A prospective multicentre study to evaluate the efficacy and tolerability of osmotic release oral system (OROS®) hydromorphone in opioid-naive cancer patients: Results of the Korean South West Oncology Group study

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BACKGROUND: Osmotic release oral system (OROS®) hydromorphone is a potent, long-acting opioid analgesic, effective and safe for controlling cancer pain in patients who have received other strong opioids. To date, few studies have examined the efficacy of hydromorphone for pain relief in opioid-naive cancer patients.

OBJECTIVES: A prospective, open-label, multicentre trial was conducted to determine the efficacy and tolerability of OROS hydromorphone as a single and front-line opioid therapy for patients experiencing moderate to severe cancer pain.

METHODS: OROS hydromorphone was administered to patients who had not previously received strong, long-acting opioids. The baseline evaluation (visit 1) was followed by two evaluations (visits 2 and 3) performed two and 14 weeks later, respectively. The starting dose of OROS hydromorphone was 4 mg/day and was increased every two days when pain control was insufficient. Immediate-release hydromorphone was the only accepted alternative strong opioid for relief of breakthrough pain. The efficacy, safety and tolerability of OROS hydromorphone, including the effects on quality of life, and patients' and investigators' global impressions on pain relief were evaluated. The primary end point was pain intensity difference (PID) at visit 2 relative to visit 1 (expressed as %PID).

RESULTS: A total of 107 patients were enrolled in the present study. An improvement in pain intensity of >50% (≥50% PID) was observed in 51.0% of the full analysis set and 58.6% of the per-protocol set. The mean pain score, measured using a numerical rating scale, was significantly reduced after two weeks of treatment, and most adverse events were manageable. Quality of life also improved, and >70% of patients and investigators were satisfied with the treatment.

CONCLUSIONS: OROS hydromorphone provided effective pain relief and improved quality of life in opioid-naive cancer patients. As a single and front-line treatment, OROS hydromorphone delivered rapid pain control.

Key Words: *Cancer; Hydromorphone; Opioid; Pain*

Une étude multicentrique prospective pour évaluer l'efficacité et la tolérabilité de l'hydromorphone par système oral à libération osmotique (SOLO®) chez des patients atteints du cancer naïfs aux opioïdes : le résultat de l'étude coréenne d'oncologie du Sud-ouest

HISTORIQUE : L'hydromorphone par système oral à libération osmotique (SOLO®) est un puissant analgésique opioïde à longue durée d'action efficace et sécuritaire pour contrôler la douleur causée par le cancer chez les patients qui ont reçu d'autres puissants opioïdes. Jusqu'à présent, peu d'études ont porté sur l'efficacité de l'hydromorphone pour soulager la douleur chez des patients atteints du cancer naïfs aux opioïdes.

OBJECTIFS : Les chercheurs ont mené un essai multicentrique prospectif ouvert pour déterminer l'efficacité et la tolérabilité de l'hydromorphone par SOLO comme thérapie opioïde unique en première ligne chez les patients souffrant de douleur modérée à grave causée par le cancer.

MÉTHODOLOGIE : L'hydromorphone par SOLO a été administrée à des patients qui n'avaient pas reçu de puissants opioïdes à longue durée d'action auparavant. L'évaluation initiale (visite 1) était suivie de deux évaluations (visites 2 et 3) effectuées deux et 14 semaines plus tard, respectivement. La dose d'hydromorphone par SOLO initiale était de 4 mg/jour et accrue tous les deux jours lorsque le contrôle de la douleur était insuffisant. L'hydromorphone à libération immédiate était le seul autre puissant opioïde accepté pour soulager les accès douloureux paroxystiques. Les chercheurs ont évalué l'efficacité, l'innocuité et la tolérabilité de l'hydromorphone par SOLO, y compris les effets sur la qualité de vie, de même que les impressions globales des patients et des investigateurs. Le paramètre primaire était la différence d'intensité de la douleur (DID) lors de la visite 2 par rapport à la visite 1 (exprimé en pourcentage de DID).

RÉSULTATS : Au total, 107 patients ont participé à la présente étude. Les chercheurs ont remarqué une diminution de l'intensité de la douleur de plus de 50 % (≥50 % DID) chez 51,0 % du groupe d'analyse totale et de 58,6 % du groupe respectant le protocole. L'indice de douleur moyen, mesuré d'après une échelle d'évaluation numérique, avait considérablement diminué au bout de deux semaines de traitement, et la plupart des événements les plus indésirables pouvaient être gérés. La qualité de vie s'était également améliorée, et plus de 70 % des patients et des investigateurs étaient satisfaits du traitement.

