Efficacy of Rhenium-186-Etidronate in Prostate Cancer Patients with Metastatic Bone Pain

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Rhenium-186-etidronate has been developed for pain relief of bone metastases and has previously been studied with regard to toxicity, pharmacokinetics and dosimetry. Its palliating effect on bone pain has not been studied extensively. To justify further efficacy investigations, patients participating in two toxicity studies were studied using a strict pain assessment methodology. **Methods:** Forty-three patients entered the study, 37 of whom were evaluable for pain assessment. Administered dosages ranged from 1295 MBq (35 mCi) to 3515 MBq (95 mCi) ^{186}Re-etidronate. Pain relief was assessed using a handwritten diary containing questions reflecting the multidimensional character of chronic pain. The diary was marked twice daily for a maximum of 10 wk (2 wk prior to and 6/8 wk after the injection). A response was determined using a specific decision rule, in which pain intensity, medication index and daily activities were core determinants. **Results:** A response was reached in 54% (20 of 37) of the patients and varied from 33% (n = 6) in the "35-mCi" group to 78% (n = 7) in the "50/65-mCi" group to 70% (n = 7) in the "80/95-mCi" group. **Conclusion:** Pain assessment using the multidimensional pain model showed that ^{186}Re-etidronate is an effective agent in the treatment of metastatic bone pain in prostate cancer and warrants further placebo-controlled studies.

Key Words: prostate cancer; bone metastases; rhenium-186-HEDP; pain response

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The skeleton is the second most common site for metastases in patients with prostate cancer. These metastases require palliative treatment for pain. Systemic therapy using bone-seeking radiopharmaceuticals is a promising method in the treatment of these painful bone metastases. Recently, rhenium-186-1, 1-hydroxy-ethylidene diphosphonate (^{186}Re-etidronate) has been developed to reduce pain (*1–4*). Previously, our group reported data on the pharmacokinetics and toxicity of ^{186}Re-etidronate in patients with prostatic or breast cancer (*5–8*). However, only limited efficacy data are available thus far (*2–4*).

The determination of the efficacy of any analgesic therapy is hampered by the highly subjective character of chronic pain (*9*). It is well recognized that chronic pain (including cancer pain) is a multidimensional phenomenon consisting of five dimensions, four of which concern psychological processes (*10*). These five dimensions together form a complex pattern of relations (Fig. 1).

Assessing pain in patients gives rise to several methodological problems that need to be addressed to adequately understand pain. First, a major discrepancy may consist between the patient's pain experience and the physician's impression (*11*). Second, the reliability of pain assessment will be influenced by the setting in which the patient is questioned (whether in the hospital environment or at home) (*12,13*). Third, daily assessment will improve the reliability compared to weekly scores due to the well-known problems of human memory (*14*).

Therefore, in our study, the patient assesses his pain daily, preferably outside the hospital environment, using a pain diary which contains questions reflecting the multidimensional character of chronic pain—such as the McGill Pain Questionnaire (*15*). The patient describes the relevant aspects of his pain and reports them systematically on a daily basis, thereby providing the most accurate picture of his pain.

Like other medical interventions, ^{186}Re-etidronate directly influences the sensoric dimension of pain. Initially, changes in the sensoric aspects (in particular the intensity of the pain) are of interest. Nevertheless, these changes immediately result in changes in various aspects of the other dimensions of pain and vice versa. To determine the response during relatively short follow-up periods of efficacy studies, a strict decision rule has to be used which considers the reciprocal influence of pain intensity, use of analgesics and daily activities.

This report describes the beneficial effect of ^{186}Re-etidronate in patients who entered open-label Phase I/II studies with endocrine-resistant prostate cancer using this pain assessment methodology.

MATERIALS AND METHODS

Patients

The study protocols were approved by the Institutional Review Board of the University Hospital Utrecht. All patients gave written informed consent. The studies were structured to evaluate the toxicity of ^{186}Re-etidronate: an escalating dosage protocol and a protocol using a fixed dosage of 1295 MBq ^{186}Re-etidronate. The study designs have been previously reported (*6,7*).

