others, sleep, and enjoyment of life were not significantly affected, and pain relief was maintained after drug conversion (data not shown).

According to the results of the EORTC-QLQ-C30 survey, the physical functioning significantly improved on day 14 as compared to the baseline ($p = 0.015$). Emotional, cognitive, and social functioning of the patients were maintained ($p > 0.05$) after drug conversion. On the symptoms scale of the survey, there was a significant decrease in pain ($p = 0.030$) and diarrhea ($p = 0.020$) on day 14 as compared to the baseline, and the global health status of the patients was comparable. At the end of the trial, a total of 61.2 percent patients and 60.2 percent investigators rated the drug as either effective, highly effective, or very effective. A total of 88 patients (89.8 percent) preferred OROS® hydromorphone over their previous analgesic, with the following three reasons being the most common (in decreasing order): simple with less

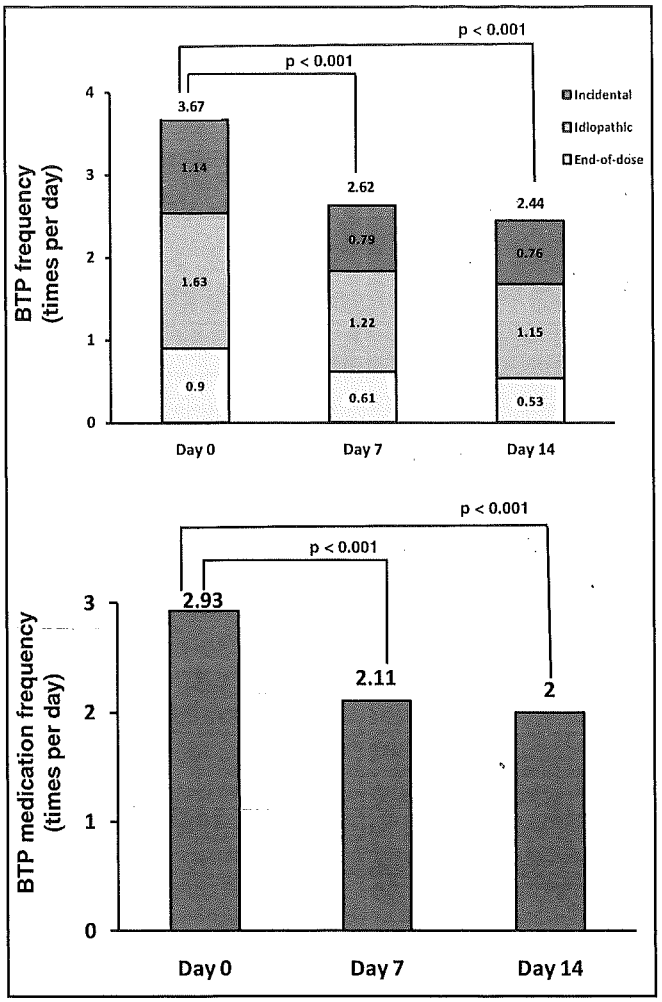

Figure 3. A: Frequency of BTP and its subtypes. Each bar represents the mean of all the average BTP frequencies observed for 3 days prior to the respective visit (n = 98). Light gray bars: end-of-dose BTP; gray bars: idiopathic BTP; and dark gray bars: incidental BTP. Repeated one-factor analysis was performed, and $p < 0.05$ was considered significant. B: Frequency of BTP medication. Each bar represents the mean of all the average BTP medication frequencies for 3 days prior to the respective visit (n = 98). Repeated one-factor analysis was performed, and $p < 0.05$ was considered significant.

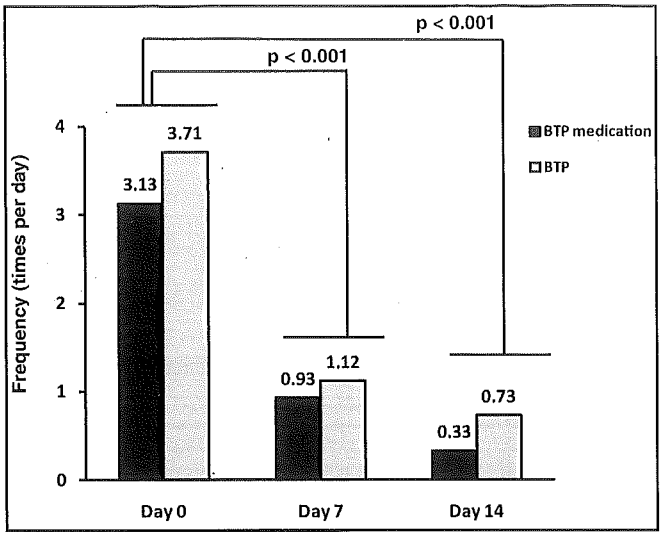

Figure 4. Frequency of BTP and BTP medication in a subset of patients with a >50 percent response rate. A subset of patients who showed a >50 percent decrease in pain intensity were included for analysis of BTP frequency and BTP medication frequency. Dark gray bars: BTP medication frequency; light gray bars: BTP frequency. Wilcoxon signed-rank test was performed, and $p < 0.05$ was considered significant.

frequency of administration, decrease in the use of rescue opioids for BTP control, and consistent pain relief.

