Managing Cancer Pain and Symptoms of Outpatients by Rotation to Sustained-release Hydromorphone

A Prospective Clinical Trial

Stefan Wirz, MD, Hans Christian Wartenberg, MD, Christian Elsen, Maria Wittmann, MD, Marta Diederichs, and Joachim Nadstawek, MD

Purpose: In this prospective clinical trial we examined the technique of opioid rotation to oral sustained-release hydromorphone for controlling pain and symptoms in outpatients with cancer pain.

Methods: Before and after rotation, 50 patients were assessed by Numerical Analog Scales [Numerical Rating Scales (NRS)], or as categorical parameters, and analyzed by descriptive and confirmatory statistics (ANOVA, Wilcoxon, χ^2).

Results: Rotation was successful in 64% of patients experiencing pain (60%), and gastrointestinal (32%) and central (26%) symptoms under oral morphine (38%), transdermal fentanyl (22%), tramadol (20%), oxycodone (12%), or sublingual buprenorphine (8%). NRS of pain (4.1 to 3.2; $P = 0.015$), gastrointestinal symptoms, especially defecation rates ($P = 0.04$), and incidence of insomnia improved after an increase in morphine-equivalent doses from 108.9 to 137.6 mg/d without modifying concomitant analgesics or coanalgesics.

Conclusions: Switching the opioid to oral hydromorphone may be a helpful technique to alleviate pain and several symptoms, but it is still not clear to what extent the underlying mechanisms, such as the technique of rotation itself, better dose adjustment, or using a different opioid have an impact.

Key Words: hydromorphone, opioid, rotation, symptom, cancer pain, outpatient, constipation

(*Clin J Pain* 2006;22:770–775)

Pain and symptoms have a negative impact on the quality of life of patients with cancer pain. Despite the publication of guidelines, many patients still suffer from inadequate analgesia and experience side-effects from their opioid medication, forcing them to discontinue opioid therapy.[1–4]

Various schemes for the management of opioid-related symptoms comprise the use of several substances, for example, laxatives, antiemetics, and psychotropic drugs. However, improvements in the incidence and severity of symptoms have also been attributed to the technique of rotating opioids. Few prospective investigations have been published on pain and side-effects after rotation of cancer patients to oral sustained-release hydromorphone, especially on hydromorphone.[5,6] Therefore, we evaluated the technique of opioid rotation for the management of pain and symptoms by administering oral sustained-release hydromorphone to outpatients with outpatient cancer pain.

METHODS

Study Design, Assessment

This investigation was a controlled, prospective, observational cohort study. Data were collected over a period of 5 consecutive days before and after rotation to hydromorphone, interrupted by an adaptation period of 14 days. Demographic and general medical data, for example, age, sex, cancer diagnosis, concurrent diseases or disorders, were obtained by examining and interviewing the outpatients directly. Patients assessed their own general condition on a 100 mm scale at the beginning of the investigation (0 = worst condition, 100 = no impairment, best condition).

Pain at rest was assessed via Numerical Rating Scales (NRS, 0-10, 0 = no pain, 10 = worst pain imaginable), at 4 time points over 5 consecutive days (7.00 AM, 1.00 PM, 7.00 PM, and 10.00 PM).

The investigators filled in a standardized questionnaire form listing central, gastrointestinal, and other symptoms. Patients rated the symptoms sedation, dizziness, nausea, "the subjective sensation of being constipated," dry mouth, and itching by 11 step NRS Scales (NRS, 0-10, 0 = no symptom, 10 = worst symptom imaginable) (numerical parameters). Incidences of myoclonic jerks, insomnia, emesis, and defecation rate that could not be rated by NRS were counted (categorical parameters).