CONCLUSIONS : L'hydromorphone par SOLO apportait un soulagement efficace de la douleur et améliorait la qualité de vie chez les patients atteints du cancer naïfs aux opioïdes. Sous forme de traitement unique de première ligne, l'hydromorphone par SOLO assurait un contrôle rapide de la douleur.

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Pain is one of the most common symptoms of cancer, reported in 52.1% of all cancer patients and >80% of terminal cancer patients in Korea (1). Active treatment, which considers the patient's pain intensity, may alleviate the patient's fear of pain, and improve treatment satisfaction and quality of life. According to the literature, immediate cancer pain management improves the patient's functional abilities and quality of life, and reduces hospital visits, thereby lowering the cost of cancer pain treatment both directly and indirectly (2). Therefore, early and active management of cancer pain, based on pain intensity, is important for improving patients' satisfaction with treatment, as well as quality of life.

According to the WHO pain ladder, if pain persists or increases despite administration of nonopioids (step 1) or weak opioids (step 2), the treatment is switched to a strong opioid for moderate to severe cancer pain. According to recent recommendations, however, opioid-naive patients experiencing moderate to severe pain should receive rapid titration of short-acting opioids, and patients with chronic persistent pain controlled by stable doses of short-acting opioids should be given long-acting opioids, with a rescue dose for breakthrough pain. Although the appropriate time point for starting strong opioids should be individualized, active upfront use of strong opioids is widely accepted.

Osmotic release oral system (OROS®; Alza Corporation, USA) hydromorphone is a long-acting opioid formulation that provides a potent analgesic effect for cancer pain (3,4). It maintains a constant blood concentration throughout the 24 h dosing interval, providing long-lasting analgesia (5). The efficacy and safety of OROS hydromorphone was proven with a starting dose of 8 mg among chronic noncancer pain patients who were naive to strong analgesics (6). However, there are very limited data demonstrating the efficacy and safety of OROS hydromorphone in cancer patients without previous exposure to a strong opioid analgesic. Recently in Europe, efficacy and safety were compared between starting doses of 4 mg and 8 mg; the lower dose (4 mg) demonstrated better tolerability and a lower number of treatment terminations at a comparable level of pain control with high treatment satisfaction (7). However, this study was also limited to patients with severe, chronic, noncancer pain associated with osteoarthritis and osteoporosis. Cancer patients are more vulnerable, and experience a higher incidence of adverse events compared with noncancer patients. Therefore, it is necessary to evaluate the efficacy and safety of a long-acting strong opioid as an upfront therapy for pain management in cancer patients.

The objective of the present study was to evaluate the efficacy and tolerability of OROS hydromorphone in opioid-naive cancer patients experiencing moderate to severe cancer pain. In the present study, 4 mg of OROS hydromorphone was used as a starting dose, which is the recommended amount for noncancer patients in the literature (7). The outcome of the present study will provide meaningful information on the clinical benefit of OROS hydromorphone as an upfront therapy in opioid-naive cancer patients.

METHODS

Study design

The present study was a prospective, open-label, multicentre, single-arm trial, conducted at 11 tertiary hospitals in South Korea from December 2011 to September 2012. It consisted of a two-week efficacy evaluation phase and a 12-week extension phase. During the efficacy evaluation, cancer pain was controlled using hydromorphone as a single strong opioid analgesic. After the efficacy evaluation, patients were given the choice to participate in the extension phase. During the extension phase, other strong opioids were permitted, if necessary, as long as OROS hydromorphone was continued.

The present study was approved by the institutional review boards of each centre, and was conducted in accordance with the Declaration of Helsinki and good clinical practice guidelines.

Study participants

Patients ≥20 years of age with an average pain intensity of ≥4 on a numerical rating scale (NRS) during the past 24 h and requiring analgesics regularly were eligible to participate. Eligible patients had not taken a long-acting strong opioid analgesic within 60 days before enrollment. Patients were excluded if they: had a history of drug or alcohol abuse within the past six months; had a history of hypersensitivity to hydromorphone; were unable to swallow solid oral formulations (eg, due to dysphagia, vomiting, paralytic ileus or intestinal obstruction); had taken monoamine oxidase inhibitors (such as moclobemide, selegiline or toloxatone) within the two-week period before study entry; were scheduled to receive radiotherapy between the first (visit 1, day 1) and second evaluation (visit 2, day 14); and had a history of radiotherapy performed on the site of current pain. All patients provided written informed consent before participation.