Safety outcomes

Of the 114 patients, a total of 104 (91.2 percent) patients reported AEs, the most frequent being constipation, dizziness, somnolence, nausea, dyspnea, and vomiting (Tables 2 and 3). The most frequent AEs leading to patient withdrawal were nausea, somnolence, vomiting, and dyspnea. Most AEs were considered mild or moderate in severity, and 32 percent of the reported AEs were assessed as related to the study treatment. SAEs were observed in 29 of 114 (25.4 percent) patients, and two of these events were study related. A majority (93.1 percent) of the SAEs were unrelated to the study medication. There were seven deaths in the trial, but none was assessed as treatment related. No clinically significant changes in any of the other safety measures were observed during the study. A total of six patients discontinued the trial due to AEs.

Table 2. Summary of AEs and SAEs

Variable	Patients, n (percent) (N = 114)
Patients with AEs	104 (91.2)
Total AEs	439
Possibly related AEs	139 (32)
Patients with SAEs	29 (25.4)
Deaths	7 (6.1)

DISCUSSION

Management of BTP has been a major challenge in comprehensive cancer care. Several studies have

Table 3. Summary of AEs						
AE	Patients, n (percent)	Events, n (percent)	Severity, n (percent)			Possibly related
			Mild	Moderate	Severe	
Constipation	60 (52.6)	78 (17.8)	73 (19.5)	4 (9.8)	1 (4.2)	26
Dizziness	52 (45.6)	74 (16.9)	73 (19.5)	1 (2.4)	0 (0)	22
Somnolence	39 (34.2)	51 (11.6)	48 (12.8)	3 (7.3)	0 (0)	14
Nausea	33 (28.9)	44 (10.0)	43 (11.5)	1 (2.4)	0 (0)	11
Dyspnea	30 (26.3)	44 (10.0)	43 (11.5)	1 (2.4)	0 (0)	12
Vomiting	28 (24.6)	40 (9.1)	39 (10.4)	1 (2.4)	0 (0)	13
Asthenia	23 (20.2)	29 (6.6)	29 (7.8)	0 (0)	0 (0)	13
Diarrhea	6 (5.3)	9 (2.1)	8 (2.1)	1 (2.4)	0 (0)	1

focused on developing effective opioid conversion-based therapeutic regimens for cancer pain treatment. The results of this study support those of previous studies,[13,15] showing that cancer patients can easily undergo drug conversion from IR formulation of one type of opioid to ER formulation of another type of opioid. Further, our data show that OROS® hydromorphone was more effective than IR oxycodone in controlling BTP as well as baseline cancer pain. Between day 0 and day 7, a significant decrease was observed in the frequency of all the BTP subtypes. The effect was more pronounced when the OROS® hydromorphone dosage was appropriately titrated. Furthermore, the BTP medication frequency also decreased significantly on day 7 and day 14, and a large majority of patients preferred OROS® hydromorphone to their previous analgesic. Furthermore, a statistically significant reduction in the end-of-dose BTP frequency was observed; this can be attributed to either increase in dose or the long duration of action of OROS® hydromorphone. The fact that nearly half of the patients did not need dose increase suggests that the reduction in BTP frequency is probably due to the long duration of action of the drug. It has been previously shown there are lesser peak-trough fluctuations in the sustained-release (SR) formulation of hydromorphone than in the IR formulation (61 percent vs 172 percent).[19] Angst et al. have shown that plasma concentration of SR hydromorphone formulation peaks later than that of the IR formulation (12 hours vs 0.8 hours), but the peak is maintained for a significantly longer period at a >50 percent peak concentration. Consequently, the analgesic effects of SR hydromorphone peak later than those of the IR formulation (9 hours vs 1.5 hours) but are maintained longer at >50 percent peak analgesic effect (13.3 ± 6.3 hours vs 3.6 ± 1.7 hours), thus explaining the long duration of action of the SR formulation.[20]

Patients also reported an overall decrease in pain intensity during the day as well as in the night. The consistent activity of OROS® hydromorphone is explained by its push-pull mechanism of action, whereby the rate of drug release is solely dependent on the osmotic gradient of the gastrointestinal (GI) cavity and is independent of GI motility, pH, and presence/absence of food.[9,21] As the pH of the GI tract remains more or less steady, a constant amount of drug is released for an extended period.[20] The fact that a majority of the patients had advanced metastatic disease may explain the few dose escalations required in the study, while most of the patients did not require a change in dose.