Received for publication July 26, 2005; accepted June 15, 2006.
From the Clinic for Anesthesiology and Intensive Care Medicine, Pain Clinic Department, University of Bonn, Sigmund-Freud-Str. 25, D-53105 Bonn, Germany.
The authors wish to state that no grants or other financial support have influenced the course or results of the study.
Reprints: Stefan Wirz, MD, Clinic for Anesthesiology and Intensive Care Medicine, Pain Clinic, University of Bonn, Sigmund-Freud-Str. 25, D-53105 Bonn, Germany (Schmerzambulanz, Klinik und Poliklinik für Anästhesiologie und Operative Intensivmedizin, Rheinische Friedrich-Wilhelms-Universität, Sigmund-Freud-Str. 25, D-53105 Bonn, Deutschland) (e-mails: s.wirz@web.de; postoperativ@web.de).

Patients

After approval by the local ethics committee and informed written consent, 50 patients were enrolled in the study provided they met one of the following inclusion criteria: insufficient control of pain (defined as pain at rest with an NRS higher than 4) or symptoms (defined by an NRS higher than 4 for "numerical" variables and for "categorical" variables), incidence of emesis, insomnia, more than 2 myoclonic jerks per day, and a stool-free interval of more than 72 hours in the previous 7 days. Further inclusion criteria were: cancer-related nociceptive pain, outpatient treatment, a good general condition with the ability to walk unaided, and current opioid therapy, according to WHO-scheme stage II and III, with opioids other than hydromorphone. Criteria for exclusion comprised: communication deficits, neuropathic pain, hepatic or renal impairment, conditions likely to interfere with oral administration or drug absorption in the gastrointestinal tract, being bed-ridden, infections, chemotherapy, radiotherapy, entering the terminal phase, prior history of drug addiction or alcohol abuse, and concurrent treatment with further opioids.

Medications

For opioid rotation, patients received an oral formulation hydromorphone (capsule), a semisynthetic strong opioid with mu-agonist properties, and a prolonged duration of action of 12 hours. Its oral bioavailability is similar to morphine. Most references display an equivalence factor to morphine of 5 rather than 7.5.[7–14]

During the course of the study, no other opioids or formulations of hydromorphone were allowed. Despite other recommendations or guidelines, breakthrough pain was treated with the oral sustained-release formulation of hydromorphone, as no oral immediate-release formulation was available in Germany at the time of this investigation. Patients were instructed to contact us at any time, day or night, if pain, symptoms, or other problems should arise. If this happened, the medication was to be interrupted and replaced by more effective procedures.

The administration of nonopioids, such as nonsteroidal antiinflammatory drugs (NSAIDs), and adjuvants, for example, antidepressants, anticonvulsants, laxatives, or benzoediazepines, that had been part of the patients' treatment, were continued at the same dose levels, to exclude the influence of further changes of substance.

Rotation Policy

Rotation was performed if patients fulfilled the inclusion criteria. After calculating the individual morphine-equivalence dosages of the previous opioids, patients were rotated to hydromorphone (conversion factor morphine: hydromorphone = morphine 5:1), starting with 66% of the morphine-equivalent dosage over an adjustment period of 2 weeks, and were supervised carefully by the doctors and nurses of the outpatients' clinic of the department for Anesthesiology and Intensive Care Medicine of the University of Bonn, Germany.[7–12] We defined a successful rotation by an improvement of at least 2 points in the NRS of pain at rest or of a symptom that had been a cause for rotation. In contrast, rotation was rated as unsuccessful if NRS did not improve by at least 2 points, or even deteriorated by more than 2 points.

Data Documentation and Analysis

All data obtained were documented in an electronic SPSS database, created specially for this purpose. Descriptive statistics analyzed demographic data, the use and dosages of all drugs, NRS scores of pain, and various symptoms at all time points.

Confirmatory statistics of symptoms were performed if more than 5 patients showed symptoms. A multivariate ANOVA procedure was performed to detect differences at all time points in each period. For numerical parameters we analyzed the mean scores for pain or symptoms from 5 consecutive days before and after rotation, using the nonparametric Wilcoxon test, and, similarly, for categorical parameters, the χ^2 test. Statistical significance was defined as $P < 0.05$.