Forty-three patients entered the study. All patients suffered from endocrine-resistant prostate cancer that was histologically (or cytologically) proven (except for one patient who was diagnosed on clinically and biochemically). Patients suffered from bone pain which required the use of analgesics and had at least four scintigraphically and radiologically proven metastatic bone lesions. Adequate platelet count ($>150 \times 10^9$/liter), leukocyte count ($>4.0 \times 10^9$/liter) and renal function (plasma creatinine levels <130 μmole/liter) were required for eligibility. Performance status according to Karnofsky had to be ≥60% and life expectancy was estimated to be at least 3 mo. Although no specific recommendations were given on how to alter the analgesic treatment, the patients were requested to keep their analgesic regimens constant.

Treatment

The preparation of ^{186}Re-etidronate was reported in detail previously (*5*). The injected dosages ranged from 1295 MBq (=35 mCi) to 3515 MBq (=95 mCi). Rhenium-186-etidronate (total volume 2 ml) was injected as a bolus through a running intravenous saline drip.

Patients were hospitalized in the nuclear medicine department

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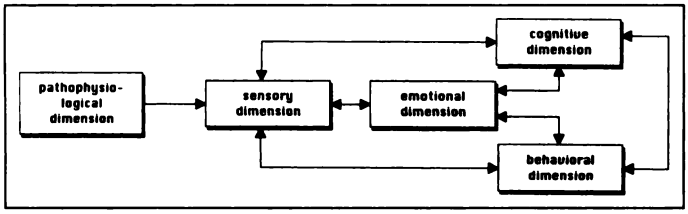

FIGURE 1. Schematic representation of the five dimensions of pain.

for 24 hr. After treatment, patients were seen and examined on a weekly basis, usually as outpatients.

Pain Assessment

A handwritten diary was used to assess each patient's pain. The diary contained validated questions for 7 days (see Appendix) and entries were recorded twice a day: at 7:30–8:30 a.m. and before going to bed. The analgesics used, the dose(s) and frequency(ies) were also reported. For each day, a medication index was calculated according to the table of analgesic conversion scores developed by Foley (*16*) (see Appendix). Each of the analgesics was given a dose equivalent, which was multiplied with the frequency of its use. The products were summed, resulting in the medication index.

The completed diary was returned to the investigators each week. In the dosage escalation and the fixed dosage protocol, the evaluation period lasted for 10 wk and 8 wk (2 wk prior to and 8–6 wk after therapy), respectively.

Additional Clinical Data

The period between the diagnosis of progression of disease (after adequate endocrine treatment) and the first injection was determined. The moment of progression was identified by a consistent rise of PSA (prostate-specific antigen) and the concommitant occurrence of painful lesions and/or the occurrence of new lesions on routine ^{99m}Tc-HDP bone scans. This period was called the pretreatment endocrine resistant episode (PERE).

A bone scan index (BSI) was determined according to Blake et al. (*17*) using a diagnostic pretherapy whole-body scintigram (400 MBq ^{99m}Tc-HDP) to provide an index of metastatic disease.

After tracer administration, several patients complained of a transient increase in pain intensity over the baseline pain. Typically, this so-called "flare" reaction started within the first week after therapy and lasted for no more than 1 wk. In this analysis, a "flare" reaction is defined as an increase in pain intensity of more than 25% which occurs in the first week after the administration of the first injection.

Data Analysis

The studies were open-label studies; so patients functioned as their own controls. For each patient, post-treatment data were compared to pretreatment data (baseline). Because scores fluctuated considerably over the week, median scores for the aforementioned dependent variables were calculated: one median score over the 2-wk pretreatment period (baseline) and weekly median scores for the 6–8-wk after treatment.

To determine the efficacy of ^{186}Re-etidronate, a decision rule was formulated, in which pain intensity, medication index and daily activities were included as core determinants. According to this decision rule, a response was defined as:

1. Pain reduction ≥25% during at least two consecutive weeks and medication index and daily activities at least constant.