Drug administration and monitoring

From the baseline (visit 1) to the second evaluation (visit 2), OROS hydromorphone was administered as a single, strong, long-acting opioid analgesic, to determine its clinical efficacy. Immediate-release hydromorphone was used as rescue medication; other strong opioids were not permitted during the first two weeks of the efficacy evaluation phase.

OROS hydromorphone was administered once daily with a starting dose of 4 mg and was recommended to be administered at 08:00 (±1 h). The average pain intensity over the past 24 h was evaluated by telephone inquiries every other day during the evaluation phase. If the average pain intensity was ≥4 on the NRS, or if the number of rescue analgesic administrations was ≥4 times over the past 24 h, the dose of OROS hydromorphone was elevated by 4 mg until an average pain intensity of ≤3 was achieved.

Compliance was evaluated based on the amount of leftover study drug. Patients were withdrawn from the study if they did not take the study drug for >3 days or for >2 consecutive days during the efficacy evaluation phase.

Opioid analgesics other than OROS hydromorphone, monoamine oxidase inhibitors, morphine agonist-antagonists, hypnotics and radiotherapies were not permitted during the two-week efficacy evaluation phase. Adjuvant drugs including acetaminophen, nonsteroidal anti-inflammatory drugs, antianxiety drugs, antidepressants, hormone therapy, corticosteroids, anticonvulsants and neuroleptics were permitted if they were administered before enrollment. However, addition or increase of the adjuvant drugs were prohibited during the efficacy evaluation phase.

Assessment

The NRS and the percentage of pain relief were used to evaluate the pain intensity and efficacy of the OROS hydromorphone. The primary end point was pain intensity difference (PID) at the second evaluation (visit 2, day 14) relative to the first evaluation (visit 1, day 1), calculated as follows:

$$\%PID = [NRS\ (visit\ 1) - NRS\ (visit\ 2)] / NRS\ (visit\ 1) \times 100.$$

The average pain intensity experienced by the patient over the past 24 h was evaluated using an NRS at each visit.

The secondary end points included the change in Korean Brief Pain Inventory (K-BPI) and the European Organization for Research and Treatment of Cancer Quality of Life (EORTC QLQ-C30) between the first evaluation and the second evaluation (Supplements 1 and 2 available at www.pulsus.com). The K-BPI measured the severity of pain in the past 24 h (including 'worst', 'usual', 'least' and 'current pain'), the effect of pain on daily life performance, the location of pain, the medication used for pain management, and the extent of pain reduction over the past 24 h or the previous week, with nine questions for each evaluation area. The EORTC QLQ-C30, comprised of 30 questions, measured health status. Other secondary endpoints included the patients' and investigators' global impression on pain relief at the second evaluation. At day 14, patients and investigators were surveyed on how effective the study drug was for pain relief. The global assessment was measured on a 5-point scale: 1 – not effective, 2 – somewhat effective, 3 – effective, 4 – very effective and 5 – extremely effective.

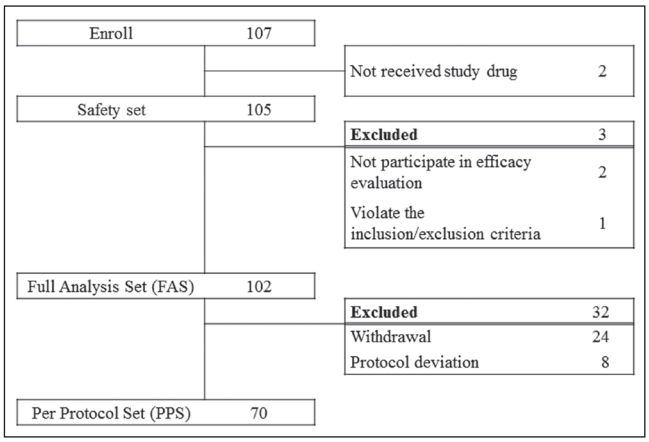

Figure 1) *Patient population set classification*

For the safety evaluation, adverse events were monitored throughout the study and were collected through subjects' self-reporting or indirectly by interviewers at every visit, including telephone inquiries. All adverse events were documented, and reports included the onset, severity and outcome information. In addition, the proportion of patients withdrawn from the study due to adverse events was analyzed.