RESULTS

Demographic and General Medical Data

Between the start of the study (March 1, 2001) and the end of the study (August 1, 2004) 50 outpatients (12 women, 38 men, mean age 60.4 ± 11.3, minimum 31, maximum 79, median 62 y) participated in the study. No patient withdrew from the study, no severe impairments of vital signs were observed. The majority of patients suffered from gastrointestinal or genitourinary cancers. Although no patient was bed-ridden, some patients were only able to walk short distances and had an inferior general condition. Pain was nociceptive in all patients, in 19 of them characterized as somatic and in 31 as visceral pain. Somatic nociceptive pain was exacerbated in 4 patients by movement (Tables 1, 2).

Indications for Rotation

The main indications for rotation, besides insufficient control of pain, were gastrointestinal symptoms and various central nervous effects. Eighteen patients suffering from insufficient pain control revealed 1 further symptom, one 2 further symptoms, and 4 patients at least 3 symptoms (Fig. 1).

TABLE 1. Demographic and Medical Data, n = 50 Patients

	Parameter
Gender (m/f)	12/38
Mean age (y) (minimum – maximum)	60.4 (31 – 79)
General condition (0 = worst – 100 best) (minimum – maximum, SD)	37.4 (3 – 81, ± 20.4)
Walking distance less than 200 m (n)	5

TABLE 2. Cancer Diagnoses, n = 50 Patients

Cancer Diagnosis	Number
Urologic cancer	16
Gastrointestinal cancer	12
Lung cancer	7
Breast cancer	4
Gynecologic cancer (except breast cancer)	3
Others (lymphoma, melanoma, etc.)	8

Analgesics

Opioids

The mean duration of a previous opioid therapy before rotation was 25.8 weeks (minimum 1 wk, maximum 104 wk, SD ± 30.8). Before rotation, opioid use comprised oral controlled-release formulations of morphine (n = 19) or oxycodone (n = 6), tramadol (n = 10), transdermal fentanyl (n = 11), or sublingual buprenorphine (n = 4). Patients with fentanyl patches (7 out of 11), patients with sustained-release tablets of morphine (14 out of 19) or oxycodone (3 out of 6) received fast-acting formulations of morphine tablets as rescue medication, whereas patients with sustained-release tramadol (6 out of 10) were given tramadol drops additionally. Patients (3 out of 4) on continuous medication with buprenorphine took further sublingual tablets in the event of breakthrough pain. Including their rescue medications, patients' daily mean morphine-equivalent doses for opioids were: transdermal fentanyl 279.5 mg/d, morphine 60.5 mg/d, oxycodone 120.0 mg/d, tramadol 130 mg/d, and buprenorphine 60 mg/d.

After rotation, daily mean morphine-equivalent dosage changed from 108.9 mg (SD ± 115.8 median 60, minimum 10, maximum 600 mg/patient/d) to 137.6 mg/d (SD ± 117.2, median 80, minimum 20, maximum 480 mg/d) ($P = 0.07$, which was insignificant). The dosage of oral controlled-release hydromorphone was 27.5 mg/d (SD ± 23.4, median 16, minimum 4, maximum 96 mg/d), with a mean of single doses of 12.4 mg (SD ± 9.9, median 8, minimum 4, maximum 48 mg).

Forty-five patients received hydromorphone twice per day, and 5 more frequently. To treat pain caused by mobilization (walking), doses for a regular single additional administration of hydromorphone were 8 mg once a day each in 3 patients, and 20 mg (16 mg + 4 mg capsule) in 1 patient. According to his personal request, a fifth outpatient received 16 mg at 4 time points, as he was used to taking analgesics at these times. Despite the slow pharmacokinetic action, patients rated this pain management as effective. No patient required further opioids or additional dose adjustment. No patient required further opioids or additional dose adjustment.