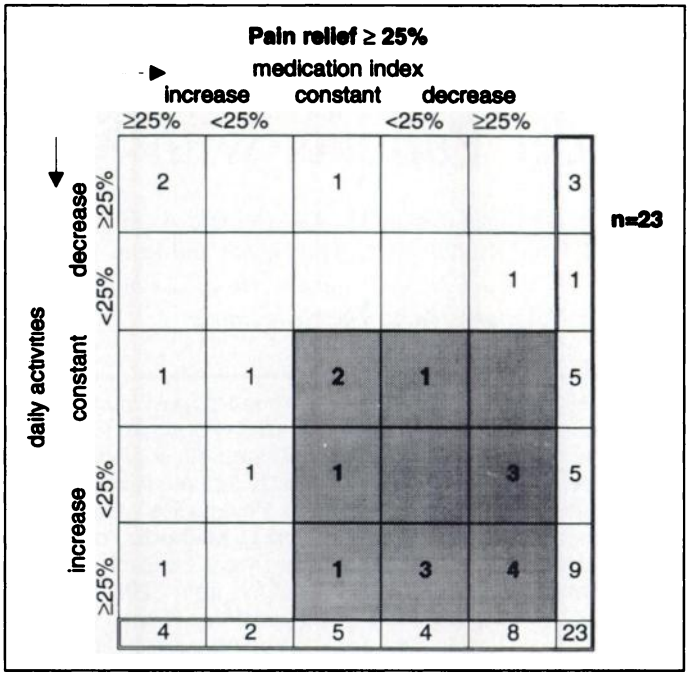

FIGURE 2. Number of patients showing at least 25% pain relief in combination with changes in medication index and daily activities. Shaded area indicates patients fulfilling the response criteria.

2. Pain reduction <25% during at least two consecutive weeks and improvement of one of the two other factors (medication index and daily activities) ≥25% during at least two consecutive weeks, while the remaining factor at least remained constant.

To detect statistically significant differences of $p < 0.05$ between the responders and nonresponders and also between the various dosage groups, statistical analyses were performed on the dependent variables, using the t-test for independent observations, Mann Whitney U-test, the Kruskall-Wallis test and (M)ANOVA using Systat 5.0 software (SYSTAT, Inc, Evanston IL). Adjustments were made for the confounding effect of age, flare, BSI and PERE. The same procedure was followed in case of differences in the baseline data concerning the dependent variables.

RESULTS

Forty-three patients entered the study. Six patients' data were excluded from the analysis because of early death (n = 2), incomplete datasets (n = 2) and minimal baseline pain (n = 2).

According to decision rule criteria, a response was observed for at least two consecutive weeks in 54% (20/37) of the patients (Figs. 2 and 3). The response rate decreased to 35% (13/37) when the duration was at least four consecutive weeks (Table 1). No statistically significant differences in dependent variables (and also age, BSI, PERE and flare reactions) between the responders and nonresponders could be detected prior to the injection. The overall percentage of patients with a flare reaction was 38%; this was 40% for the responders and 35% for the nonresponders. The responders showed statistically significant improvement ($p < 0.05$) in mood after therapy as compared to the nonresponders.

The injected dosages ranged from 1295 MBq (35 mCi) to 3515 MBq (95 mCi). For statistical analysis—to avoid very small groups—administrations were combined into three groups: the 35-mCi group (n = 18), the 50/65-mCi group (n =

