A Randomized, Double-Blind, Double-Dummy, Crossover Trial Comparing the Safety and Efficacy of Oral Sustained-Release Hydromorphone With Immediate-Release Hydromorphone in Patients With Cancer Pain

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Purpose: **To evaluate the safety and efficacy of a new slow-release preparation of hydromorphone (SRH) in the treatment of cancer pain.**

Patients and Methods: **Ninety-five adult patients from three Canadian Palliative Care Centers with no evidence of mental impairment received treatment for cancer pain with an oral opioid analgesic. After informed consent was obtained, patients underwent titration to a stable dose of immediate-release hydromorphone (IRH) for 48 hours, and were then randomized to receive IRH or SRH for 5 days in a double-blind basis. During day 6, a crossover took place, and patients received the alternate drug for 5 days. Pain intensity was assessed using a visual analog scale (VAS) and ordinal scale (OS). Side effects were assessed using VAS. Patients and investigators made a blinded global rating of efficacy a blinded final choice between SRH and IRH.**

Results: **In 75 assessable patients, pain intensity of the VAS and OS were (mean ± SD) 27 ± 21 and 1.3 ± 0.6 on IRH, versus 29 ± 21 ($P = .13$) and 1.3 ± 0.6 ($P = .19$) on SRH, respectively. The total number of extra doses of opioids, global rating, and final blinded choice by both patients and investigators were not significantly different between IRH and SRH. Differences in side effects were not significant.**

Conclusion: **Our findings suggest that SRH is as safe and effective as IRH in the treatment of cancer pain.**

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HYDROMORPHONE and morphine are safe and effective opioid agonists frequently used in the management of cancer pain.[1,2] Patients frequently need to change from one of these opioids to the other because of the development of side effects or insufficient analgesia.[3,4] Although a number of safe and effective slow-release preparations of morphine are available,[5,6] there are no available long-acting preparations for hydromorphone. For this reason, when patients need to change from slow-release morphine (SRM) to hydromorphone, they are forced to take hydromorphone every 4 hours.

The purpose of this randomized, placebo-controlled study is to assess the safety and efficacy of a new slow-release preparation of hydromorphone in patients with cancer pain.

PATIENTS AND METHODS

This multicenter trial included 95 patients from three centers (University of Alberta, Edmonton, 75 patients; McGill University, Montreal, 12 patients; and University of Ottawa, Ottawa, eight patients).

All patients were ≥ 18 years of age and gave written informed consent. All patients had pain from cancer and were currently receiving treatment with an oral opioid analgesic. Life expectancy for all patients was estimated by the treating physicians to be longer than 4 months.

Exclusion Criteria

Patients who met the following criteria were excluded from the study: (1) use active anticancer therapy, with exception of hormones, within 2 weeks of study entry; (2) physical or mental inability to answer questions and comply with the treatment protocol; (3) history of hypersensitivity to hydromorphone or any related compound; (4) impaired renal or hepatic function; (5) significantly impaired ventilatory function (clinically present dyspnea at rest); (6) current use of an investigational drug; (7) pregnancy or lactation. (8) unwillingness or inability to cooperate or give written, informed consent; and (9) inability to take oral medication.

Medications

Immediate-release hydromorphone (IRH) hydrochloride tablets and identical placebo were provided by Knoll Pharma, Markham, Canada.

Study Design

Eligible patients who agreed to participate were titrated to stable pain control using IRH every 4 hours. Once stable control (defined as ≤ 20 in a 0 to 100 visual analog scale [VAS]) was achieved for at least 48 hours, or if patients already had stable pain on IRH, patients were randomized to receive either IRH or slow-release hydromorphone (SRH) over a period of 5 days. Patients who were

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randomized to receive IRH received a dose of medication every 4 hours and a placebo dose of SRH every 12 hours. Conversely, patients who received SRH received placebo IRH every 4 hours. During day 6, a crossover took place, and patients received the alternate drug for a period of 5 days.

The dose of study medication remained constant during the randomization period. If medication for extra pain was needed, patients were allowed to receive extra doses of IRH. Each dose was approximately 10% of the daily opioid requirement. After completion of the double-blind trial, patients were offered the option of remaining on the SRH preparation in an open follow-up study for a maximum of 3 months.

Other than the regular protocol and rescue medications, no other opioid analgesics were administered during the course of the study. Patients were instructed not to add any other analgesic agents during the double-blind phase of the study. All other medications prescribed before enrollment were maintained, and no changes were allowed later than 48 hours before study randomization.

Assessments

During the crossover study, the following assessments were made.