NSAIDs

Use of NSAIDs comprised celecoxib (19 patients, mean daily dose 389.5 ± 45.9, median 400, minimum 200, maximum 400 mg/d), valdecoxib (8 patients mean daily dose 23.4 ± 4.4, median 25, minimum 12.5, maximum 25 mg/d), or ibuprofen (3 patients mean daily dose 1166.7 ± 351.2, median 1200, minimum 800, maximum 1500 mg/d). Additionally, 25 patients received dipyrone drops (mean daily dose 3.9 ± 1.1, median 4, minimum 2, maximum 6 g/d), which is available in Germany, and 2 patients flupirtine (mean daily dose 250, minimum 200, maximum 300 mg/d).

Coanalgesics

As psychotropic and sleep-inducing medication, 18 patients received amitriptyline (n = 15, 25 mg/d; n = 3, 10 mg/d), and 1 patient lorazepam (2.5 mg/d). As antiemetics, 14 patients took metoclopramide (mean 8 mg/d), 4 ondansetron (mean 4 mg/d), and one 2 mg/d of haloperidol. Despite the policy of prescribing laxatives, 15 patients received no laxatives because they refused. Twelve patients received sodium picosulfate (mean 18.2 mg/patient), 20 polyethylene glycol (mean 1.35 sachets = 18.6 g/patient), and 4 other laxatives.

Pain

Mean NRS for pain of both assessment periods differed significantly, as shown in Table 3. During the assessment period of 5 days, the NRS for pain did not

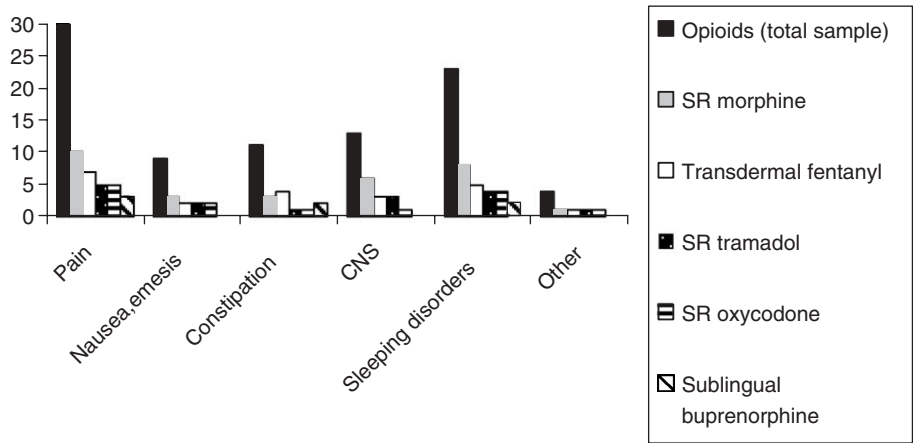

FIGURE 1. Indications for opioid rotation and original opioids, n = 50 patients multiple answers possible. SR indicates sustained-release.

TABLE 3. Rotation Due to Pain and Symptoms: Changes Symptoms in Various Subgroups Multiple Answers Possible

	Numerical Parameters			
Indication (NRS > 4)	**Patients Rotated (n)**	**Before Rotation NRS (Mean, SD)**	**After Rotation NRS (Mean, SD)**	**Statistical Significance *P***
Pain	30	4.1 ± 2.3	3.2 ± 1.7	0.015
Sedation	2	5	5	Not done
Itching (pruritus)	1	5	3	Not done
Nausea	9	4.5 ± 3.5	2.3 ± 2.9	0.07
"Feeling constipated" Incidence	11	5.9 ± 1.8	4.3 ± 2.9	0.09
Defecation rate/patient/d	11	0.1	0.5	0.04
	Categorical Parameters—No. Patients With Symptoms			
Indication	**Patients Rotated (n)**	**Before Rotation (n)**	**After Rotation (n)**	**Statistical Significance *P***
Stool free interval > 72 h	4	4	2	Not done
Emesis	9	9	4	0.3
Myoclonus	6	6	4	Not done
Nightmares	5	5	3	Not done
Sleep onset insomnia	16	16	8	0.1
Sleep maintenance insomnia	23	23	12	0.1