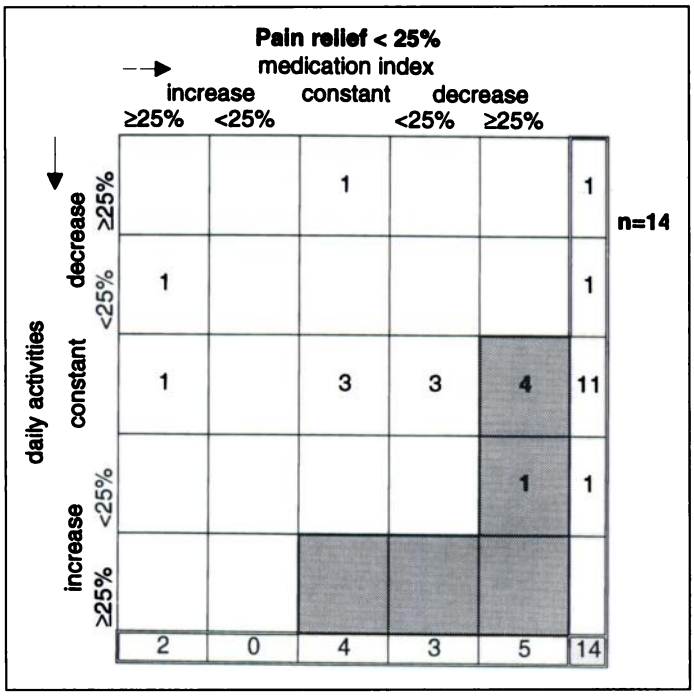

FIGURE 3. Number of patients showing less than 25% pain relief in combination with changes in medication index and daily activities. Shaded area indicates patients fulfilling the response criteria.

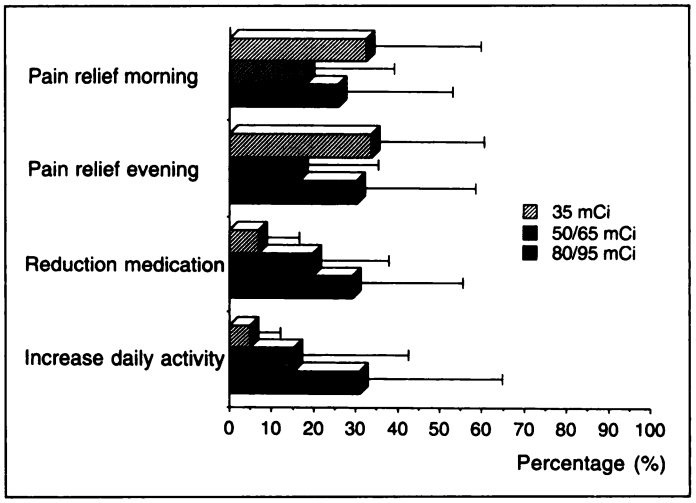

FIGURE 4. Degree of response after ^{186}Re-etidronate treatment according to the decision rule.

9) and the 80/95-mCi group (n = 10). The percentage of responders according to the decision rule increased from 33% (n = 6) in the 35-mCi group to 78% (n = 7) in the 50/65-mCi group to 70% (n = 7) in the 80/95-mCi group. The patients in the highest dosage group were significantly ($p < 0.05$) older than the patients in the other two groups. There were also differences between the groups concerning the frequency of a flare reaction. The percentages of patients with a flare reaction for the 35-mCi group, the 50/65-mCi group and the 80/95-mCi group were 67%, 43% and 14%, respectively. Whereas flare reaction did not correlate with the dependent variables, age showed statistically significant correlations with the duration of pain relief in the evening ($p = 0.002$) and also with the duration and the degree of increase in daily activities ($p = 0.004$, $p < 0.0001$) (Figs. 4 and 5). Comparison of these data did not reveal statistically significant differences between the three groups. No statistically significant differences could be detected with regard to the other dependent variables. We adjusted for the confounding effect of age.

TABLE 1
Degree and Duration of Response after Rhenium-186-Etidronate Treatment During Six-Week Follow-up Period

Variables	Mean (±s.d.)
Duration of pain relief (morning)	3.65 (2.76) wk
Degree of pain relief (morning)	25.05 (24.24) %
Duration of pain relief (evening)	4.06 (2.37) wk
Degree of pain relief (evening)	26.50 (23.70) %
Duration reduction Medication index	4.06 (2.76) wk
Degree reduction Medication index	19.20 (19.93) %
Duration increase Daily activities	2.86 (2.85) wk
Degree increase Daily activities	17.75 (26.21) %

Mean values and standard deviations for all responders are given.