Pain intensity was assessed four times a day using a 0 to 100 VAS (0, no pain; 100, worst possible pain). The visual analog was completed in two modalities: patient daily diary and assessment during the visit. The assessments took place at the same time for each patient. The time was chosen by the patient and investigator within four possible daily intervals: 8:00 to 11:00 AM, 12:00 to 3:00 PM, 4:00 to 7:00 PM, and 8:00 to 11:00 PM, respectively. Patients were phoned every day by one of the investigators to be reminded to complete the forms and to discuss pain control. During each visit at the end of each phase, patients completed a visual analog in front of the investigator.

Pain intensity was also scored using an ordinal scale (0, no pain; 3, severe pain) at the completion of each VAS rating.

On admission to the study, all patients were assessed using the Edmonton staging system for cancer pain.[7] This system gives patients a score of 1 (good prognosis) to 3 (poor prognosis), according to the presence or absence of poor prognostic factor for pain control, such as neuropathic or incidental pain syndrome, previous opioid dose or rapid tolerance, history of alcoholism or drugs, and somatization or cognitive failure. Good pain control is achieved with opioids and adjuvant drugs in more than 90% of stage 1 patients versus approximately 50% of stage 3 patients.

Global evaluation by the patients was also assessed. On day 6 and day 11 of the randomized phase, patients were asked to rate the overall effectiveness of the study medication using a verbal rating scale (1, poor; 5, excellent).

Each day all patients scored the existence and severity of a number of adverse side effects, including nausea, vomiting, restlessness, drowsiness, itchiness, agitation, constipation, and dry mouth using VAS scores (0, none; 100, worst possible), ie, 0, no nausea; 100, worst possible nausea, and so forth.

Statistical Analysis

Demographic data were summarized by grouping patients according to their initial treatment (IR or SR) and overall for all patients combined. Parametric results (age, height, weight, duration of illness) were analyzed using analysis of variance (ANOVA) with patient, treatment, sequence, and center as main factors, and treatment by center interaction, to compare between the two sequence groups. If center and treatment by center interaction were not significant, these factors were dropped from the model and the results of the reduced model were reported. Nonparametric results were compared between groups based on initial treatment using the Cochran-Mantel-Haenszel (CMH) test adjusted for center.

Dose of study medication was analyzed by ANOVA with drug, phase (A or B), and sequence as main factors to test for differences between similar formulations over the two treatment phases, ie, comparing active IR with placebo IR. For the pain evaluations (on the VAS) and the symptom scores (on the VAS), the baseline results (day 1 or baseline value if no titration period was performed) were analyzed using the ANOVA procedures with sequence, center and sequence by center as factors to detect differences between treatment sequences at the start of the double-blind phase. The results over the double-blind phase were analyzed initially by ANOVA with center, patient, drug (IR or SR), and phase (A or B) as main factors, and with drug by center and phase by center interactions. Because of the 2×2 design, the degrees of freedom of the models did not allow for inclusion of a carryover effect; therefore, an orthogonal contrast was conducted on the patient sum of squares to obtain a carryover effect. If a significant carryover effect was noted, the results at day 6 were compared by ANOVA between the two treatment sequences.

Pain intensity ratings were analyzed by a categorical modeling procedure with sequence, drug, and phase as factors and by ANOVA as described above, under the assumption that the ratings represent a crude measurement of a continuous underlying distribution.

The data from the patient diaries (pain and symptoms) were averaged over each phase (titration, double-blind phase A, double-blind phase B, month 1, month 2, and month 3). For the double-blind phase, VAS pain score averages were calculated for evaluations performed within one of four daily time intervals. ANOVA were performed as described above.

The use of rescue medication as recorded during the double-blind phase in the patient diaries was used to calculate the following for each phase: the total dose in milligrams taken for each overall mean dose per phase and the number of days rescue medication was taken per phase. These measurements were analyzed by ANOVA.

Ethics Approval

The protocol was approved by the institutional review boards in Ottawa (Elizabeth Bruyere Health Science Center), Montreal (Royal Victoria Regional Hospital), and Edmonton (Caritas Health Group, Alberta Cancer Board). All patients gave written consent before participating in the study.

RESULTS

A total of 95 patients was recruited for the study (75 patients from Edmonton, 12 patients from Montreal, and eight patients from Ottawa). Forty-six patients were randomized to initially receive IRH, and 49 patients initially received SRH. Patient characteristics are listed in Table 1.