NRS, 0-10, 0 = no pain or symptom, 10 = worst pain or symptom imaginable.

vary significantly between day 1 and 5 (before rotation: $P = 0.66$, after rotation: $P = 0.34$). The mean NRS for pain obtained at different time points were similar (before rotation: 7.00 AM: mean 4.7, median 4, SD ± 2.8; 1 PM: mean 4.5, median 4, SD ± 2.4; 7 PM: mean 4.5, median 4, SD ± 2.5; 10 PM: mean 3.9, median 3, SD ± 2.3; after rotation: 7.00 AM: mean 3.4, median 3, SD ± 2.3; 1 PM: mean 3.4, median 3, SD ± 2.0; 7 PM: mean 3.2, median 3, SD ± 1.9; 10 PM: mean 2.8, median 3, SD ± 1.7).

Central Symptoms

Central symptoms, such as day-time sedation, dizziness, myoclonic jerks, or nightmares were rare (Table 3, Tables 4A, B).

Gastrointestinal Symptoms

Rotation reduced the number of patients suffering from emesis from 9 to 4 ($P = 0.34$) (only 6 of them with an NRS for nausea > 4), whereas *their* mean NRS for nausea decreased from 4.5 to 2.3 ($P = 0.07$). Overall, mean NRS for nausea of *all* patients changed, but the change was insignificant. Nine patients demanded rotation because of emesis, but further patients with this symptom did not request rotation because of emesis, but for other reasons.

Constipation was the reason for rotation in 11 patients, leading to improvements in mean NRS for constipation from 5.9 to 4.3 ($P = 0.09$) (mean of *all* patients: 2.4 to 2.0) and in mean daily defecation rates from 0.1 to 0.5 ($P = 0.04$) (*entire* sample 1.0 to 0.9). The number of patients with a stool-free interval of more than 72 hours fell from 4 to 2.

Other Symptoms

Generally, the impact of itching and dry mouth was rated as low. Insomnia was the reason for opioid rotation in 23 cases. Eighteen of these 23 patients suffered primarily from pain. In contrast, 18 of the 30 patients with pain as their main complaint suffered from insomnia. The overall incidence of insomnia in the entire population improved (Tables 3, Tables 4A, B).

TABLE 4A. Self-rated Symptoms of the *Entire* Population: Changes in Mean NRS

Symptom	**Before Rotation NRS (Mean, SD)**	**After Rotation NRS (Mean, SD)**	**Statistical Significance *P***
Dizziness	1.0 ± 1.4	1.0 ± 1.4	Not done
Sedation	2.6 ± 1.5	2.8 ± 1.7	0.5
Dry Mouth	1.7 ± 1.9	2.0 ± 2	0.4
Itching (Pruritus)	0.4 ± 1.3	0.2 ± 0.7	0.6
"Feeling constipated"	2.4 ± 2.5	2.0 ± 2.5	0.1
Nausea	1.5 ± 2.1	1.2 ± 1.6	0.2

NRS, 0-10, 0 = no symptom, 10 = worst symptom imaginable; n = 50.

TABLE 4B. Symptoms of the *Entire* Population: Mean Incidences Calculated per 24 Hours

Symptom	**Before Rotation Incidence/24 h**	**After Rotation Incidence/24 h**	**Statistical Significance *P***
Emesis	0.2	0.1	0.3
Defecation/day	0.9	0.9	0.7
Myoclonus	0.2	0.2	0.5
Nightmares	0.1	0.1	0.5
Onset insomnia	0.3	0.2	0.02
Maintenance insomnia	0.5	0.2	0.003

n = 50.