DISCUSSION

The determination of the efficacy of ^{186}Re-etidronate in patients with endocrine-resistant prostate cancer was a secondary objective of two clinical studies primarily aimed at evaluating the toxicity associated with various dosages of ^{186}Re-etidronate.

Pain assessment using bone-seeking radiopharmaceuticals is very complex and responses are hard to objectify, as illustrated by studies using ^{89}Sr-chloride (*18,19*) and those published by Maxon et al. using ^{186}Re-etidronate (*2–4*). In their study on the palliative effects of ^{89}Sr-chloride compared to external beam radiotherapy, Quilty et al. (*18*) scored overall improvement, using a five-point adjective scale, by totalling the scores given for general condition, mobility, analgesic intake and pain. The percentage of patients with a substantial or dramatic improve-

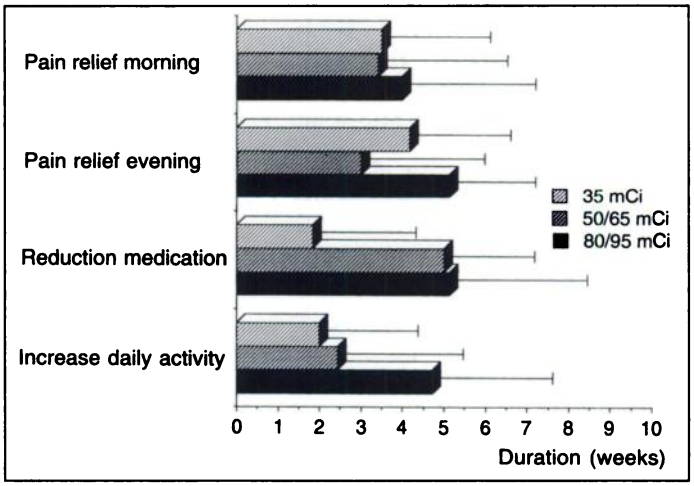

FIGURE 5. Duration of response after ^{186}Re-etidronate treatment according to the decision rule.

ment after ^{89}Sr-chloride was about 30%. Porter et al. (*19*), however, reported complete pain responses after ^{89}Sr-chloride ranging from 30% to 60%. In the latter study, a randomized Phase III trial to evaluate the efficacy of ^{89}Sr-chloride adjuvant to local field external beam irradiation, pain, intake of analgesics and quality of life were assessed separately. In their study of the efficacy of ^{186}Re-etidronate, Maxon et al. (*4*) used only a decline in pain intensity of at least 25% from baseline, taking no account of changes in daily activity and/or use of medication. The subsequent success rate was 77%. In the double-blind, crossover placebo-controlled study of Maxon et al. (*2*), the efficacy of ^{186}Re-etidronate was also related only to changes in pain intensity. Significant pain relief was observed in about 80% of the patients. In the well-known ROTG study on the palliative use of external beam radiotherapy in painful bone metastases, weekly pain scores were obtained (*20*). Four-point adjective scales were used for pain severity, pain frequency and also for the type and frequency of use of analgesics. Any improvement in the summed score for a week during the follow-up was considered to be related to radiotherapy. This led to the often-cited response rate of 92%.

To determine the effect of ^{186}Re-etidronate in our study, we used a rather strict decision rule. Only a reduction in pain intensity of at least 25% during a period of at least two consecutive weeks, as compared to the baseline situation, was considered to be related to ^{186}Re-etidronate therapy. At the same time, the reciprocal influence between pain intensity, use of analgesics and daily activities was taken into account as defined in the decision rule.

In most comparable studies, the improvement in pain intensity compared to the baseline, was used as the primary endpoint without adjustment for major variables such as medication index and daily activities; these variables were considered as secondary endpoints. In only a few of the published studies were the changes in pain intensity, analgesic intake and daily activities integrated into an overall response. The percentage differences of responders in the various studies have to be judged from this perspective.