Statistical analysis

The efficacy evaluation included two sets of the population; the full analysis set (FAS) and the per-protocol (PP) set. The FAS population included patients who were administered the study drug at least once, and excluded those with major violations of the inclusion/exclusion criteria or without efficacy data collected after treatment. The PP population included patients who completed the study according to the protocol. Safety and demographic characteristics were evaluated for all patients who received the study drug at least once. Final evaluations of the primary and secondary efficacy endpoints were completed for the FAS population, and the results from the PP population were analyzed. The sample size was determined on the basis of the difference in pain intensity between before and after treatment with the study drug. For this, it was hypothesized that 60% of patients would show an improvement in pain intensity of >50% after study drug administration. The number of patients required for 80% statistical power at a one-sided significance level of 2.5% was estimated, and the dropout rate was predicted to be 15%. The estimated number of patients required for the study was 99.

Changes in the second efficacy end points before and after drug administration were measured, and the differences were compared using a paired *t* test or Fisher's exact test for continuous variables, and a χ^2 test or McNemar's test for categorical variables. The secondary efficacy outcomes and the safety variables were analyzed at a two-sided significance level of 5%.

RESULTS

Patient disposition

Of the 107 patients enrolled, 105 (98.1%) received the study drug at least once and were included in the safety evaluation. The FAS population included 102 patients, excluding two who did not provide efficacy data and one who violated the inclusion/exclusion criteria. The PP population included 70 (65.4%) patients, excluding 24 who were withdrawn from the study and eight who violated the protocol (Figure 1).

Demographics and baseline characteristics

Demographics and baseline characteristics for 105 patients who provided safety data are presented in Table 1. The mean (± SD) age was 63.6±11.2 years, and there was a predominance of male patients (59.1%). The most common primary site of tumour was the lung (20.0%), followed by the colorectum (17.1%) and pancreas (7.6%). Most patients had metastatic sites (78.1%) and stage IV diseases (82.9%). Seventy-four (70.5%) patients had received active anticancer treatment before enrollment (Table 1).

TABLE 1
Demographics and baseline characteristics (n=105)

Demographic	
Age, years	
Mean ± SD	63.6±11.2
Median	65
Minimum – maximum	37–85
Male sex	62 (59.1)
Diagnosis (primary site)	
Lung cancer	21 (20.0)
Colorectal cancer	18 (17.1)
Pancreatic cancer	8 (7.6)
Head and neck cancer	6 (5.7)
Cervical cancer	4 (3.8)
Breast cancer	4 (3.8)
Esophageal cancer	4 (3.8)
Endometrial cancer	2 (1.9)
Lymphoma	1 (1)
Other	37 (35.2)
Metastasis	
No	23 (21.9)
Yes	82 (78.1)
Stage	
I	2 (1.9)
II	4 (3.8)
III	12 (11.4)
IV	87 (82.9)
Previous therapy	
No	31 (29.5)
Yes	74 (70.5)
Chemotherapy	63 (85.1)
Radiotherapy	16 (21.6)
Surgery	25 (33.8)
Other	4 (5.4)

Data presented as n (%) unless otherwise indicated

Treatment compliance and extent of exposure

Treatment compliance was evaluated at every visit. Patients were deemed to be noncompliant if they did not take the study drug for >3 days or two consecutive days. Noncompliance was considered to be a major violation of the protocol, and four patients were noncompliant.

The mean starting dose of OROS hydromorphone was 4.1±1.2 mg/day, and the mean final dose was 7.9±6.2 mg/day. The dose of OROS hydromorphone at the end of the study was 4 mg/day in 49.5% of the patients, 8 mg/day in 31.4%, 12 mg/day in 8.6% and >16 mg/day in 10.5%. The mean total duration of treatment was 36.6 days and mean dose was 6.3 mg/day.

Primary efficacy analysis

The primary efficacy end point was the difference of pain intensity measured by the proportion of patients with ≥50%PID at the second evaluation (visit 2, day 14) compared with the baseline (visit 1, day 1). Among 102 patients in the FAS population, 51.0% (n=52) achieved ≥50%PID. Among 70 patients in the PP population, 58.6% (n=41) achieved ≥50%PID (Table 2).