Efficacy of Rotation

Rotation was successful in 32 patients (64%). Pain (17) and/or symptoms (31) improved after switching from sublingual buprenorphine (3 out of 4 patients), transdermal fentanyl (8 out of 11), oral tramadol (7 out of 10), morphine (11 out of 19), and oxycodone (3 out of 6).

In 16 patients (32%) who did not show changes in pain or symptoms, the original opioids were oral oxycodone (3 out of 6), tramadol (3 out of 10), transdermal fentanyl (3 out of 11), sublingual buprenorphine (1 out of 4 patients), or oral morphine (5 out of 19). Symptoms even worsened (sedation, constipation) in 2 patients previously on morphine. In these 18 patients outpatient pain therapy was complicated, and some patients required referral to hospital.

DISCUSSION

Study Design, Patients and Methods

In contrast to prior investigations, we chose a controlled, prospective, observational design[5,7,9,15] and referred strictly to the oral route of opioid administration, using sustained-release hydromorphone.[5,16]

Most rotation studies include patients with advanced cancer who are in hospital, palliative care units or hospices. In contrast, our interest focused on *outpatients* with purely nociceptive pain, taking into account a different variety of symptoms or less severe symptoms. In accordance with similar data from palliative care units, 50 patients in our pain clinic presented with reasons for rotation of the opioid over a period of more than 3 years.[17]

The heterogeneity of our patients' demographics, cancer diagnoses, and prior opioid treatments is consistent with prior references representing clinical "real life" scenarios. In contrast to other studies, our sample revealed no organ malfunctions. This was attributable to the "outpatient" status.[18,19]

This study underlines the impact of symptoms in an outpatient setting in particular. Sometimes, references bypass clear definitions of symptoms, for example, constipation. By means of a structured protocol using NRS for quantifying the subjective impact of symptoms and the observation of incidence, this investigation followed precisely defined rules to avoid indistinct and unbiased estimates despite the unblinded nature of this study.[14,19,20]

In contrast to other studies, we did not find *significant* alterations in *all* symptoms. Possibly, enrolling larger numbers of patients into prospective, randomized, double-blind studies would produce significant differences in more symptoms. Nonetheless, we were restricted to an observational design, due to ethical issues.[17]

In contrast to previous reports we demonstrated obvious improvements in gastrointestinal symptoms in patients who had demanded rotation for those symptoms. These were partly insignificant.[5,11] Otherwise, improvements in these subgroups did not alter the frequency or severity of these symptoms in the population as a whole.

Because of the small number of outpatients presenting central symptoms as reasons for rotation, a statistical analysis of subgroups was not feasible, whereas the entire sample exhibited only slight variations. Major neuropsychiatric symptoms, such as hallucinations or agitation, did not develop at all. With regard to other references we would have expected greater changes in CNS symptoms, particularly after rotation.[5,10–12,18] This again might correlate with the better state of health of the outpatients.

An improvement in insomnia in a *subgroup* rotated for this symptom was not significant. We interpret the decrease in incidence of sleeping disorders in the *entire* sample as a result of a more effective pain therapy after opioid rotation.[7,10]

However, the symptoms of most patients were alleviated, although a third of the patients (n = 18) still suffered from symptoms. This may relate to the variety of symptoms. Unfortunately, the number of patients (50) and the smaller size of the subgroups with different cancer diagnoses or previous opioids did not allow a confirmatory analysis of possible influences of those determinants.

In our heterogeneous sample, a "low" or "medium dose opioid therapy" correlated to pain and symptoms indicating rotation. Sometimes, calculations of mean opioid dosages are omitted in such heterogeneous populations.[8]

The higher frequency of successful switches from sublingual buprenorphine, transdermal fentanyl, and oral tramadol to oral hydromorphone might be due either to the mode of administration or to substance effects, and not to the technique of rotation itself.[20–24]

In particular, this may be relevant for the mild mu-agonist tramadol, because of its additional serotonergic and noradrenergic properties. Although tramadol is classified as a step II opioid on the WHO ladder, prior references also enroll patients with tramadol in rotation studies for pragmatic reasons.[8]

Furthermore, the scope of daily mean morphine equivalents in groups with different previous opioids (60 to nearly 300 mg/d) may indicate inadequate dosing before rotation, at least in patients on morphine or tramadol.