In this study, the response rate for ^{186}Re-etidronate was determined to be 54%. Although the results of the various administered dosages might suggest a dosage-response effect, this did not reach statistical significance, probably due to the relatively small number of patients. The median duration of the effect could not be determined accurately because the evaluation period after therapy lasted only 6–8 wk and many patients still had favorable palliation after the study period. Given the favorable tolerability of ^{186}Re-etidronate (*6–8*), this treatment has considerable efficacy in this end-stage patient group. The methodology for reliable pain assessment used in this study is accurate but laborious. The use palmtop computers with a similar built-in questionnaire would be one way to solve this problem.

CONCLUSION

This study revealed a 54% response rate with ^{186}Re- etidronate in the treatment of patients with prostate cancer and metastatic bone pain using strict criteria. However, the true efficacy of ^{186}Re-etidronate can only be determined using longer observation periods and adjusting for possible placebo effects with a randomized, double-blind study design. The question of the optimal dosage has yet to be answered. Various randomized, double-blind studies addressing these issues are in progress.

APPENDIX

Pain Diary

At 7:30–8:30 a.m.

1. Describe the intensity of your pain at this moment
   I _____ I
   no pain — most severe possible pain
2. Describe your present mood
   I _____ I
   very bad — very good
3. How did you sleep last night?
   I _____ I
   very well — not at all
4. For how many hours did you sleep last night?
   . . . . . hours

Before Sleeping

1. Describe the intensity of your pain at this moment
   I _____ I
   no pain — most severe
2. Describe your present mood
   I _____ I
   very bad — very good
3. Have you taken pain-reducing medication over the last 24 hr?
   ___ yes
   ___ no
   If yes,

Name	/Frequency	/Dose

4. State whether you were able to perform these tasks. It does not matter whether or not you were able to do them.*

	I was able	I was able independently, but with difficulty,	I was able only with assistance	I was unable
To sit or rise from a chair	○	○	○	○
To get (un)-dressed and put on shoes	○	○	○	○
To wash myself	○	○	○	○
To walk a short distance	○	○	○	○
To walk a long distance	○	○	○	○
To do work around the house	○	○	○	○
To visit people	○	○	○	○
To perform manual labor	○	○	○	○

*This scale was derived from: Haes JCJM. The quality of life of cancer patients. Thesis, University of Leiden, The Netherlands, 1988.

5. How have you coped with your activities today?
   ___ very well
   ___ well
   ___ moderately
   ___ badly
   ___ very badly
6. How satisfied have you been over the last 24 hr?
   ___ very satisfied
   ___ reasonably satisfied
   ___ fairly satisfied
   ___ dissatisfied
   ___ very dissatisfied

Analgesic Conversion Scores

		Score for unit dosage
Non-narcotic		
Acetoaminophen		≤500 mg = 1
Aspirin		≤500 mg = 1
Ibuprofen		≤200 mg = 1
Diflunisal		250 = 1
Etodolac		≤300 mg = 1
Toradol		1110 mg = 2
Narcotic		
Darvocet-N		100 mg = 4
Darvon		65 mg = 4
Fentanyl-Transdermal		100 μg/hr = 6
Hydrocodone		5 mg = 2
Hydromorphone	-Oral	2 mg = 6
	-Injection	1 mg = 16
Levorphanol	-Oral	2 mg = 12
	-Injection	1 mg = 12
Lorcet		10 mg = 4
Meperdine	-Oral	50 mg = 4
	-Injection	50 mg = 16
Morphine sulphate	-Oral	10 mg = 4
	-Injection	10 mg = 24
Percet		1 tab = 4
Percodan		1 tab = 4
Roxicet		1 tab = 4
Tylenol #3		1 tab = 4
Tylox		1 tab = 4
Vicodin		5 mg = 2

The medication index can be calculated by multiplying the number of unit dosages per 24 hr by the conversion factor from this table and by summing all the scores.

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