Twenty patients did not complete the double-blind phase of the study (12 while receiving IRH and eight while receiving SRH). Eleven patients developed in-

Table 1. Patient Characteristics

	No. of Patients (N = 95)
Mean age ± SD (years)	62 ± 12
Female/male	49/46
Location of primary tumor	
Lung	15
Prostate	17
Breast	14
Colorectal	9
Genitourinary	20
Other	20
Total	95
Edmonton staging system	
I	0
II	4
III	86
Not reported	1
Total	95
Mean daily hydromorphone dose (mg/d)	75 ± 79

tercurrent medical problems, six patients (three on SRH and three on IRH) dropped out because of unsatisfactory analgesic response, one patient discontinued because of noncompliance, one patient withdrew consent for participation, and one patient died while receiving IRH. Age, previous opioid dose and Edmonton staging system scores were not significantly different between assessable and nonassessable patients. Thus, a total of 75 patients completed the titration/double-blind phase of the study.

The mean daily dose for IRH and SRH was 75 mg and 78 mg, respectively, when given as the active dose (P = not significant). There were no significant differences in total daily dose for the two phases of the study. Table 2 lists the results with regard to pain intensity and rescue analgesics. There was no difference between IRH and SRH with regard to pain intensity as measured by both VAS and ordinal pain intensity scales, daily number of extra doses of analgesics, and daily milligrams of extra doses of analgesics. In the case of pain evaluation from the patient's daily diary, no significant differences were found between the two drugs for period, carryover, or center effects. In the case of the pain evaluation at the time of investigator assessments (day 6 and day 11), although there was no significant difference between formulations and no significant period defect, there was a significant carryover effect for pain intensity both in the VAS (P = .02), and the pain intensity rating (P = .03).

There was no significant difference in pain intensity or use of extra doses of hydromorphone between the four different daily intervals for both IRH and SRH.

No significant differences were observed in the intensity of nausea, sedation, constipation, and vomiting between IRH and SRH.

Table 3 lists the overall global rating of the study medications by patient and investigator after the completion of the study. The majority of patients and investigators rated both medications between good and very good. No significant differences were observed between IRH and SRH.

Table 4 lists the final blinded choice between IRH and SRH for patient and investigators: 35 patients (47%) and 61 investigators (81%) expressed no difference between IRH and SRH. Among those patients and investigators who expressed a preference, the distribution was almost identical between IRH and SRH. The results for the distribution were not significantly different between IRH and SRH.

Table 5 lists the results of pain intensity and other symptoms during the open follow-up phase. These results suggest that pain intensity, average daily dose of hydromorphone, drowsiness, nausea, vomiting, and constipation remained in good control during the follow-up period.

In no case was it necessary to discontinue IRH or SRH because of severe toxicity.

Table 2. Results After the Completion of the Double-Blind Study

	IRH	P	SRH
Pain intensity VAS (0-100)	27 ± 21	.14	29 ± 21
Average from patient diary			
On day 6 or day 11	30 ± 22	.46	34 ± 21
Pain intensity (ordinal scale; 0-3)	1.3 ± 0.6	.19	1.3 ± 0.6
Average from patient's diary			
On day 6 or day 11 (0-3)	1.5 ± 0.6	.21	1.6 ± 0.6
Total no. of analgesic rescue doses	10 ± 8	.50	9 ± 7
Mean daily IRH rescue dose (mg)	20 ± 33	.16	16 ± 21

NOTE. Results are expressed as mean ± SD.

Table 3. Global Rating of Both Drugs by Patients and Investigators

	Patients				Investigators			
	IRH		SRH		IRH		SRH	
Overall Rating	No.	%	No.	%	No.	%	No.	%
Excellent	2	3	3	4	3	4	3	4
Very good	20	27	18	23	32	41	33	41
Good	38	51	37	47	36	46	36	45
Fair	13	17	18	23	6	8	8	10
Poor	2	3	3	4	1	1	0	
Not reported	9		7		6		7	
Total*	84		86		84		87	

*Total number of patients is more than 75 because a global rating was obtained in patients who participated in at least one of the two double-blind phases.

Table 4. Final Blinded Choice by Patients and Investigators

Preference	Patient		Investigator	
	No.	%	No.	%
IRH	19	26	7	9
SRH	20	27	7	9
No preference	35	47	61	81
Not reported	1		0	
Total	75		75	

NOTE. No significant difference was observed between IRH and SRH.

DISCUSSION

In this randomized, crossover, double-blind study, we compared the analgesic and side effects of SRH and IRH in patients with cancer pain.