Following rotation to hydromorphone, patients tolerated higher morphine-equivalent doses (increase of about 25%). The conversion factors for hydromorphone and morphine are still being discussed. In agreement with our clinical practice and in accordance with a majority of references, we chose a conversion ratio of 1:5, creating statistically insignificant results.[7–12] Even so, other references report a conversion factor of 1:7.5, which would have produced significance of mean morphine-equivalent doses.[11,14,15]

Despite the presence of symptoms, outpatients demonstrated variations in their willingness to use the prescribed coanalgesics, especially laxatives. In the absence of symptoms, these patients might have been able to tolerate higher doses of their previous opioid. Thus, during this study, the technique of *rotation* itself may have been less effective than a more effective dose, or

closer monitoring of outpatients. However, despite the increase in morphine-equivalent doses, symptoms were alleviated in 2/3 of patients *without* changing the concomitant medication used for symptom control.

Although the use of sustained-release formulations for the treatment of breakthrough pain does not accord with clinical guidelines, 4 patients benefited from this procedure. Because a fast acting oral hydromorphone is now available in our country, this procedure is no longer warranted. The decrease in the use of rescue medication (from 30 to 4 patients) might imply a more effective pain therapy post rotation. However, it is still not clear whether this improvement is due to the technique of rotation itself, the increasing opioid dose, or a better pharmacokinetic profile of the substance hydromorphone.

Several opioids have been examined as suitable "target" substances for rotation, for example, fentanyl, methadone, or hydromorphone. The efficacy and safety of hydromorphone have been demonstrated in prior investigations.[7,16,17,20,25]

Again, our study underlines the benefits of rotating to this substance by the reduction in pain and symptoms. Its pharmacokinetic properties, such as a strong first-pass metabolism and a small plasma-protein binding, might be advantageous in cancer patients. Previous data on hydromorphone demonstrated the low impact of glucuronides on palliative-care patients, even those with organ dysfunctions, resulting in a low incidence of symptoms.[5,7,9,15,26]

CONCLUSIONS

It is still not clear whether the mere technique of rotation, better dose adjustment, or the use of several different opioids caused the improvements in pain and symptoms. However, our investigation demonstrates the possible advantages of switching to hydromorphone if there is inadequate pain and symptom control.

ACKNOWLEDGMENTS

The authors gratefully thank the nurses of the outpatients' pain clinic of the University of Bonn, Germany, for their collaboration and help.