The mean pain score on the NRS was 5.6±1.3 at baseline and 3.4±2.1 at the final evaluation (visit 3, week 14) in the FAS population, revealing

TABLE 2
% Pain intensity difference (PID) and change in average pain intensity

		≥50% PID		Change in average pain intensity			
Population	n	n	% (95% CI)	Baseline	End point	End point – baseline	P*
Full analysis set	102	52	51.0 (41.3–60.7)	5.6±1.3	3.4±2.1	−2.2±2.1	<0.0001
Per-protocol	70	41	58.6 (47.0–70.1)	5.6±1.3	3.0±1.3	−2.6±1.9	<0.0001

*Data presented as mean ± SD unless otherwise indicated. *P value calculated using Wilcoxon signed rank test*

TABLE 3
Korean Base Pain Inventory (K-BPI) and European Organization for Research and Treatment of Cancer Quality of Life (EORTC QLQ-C30) scores

		Baseline	End point	Mean difference		
	n	Mean ± SD	Mean ± SD	Mean ± SD	95% CI	P*
K-BPI score						
Full analysis set						
Pain severity score†	102	4.8±1.2	3.3±1.7	–1.5±1.7	−1.9 to −1.2	<0.0001
Pain interference score‡	102	3.7±1.6	2.8±1.8	–1.0±1.7	−1.3 to −0.6	<0.0001
Per-protocol						
Pain severity score	70	4.8±1.3	3.2±1.6	–1.6±1.6	−2.0 to −1.3	<0.0001
Pain interference score	70	3.8±1.6	2.7±1.7	–1.1±1.5	−1.5 to −0.8	<0.0001
EORTC QLQ-C30						
Full analysis set						
Global health status/quality of life	102	37.2±18.3	47.4±19.8	10.2±19.0	6.5 to 13.9	<0.0001
Physical functioning	102	54.3±23.9	61.6±23.8	7.3±18.7	3.6 to 10.9	0.0002
Role functioning	102	45.9±31.9	38.9±29.2	–7.0±28.8	−12.7 to −1.4	0.0153
Emotional functioning	102	35.8±26.3	28.6±26.0	–7.2±25.0	−12.1 to −2.3	0.0045
Cognitive functioning	102	44.4±24.3	40.2±22.5	–4.2±18.4	−7.9 to −0.6	0.0218
Fatigue	102	50.4±25.5	43.1±23.2	–7.3±21.9	−11.6 to −3.0	0.0011
Nausea and vomiting	102	9.5±18.1	9.8±18.2	0.3±20.3	−3.7 to 4.3	0.8712
Pain	102	70.4±21.1	50.7±26.9	–19.8±30.4	−25.7 to −13.8	< 0.0001
Dyspnea	102	31.7±31.9	24.8±29.9	–6.9±24.5	−11.7 to −2.1	0.0057
Insomnia	102	51.6±34.3	38.6±33.7	–13.1±31.9	−19.3 to −6.8	< 0.0001
Appetite loss	102	43.5±36.3	36.9±33.1	–6.5±34.5	−13.3 to 0.2	0.0584
Constipation	102	26.5±31.9	27.8±30.8	1.3±33.1	−5.2 to 7.8	0.6912
Diarrhea	102	8.2±20.7	3.9±12.7	–4.2±18.0	−7.8 to −0.7	0.0188
Financial difficulties	102	44.1±34.5	39.5±33.7	–4.6±25.7	−9.6 to 0.5	0.0753
Per-protocol						
Global health status/quality of life	70	36.7±16.6	48.9±19.1	12.3±20.9	7.3 to 17.3	<0.0001
Physical functioning	70	52.6±23.1	62.4±21.8	9.8±19.0	5.3 to 14.3	<0.0001
Role functioning	70	45.7±31.2	35.2±25.8	–10.5±32.4	−18.2 to −2.7	0.0088
Emotional functioning	70	35.1±26.0	24.6±22.5	–10.5±27.0	−16.9 to −4.0	0.0018
Cognitive functioning	70	41.4±23.5	37.1±20.7	–4.3±19.4	−8.9 to 0.3	0.0687
Fatigue	70	49.0±24.3	39.4±20.0	–9.7±21.5	−14.8 to −4.6	0.0003
Nausea and vomiting	70	9.3±17.4	8.3±15.1	–1.0±19.0	−5.5 to 3.6	0.6764
Pain	70	67.9±20.3	43.6±24.0	–24.3±30.1	−31.5 to −17.1	<0.0001
Dyspnea	70	34.8±31.8	25.7±30.1	–9.0±27.2	−15.5 to −2.6	0.0069
Insomnia	70	45.2±32.1	28.6±27.4	–16.7±32.5	−24.4 to −8.9	<0.0001
Appetite loss	70	41.9±34.4	32.9±31.3	–9.0±36.3	−17.7 to −0.4	0.0408
Constipation	70	26.2±31.0	27.6±30.0	1.4±38.3	−7.7 to 10.6	0.7556
Diarrhea	70	9.0±22.6	3.3±11.6	–5.7±21.2	−10.8 to −0.7	0.0274
Financial difficulties	70	45.2±33.6	38.1±30.7	–7.1±24.7	−13.0 to −1.3	0.018