Hanna et al.[22] compared the efficacy and safety of once-daily OROS® hydromorphone with a twice-daily SR formulation of morphine in patients with chronic cancer pain and showed that compared to morphine, OROS® hydromorphone provided significantly better pain relief in the evening, probably due to its longer duration of action. The results of these studies are in agreement with ours and, overall, show the effectiveness of once-daily OROS® hydromorphone following opioid rotation in cancer pain management.

While being effective, OROS® hydromorphone did not significantly affect patient's quality of life. In fact,

the general activity, mood, ability to walk, work, relationships, sleep, and enjoyment of life were maintained in most patients. A majority of patients preferred the OROS® hydromorphone to their previous drug, mainly because the ER feature of hydromorphone required them to take only one tablet per day as opposed to four tablets per day for the IR formulation. The most common AEs affected the GI and nervous systems, and only six patients discontinued the study because of AEs. These side effects were similar to those associated with any other opioid used for cancer pain management. Overall, OROS® hydromorphone was reasonably well tolerated. Although nonopioid drugs were permitted during the study when needed, the effects of opioid drugs are much more potent; therefore, the effectiveness and safety results observed in the study were concluded to be a direct consequence of OROS® hydromorphone.

Conversion ratios are a critical part of opioid rotation-based pain therapy. In general, conversion ratios for various opioids such as oxycodone and fentanyl transdermal have been standardized with respect to morphine.[23] However, it cannot be overemphasized that these conversion ratios merely serve as an initial guideline, and the appropriate dose is eventually decided based on patient's response. For example, even though the suggested conversion ratio from morphine to hydromorphone is 5:1, ratios of up to 8:1 have been effectively used for the treatment of malignant and nonmalignant pain.[24] In the present study, a ratio of 2.5:1 controlled-release oxycodone to hydromorphone hydrochloride showed effective pain control. Wallace et al.[13] evaluated the outcomes following conversion from previous opioid therapy to OROS® hydromorphone using a 5:1 conversion ratio, which is similar to the ratio used in our trial in terms of morphine equivalents, in subjects with either chronic malignant or nonmalignant pain, and found that OROS® hydromorphone was well tolerated.

In our study, nearly 20 percent of the patients showed a >50 percent response rate in pain intensity from day 0 to day 14 and a dramatic decrease in the BTP frequency and BTP medication frequency. A recent report on Japanese cancer patients stated that there exists a link between the genetic makeup of a patient and the response to morphine.[25] It was observed that patients with a particular genetic polymorphism experienced more AEs, whereas those without the polymorphism responded better to morphine treatment. A similar link may possibly exist between a patient's genetic makeup and hydromorphone response, which may explain the better-responding subset. However, further studies are needed to validate this possibility.[5]

A recent review of the changes in pain management strategies in Korean hospitals over a period of 5 years[26] suggests that several cancer patients fail to receive adequate and appropriate analgesic dose for their pain. Another recent study has revealed that even though the ER opioids are commonly used in Korea for cancer pain management, their dosages are not in consensus with the standard recommendations, possibly because of the lack of available data on the response of Korean cancer patients to opioids and opioid rotations.[27] The current study provides valuable insights into the response of Korean cancer patients to hydromorphone and opioid conversion regimens and, thus, will facilitate the development of better treatment designs for cancer pain management.

The limitation of the trial is its open-label design. A double-blinded placebo-controlled, crossover trial is warranted to further demonstrate the effectiveness of OROS® hydromorphone. A further limitation of the study design was that it did not allow for a washout phase prior opioid switching, which may have confounded the results. Additionally, as OROS® hydromorphone doses were available only in 8 mg and 16 mg units, the dose titration may not have been optimal.

CONCLUSION

In conclusion, this study clearly demonstrated that OROS® hydromorphone was more effective in controlling chronic and breakthrough cancer pain as compared to the preceding treatment with IR oxycodone. It also showed that patients can undergo conversion from IR oxycodone to once-daily OROS® hydromorphone at a 2.5:1 controlled-release oxycodone to hydromorphone hydrochloride conversion ratio.

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