REFERENCES

1. Hanks GW, Conno F, Cherny N, et al. Expert Working Group of the Research Network of the European Association for Palliative Care. Morphine and alternative opioids in cancer pain: the EAPC recommendations. *Br J Cancer*. 2001;84:587–597.
2. Hanks GW, de Conno F, Ripamonti C, et al. Expert Working Group of the Research Network of the European Association for Palliative Care. Morphine in cancer pain: modes of administration. *BMJ*. 1996;312:823–826.
3. World Health Organisation. *Cancer Pain Relief, with a Guide to Opioid Availability*. 2nd ed. Geneva: World Health Organisation; 1996.
4. Reuben DB, Mor V, Hiris J. Clinical symptoms and length of survival in patients with terminal cancer. *Arch Intern Med*. 1988; 148:1586–1591.
5. De Stoutz ND, Bruera E, Suarez-Almazor M. Opioid rotation for toxicity in terminal cancer patients. *J Pain Symptom Manage*. 1995;10:378–384.
6. Fallon M. Opioid rotation: does it have a role? *Palliat Med*. 1997;11:177–178.
7. Bruera E, Pereira J, Watanabe S, et al. Opioid rotation in patients with cancer pain. A retrospective comparison of dose ratios between methadone, hydromorphone, and morphine. *Cancer*. 1996;78: 852–857.
8. Grilo RM, Bertin P, Scotto di Fazano C, et al. Opioid rotation in the treatment of joint pain. A review of 67 cases. *Joint Bone Spine*. 2002;69:491–494.
9. Lawlor P, Turner K, Hanson J, et al. Dose ratio between morphine and hydromorphone in patients with cancer pain: a retrospective study. *Pain*. 1997;72:79–85.
10. Mercadante S. Opioid rotation for cancer pain: rationale and clinical aspects. *Cancer*. 1999;86:1856–1866.
11. Sarhill N, Walsh D, Nelson KA. Hydromorphone: pharmacology and clinical applications in cancer patients. *Support Care Cancer*. 2001;9:84–96.
12. Quigley C, Wiffen P. A systematic review of hydromorphone in acute and chronic pain. *J Pain Symptom Manage*. 2003;25:169–178.
13. Parab PV, Ritschel WA, Coyle DE, et al. Pharmacokinetics of hydromorphone after intravenous, peroral and rectal administration to human subjects. *Biopharm Drug Dispos*. 1988;9:187–199.
14. Moriarty M, McDonald CJ, Miller AJ. A randomised crossover comparison of controlled release hydromorphone tablets with controlled release morphine tablets in patients with cancer pain. *J Clin Res*. 1999;2:1–8.
15. Lee MA, Leng MEF, Tiernan EJJ. Retrospective study of the use of hydromorphine in palliative care patients with normal and abnormal urea and creatinine. *Palliat Med*. 2001;15:26–34.
16. Drake R, Longworth J, Collins JJ. Opioid rotation in children with cancer. *J Palliat Med*. 2004;7:419–422.
17. Mercadante S, Casuccio A, Fulfaro F, et al. Switching from morphine to methadone to improve analgesia and tolerability in cancer patients: a prospective study. *J Clin Oncol*. 2001;19: 2898–2904.
18. Bruera E, Franco JJ, Maltoni M, et al. Changing pattern of agitated impaired mental status in patients with advanced cancer: association with cognitive monitoring, hydration, and opioid rotation. *J Pain Symptom Manage*. 1995;10:287–291.
19. Hays H, Hagen N, Thirlwell M, et al. Comparative clinical efficacy and safety of immediate release and controlled release hydromorphone for chronic severe cancer pain. *Cancer*. 1994;74:1808–1816.
20. Radbruch L, Sabatowski R, Loick G, et al. Constipation and the use of laxatives: a comparison between transdermal fentanyl and oral morphine. *Palliat Med*. 2000;14:111–119.
21. Smith MT, Watt JA, Cramond T. Morphine-3-glucuronide-a potent antagonist of morphine analgesia. *Life Sci*. 1990;47:579–585.
22. Quigley C, Joel S, Patel N, et al. Plasma concentrations of morphine, morphine-6-glucuronide and morphine-3-glucuronide and their relationship with analgesia and side effects in patients with cancer-related pain. *Palliat Med*. 2003;17:185–190.
23. Hagen NA, Foley KM, Cerbone DJ, et al. Chronic nausea and morphine-6-glucuronide. *J Pain Symptom Manage*. 1991;6:125–128.
24. Daeninck PJ, Bruera E. Reduction in constipation and laxative requirements following opioid rotation to methadone: a report of four cases. *J Pain Symptom Manage*. 1999;18:303–309.
25. Benitez-Rosario MA, Feria M, Salinas-Martin A, et al. Opioid switching from transdermal fentanyl to oral methadone in patients with cancer pain. *Cancer*. 2004;101:2866–2873.
26. Bruera E, Sloan P, Mount B, et al. 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. Canadian Palliative Care Clinical Trials Group. *J Clin Oncol*. 1996;14:1713–1717.