**P value calculated using a paired* t *test. †Pain Severity Score was calculated by adding the scores for questions 2, 3, 4 and 5, and dividing the sum by 4. ‡Pain Interference Score was calculated by adding the scores for questions 8 a, b, c, d, e, f and g, and dividing the sum by 7*

a statistically significant difference (decrease of 2.2±2.1; P<0.0001). The mean pain intensity decreased by 2.6±1.9 in the PP population.

For additional information, the rate of >30% improvement in %PID (≥30%PID) at the second evaluation was analyzed. A ≥30%PID was observed in 68.6% (n=70) of the FAS population and 81.43% (n=57) of the PP population.

Secondary efficacy analysis

Major secondary efficacy end points included changes in the K-BPI score and EORTC QLQ-C30, as well as patients' and investigators' global assessment of pain control.

From the K-BPI score, the pain severity score (calculated by adding the scores for questions 2, 3, 4 and 5, and dividing the sum by 4)

TABLE 4
Global assessment

	Investigator	Patient	P*
Full analysis set, n	77	77	0.9636
Not effective	20 (26.0)	21 (27.3)	
Not effective	3 (3.9)	5 (6.5)	
Moderate	17 (22.1)	16 (20.8)	
Effective	57 (74.0)	56 (72.7)	
Effective	41 (53.3)	36 (46.8)	
Highly effective	14 (18.2)	18 (23.4)	
Extremely effective	2 (2.6)	2 (2.6)	
Per-protocol, n	65	65	0.9739
Not effective	16 (24.6)	17 (26.2)	
Not effective	3 (4.6)	5 (7.7)	
Moderate	13 (20.0)	12 (18.5)	
Effective	49 (75.4)	48 (73.9)	
Effective	35 (53.9)	31 (47.7)	
Highly effective	13 (20.0)	16 (24.6)	
Extremely effective	1 (1.5)	1 (1.5)	

*Data presented as n (%) unless otherwise indicated. *P values calculated using Bowker's test for symmetry*

TABLE 5
Adverse events and adverse drug reactions showing at least 2% of incidence rate

	Adverse event		Adverse drug reaction	
	n (%)	Case	n (%)	Case
Nausea	16 (15.2)	18	9 (8.6)	9
Vomiting	13 (12.4)	15	8 (7.6)	8
Constipation	12 (11.4)	12	12 (11.4)	12
Abdominal pain	6 (5.7)	6	0 (0.0)	0
Dyspepsia	4 (3.8)	4	2 (1.9)	2
Cough	5 (4.8)	5	0 (0.0)	0
Hiccups	4 (3.8)	5	2 (1.9)	2
Dyspnoea	4 (3.8)	4	0 (0.0)	0
Asthenia	7 (6.7)	7	0 (0.0)	0
Decreased appetite	8 (7.6)	8	2 (1.9)	2
Hypophagia	6 (5.7)	6	1 (1.0)	1
Dizziness	6 (5.7)	6	5 (4.8)	5
Headache	3 (2.9)	4	1 (1.0)	1
Insomnia	5 (4.8)	5	2 (1.9)	2
Pruritus	5 (4.8)	5	1 (1.0)	1
Neutropenia	3 (2.9)	4	0 (0.0)	0
Pneumonia	3 (2.9)	3	0 (0.0)	0

decreased from 4.8±1.2 to 3.3±1.7 with a statistically significant difference (P<0.0001), and pain interference score (calculated by adding the scores for questions 8a, b, c, d, e, f and g, and dividing the sum by 7) also significantly decreased from 3.7±1.6 to 2.8±1.8 (P<0.0001) in the FAS population (Table 3).