Our population consisted of terminally ill patients with severe pain, as shown by the large number of patients with stage 3 (poor prognostic) pain syndromes in the Edmonton staging system (86 patients; 91%) and the high daily dose of hydromorphone on admission to the study (75 ± 79 mg/d). These patients represented a more unstable population than patients included in previous studies of SRM[5,6] and represent the patients who are likely to receive this drug in many centers. Although the drop-out rate was higher than is the case with patients with more benign pain syndromes requiring lower doses of opioids, this study addressed a major concern of supportive care research: good results in stable populations receiving low opioid dose cannot be easily reproduced in daily clinical practice.[8,9]

A crossover study introduces unique difficulties in the planning, execution, and analysis of clinical trials.[8,9] Because of the very ill nature of the patient population, it was not possible to include a wash-out drug-free period without significantly prolonging the study, and therefore, increasing the likelihood of drop-outs resulting from clinical deterioration. This made it difficult to establish a baseline for each change of therapy and accentuated the potential bias of carryover effect from one phase to the next. However, a crossover study eliminates the problem of interindividual variation and provides the only means of obtaining a blinded final choice by patient and investigator. This choice is a powerful overall expression of satisfaction that summarizes a balance between the therapeutic and side effects of the drug.[10] In previous studies, our group[11-13] and other investigators[13] have found that significant differences in the main therapeutic outcome are not always associated with blinded patient choice. This is particularly relevant in the case of drugs with significant side effects. The multiplicity of devastating symptoms that coexist to varying degrees in this patient population make the measurement of a single outcome in a parallel study unlikely to adequately reflect the complex effect of the drug. If a large number of measurements take place, the interpretation of the results becomes difficult because of the complications associated with the analysis of multiple comparisons.[14]

Table 5. Results in 73 Patients who Entered the Open Phase of the Study

	Day 11	Month 1	Month 2	Month 3
No. of patients	73	52	42	36
VAS (0-100)	31 ± 21	37 ± 28	31 ± 24	35 ± 28
Pain intensity rating (0-3)	1.5 ± 0.7	1.6 ± 0.7	1.4 ± 0.8	1.5 ± 0.8
Drowsiness	28 ± 26	34 ± 30	27 ± 24	34 ± 31
Nausea	19 ± 24	15 ± 26	18 ± 23	20 ± 23
Vomiting	10 ± 18	8 ± 18	11 ± 19	13 ± 17
Constipation	18 ± 23	25 ± 30	22 ± 27	29 ± 31

NOTE. Data expressed as mean ± SD.

Carryover effect was observed for pain intensity between the first and second phase. This effect was limited to the assessments performed during the patient's visit and was not observed in the patient's daily diary assessment. Moreover, the overall intensity of pain assessment during each of the four daily intervals was within a couple of millimeters in a 0- to 100-mm VAS and unlikely to have any clinical relevance, as suggested by the overall final choice and global rating (Tables 3 and 4). The fact that pain scores did not tend to increase near the trough period suggests that SRH was a true 12-hour preparation and equipotent to IRH.

Because of the double-blind nature of this study, patients were not allowed to consider in their final choice the obvious advantage of twice-a-day dosing for SRH. However, a clear preference for a sustained-release preparation is shown by the fact that 73 of 75 patients (97%) chose to enter the open follow-up phase of the study after completion of the double-blind phase.

Both IRH and SRH showed excellent side effect profiles, with no patients needing to discontinue treatment because of side effects. The open phase follow-up suggests that both effectiveness and toxicity remained unchanged during 3 months. The number of patients on follow-up decreased over time. In general, this was because of death and intercurrent complications.

A sample size of 75 in a paired study allows for the estimation of standardized effect size of approximately 0.34, using two-tailed test with alfa equal to 0.05 and beta equal to 0.20 (80% power). In our population, this effect size is equivalent to a difference of 7.5 mm on a 100-mm VAS for pain and to 2.7 rescue doses per day.

During recent years, it has become apparent that the morphine and other opioid agonists may cause significant toxicity during repeated administration. This toxicity can be manifested as confusion,[15] agitation and generalized myoclonus,[3,16,17] pulmonary edema,[18] organic hallucinosis,[19] or chronic nausea.[20] These toxicities are likely caused by both active drug and active metabolite accumulation.[3,16,20] In these cases, a change in the type of opioid is the most useful approach. An SRH preparation will be highly convenient to patients who may need to change to hydromorphone from other opioid analgesics. It might also add to the comfort of patients who are receiving IRH with good pain control.

We conclude that SRH is safe and effective in the management of cancer pain in this very ill population on high doses of opioids.

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