Among 14 subscales of the EORTC QLQ-C30, statistically significant changes were observed for 10 subscales (global health status/quality of life (QoL), physical functioning, role functioning, emotional functioning, cognitive functioning, fatigue, pain, dyspnea, insomnia and diarrhea), but not for the remaining four subscales (nausea and vomiting, appetite loss, constipation and financial difficulties) in the FAS population. In the PP population, statistically significant changes were observed in 11 subscales, excluding cognitive functioning, nausea and vomiting, and constipation. The number of subscales revealing a mean change in score by >10 points was three (global health status/QoL, pain and insomnia) in the FAS population and five (global health status/QoL, role functioning, emotional functioning, pain and insomnia) in the PP population. Pain was the subscale revealing the most significant changes (–19.8±30.4 in the FAS population and –24.3±30.1 in the PP population) (Table 3).

Seventy-seven patients of 102 in the FAS population were evaluated for the patients' and investigators' global assessment of pain control. For the patients' global assessment, more investigators responded that the treatment was 'effective' (72.7%) than 'not effective' (27.3%). Investigators' global assessment also favoured 'effective' (74.0%) to 'not effective' (26.0%). Global assessments by the investigators and patients revealed similar results (P=0.9636) (Table 4).

Safety and tolerability

Adverse events and other safety data were analyzed for 105 patients who received the study drug. Among these, 191 cases of adverse events were reported for 76 patients (72.4%), while 53 cases of adverse drug reactions were reported for 36 (34.3%) patients.

Adverse events and adverse drug reactions occurring in >2% of patients are presented in Table 5. The most common adverse events were nausea (15.2%), vomiting (12.4%), constipation (11.4%) and abdominal pain (5.7%), while the most common adverse drug reactions were constipation (11.4%), nausea (8.6%) and vomiting (7.6%). Thirty-seven cases of serious adverse events occurred in 28 (26.7%) patients, and most of them were related to cancer.

Of the 191 adverse events, the causal relationship with the study drug was found to be 'possible' in 43 cases (22.5%) and 'probable' in 10 cases (5.2%). The severity of adverse events were 'mild' in 113 (59.2%) cases, 'moderate' in 47 (24.6%) cases, and 'severe' in 31 (16.2%) cases. In regard to the actions taken, the study drug was discontinued in 31 (16.2%), interrupted in six (3.1%), and the dose was reduced in four (2.1%) cases and increased in three (1.6%) cases. After treatment modification, most cases (69.1%) were resolved without sequelae.

DISCUSSION

The present study was a prospective, open-label, multicentre, single-arm trial to determine the efficacy and tolerability of OROS hydromorphone by measuring the PID after two weeks of hydromorphone single therapy in opioid-naive patients experiencing moderate to severe cancer pain.

Several studies have investigated the efficacy and tolerability of OROS hydromorphone in different patient groups, pain classifications and settings. Most of these studies investigated patients experiencing chronic pain who had received long-acting opioids (4,8-14). Some evaluated the efficacy and safety of OROS hydromorphone as a second-line treatment after previous long-acting opioids, such as morphine or oxycodone. However, very limited data exist on the efficacy and safety of OROS hydromorphone as front-line therapy in cancer patients. The present study involved patients who were naive to long-acting opioids, and OROS hydromorphone was used as a first-line strong opioid compound for dosing and titration.

The primary end point of the present study was %PID, and we assumed a cut-off of 50% to be a clinically meaningful decline in pain intensity. Determining the proportion of patients with a specific percentage reduction in pain intensity is widely used in the literature to evaluate treatment efficacy. A cut-off of 50% for dichotomizing pain intensity outcomes is commonly used to calculate the number needed to treat, and a 50% decline in pain intensity correlates well with other measures of pain intensity and pain relief (15-17). The proportion of patients with ≥50%PID after two weeks of treatment was 51.0% in the FAS population and 58.6% in the PP population; ≥30%PID was reported for 68.6% of the FAS population and 81.43% of the PP population in the additional analysis. Recently, Han et al (18) reported the clinical benefit of OROS hydromorphone in patients with cancer pain inadequately controlled by other analgesics. The primary end point of their study was the PID at eight weeks later, and >30% improvement of

PID (≥30%PID) was observed in 39.2% of the FAS population and 65.2% of the PP population. They reported ≥30%PID at four weeks was obtained in 34.6% of the FAS population and 54.9% of the PP population. Compared with their study, our study demonstrated superior results within a relatively short period of time. Cepeda et al (19) described the meaningful pain reduction according to pain intensity and found that a 2.4 (35%) point reduction in NRS corresponded to 'much' improvement, and 3.5 point reduction corresponded to 'very much' improvement in patients experiencing moderate pain. In our study, the average pain intensity on the NRS was reduced by 2.6 points, which is comparable for meaningful pain improvement according to Cepeda et al (19).

Several extended-release oral morphine formulations are now commercially available. Avinza (Pfizer Inc, USA) was developed for once-daily dosing, similar to OROS hydromorphone. Kadian (Actavis Pharma Inc, USA) can be used once or twice per day. Studies comparing once-daily and twice-daily administrations of extended-release morphine sulfate found that there was a statistically significant preference for once-daily dosing with significantly better and earlier improvement of physical function, and without differences in pain control or tolerability (20,21). To our knowledge, there is no direct comparative study between Avinza or Kadian and OROS hydromorphone. Avinza and OROS hydromorphone were each compared with twice-a-day oxycodone in different randomized studies (6,21). In these studies, both Avinza and OROS hydromorphone demonstrated similar pain relief and a significantly greater improvement of sleep disturbance compared with oxycodone.

Long-acting opioids are usually indicated in opioid-tolerant patients taking at least 60 mg oral morphine per day, 25 µg transdermal fentanyl per hour, 30 mg oral oxycodone per day, 8 mg oral hydromorphone per day, 25 mg oral oxymorphone per day or an equianalgesic dose of another opioid for ≥1 week(s). To follow this general guideline, it takes >1 week to achieve proper pain control when converting to long-acting opioids from short-acting or immediate-releasing opioids. Ringe et al (7) compared a lower starting dose (4 mg/day) of OROS hydromorphone to a higher starting dose (8 mg/day) in terms of tolerability, pain control and treatment satisfaction overall for subgroups of opioid-naive patients versus patients previously treated with opioids. This study was a post hoc analysis that included three different studies that used two different starting doses. Treatment satisfaction improved in a higher percentage of patients in the lower starting dose, and a lower starting dose was associated with lower overall incidence of adverse events and treatment-related events in the elderly and opioid-naive patients.

A recent study (22) evaluated the effect of OROS hydromorphone on reducing the frequency of breakthrough pain medication in patients with chronic cancer pain. In that study, OROS hydromorphone was efficient in reducing the number of cancer pain-related breakthrough pain episodes, including end-of-dose pain (22). However, only 15.3% (15 of 98) of patients showed a ≥50%PID, which is lower than the outcome achieved in the present study. The differences between the two studies were the frequency of pain monitoring and the use of analgesic dose elevation. We evaluated the pain intensity every other day by telephone inquiries, and the dose could be increased if the pain intensity was more than the optimal range. This monitoring technique may have facilitated more rapid and effective pain control compared with other studies.

Determining clinically important differences of the EORTC QLQ-C30 is difficult, and investigators suggested different values for each subscale. Maringwa et al (22) examined a meaningful change in the EORTC QLQ-C30 in a group of lung cancer patients, and concluded that the minimal, clinically meaningful score to be 9 for physical functioning, 14 for role functioning, 5 for social functioning, 14 for fatigue and 16 for pain. Based on these criteria, physical functioning and pain revealed clinically meaningful differences in our study. Considering the evaluation was only after two weeks, other subscales should be assessed after prolonged treatment.

There were several limitations to the present study. First, the primary end point was not met because the proportion of patients with ≥50%PID was short of the level expected in sample size determination. Second, the outcome of the present study should be interpreted with caution because it was a single-arm, open-label study and a bias caused by frequent telephone inquiries cannot be ruled out. However, the present study demonstrated that initial treatment with OROS hydromorphone was safe, satisfactory and somewhat effective in opioid-naive cancer patients. It may be more beneficial and faster to achieve consistent pain control by using OROS hydromorphone from the start, rather than switching to it from other immediate-releasing opioids. Furthermore, because OROS hydromorphone is administered once daily, it offers benefits of higher treatment compliance and easy titration. Although further research in the form of randomized controlled studies will be necessary, initiating pain management with a long-acting opioid, such as OROS hydromorphone, can help opioid-naive patients to reach pain relief and improve functional performance and QoL in a short period of time.

CONCLUSION

OROS hydromorphone provided effective pain relief in cancer patients, and improved activities of daily life and QoL. As a single, front-line treatment, OROS hydromorphone delivered rapid pain control, and both patients and physicians were satisfied with the level of pain management.

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