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The Relationship between the Visual Analog Pain Intensity and Pain Relief Scale Changes during Analgesic Drug Studies in Chronic Pain Patients

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Background: **Most analgesic drug studies in humans quantify drug action based on verbal reports of pain intensity and pain relief. Although measures of pain intensity and pain relief show a good overall correlation, it is not known if they relate to each other consistently over time. Such consistency is necessary if both measures are used to depict analgesic drug action *versus* time. This study examined in chronic pain patients if the relationship between visual analog pain intensity and pain relief scores was consistent during two analgesic drug studies.**

Methods: **Data from two independently performed analgesic drug studies were analyzed using linear regression. Data were split into pain intensity and pain relief scores recorded before and after patients' experience of maximum analgesia (>90% of maximum pain relief). The slopes of the linear regression line depicting pain intensity *versus* pain relief scores before and after maximum analgesia were statistically compared.**

Results: **The slope of the linear regression line before and after maximum analgesia was significantly different in both drug studies (nonoverlapping 95% confidence intervals), −2.16 ± 0.57 *versus* −1.05 ± 0.10 and −1.47 ± 0.26 *versus* −1.09 ± 0.07, respectively. These results are compatible with the observation that patients indicating the same pain intensity before and after maximum analgesia reported a different magnitude of pain relief.**

Conclusions: **The relationship between visual analog pain intensity and pain relief scores changed systematically during both analgesic drug studies. The authors hypothesize that patients' interpretation of the pain relief scale had changed during the studies and therefore suggest using the pain intensity scale to quantify analgesic drug action over time. (Key words: Analgesics; clinical trials; human; pain measurement.)**

MOST analgesic drug studies performed in humans use verbal reports of pain to quantify drug effect.[1] Most commonly pain intensity and pain relief are measured.[2] Pain intensity reflects the magnitude of pain, whereas pain relief indicates by how much a starting pain has decreased. Most commonly, pain intensity and pain relief are measured on a categorical or on a visual analog scale.[2] Compared with categorical scales, the visual analog scale may offer the advantage of providing analgesic data that are relatively bias-free.[3,4] Using the visual analog scale rather than a categorical scale may also provide greater certainty of measuring analgesic drug action with adequate sensitivity.[5-7]

Analysis of several analgesic drug studies have revealed a good correlation between measures of pain intensity and pain relief, and this has been interpreted to reflect consistency across these measures.[5] However, this analysis did not consider time as a variable. In other words, the good correlation identified between pain intensity and pain relief measures did not determine whether these measures were related to each other consistently over time. Consistency over time is important if both measures are used in pharmacokinetic and pharmacodynamic studies determining the duration of action, the time to peak effect, or the equilibration time between plasma and effect site for an analgesic agent.[8,9] If serial measures of pain intensity and pain relief do not relate to each other consistently, different pharmacodynamic parameters could result depending on which measure is used.

Doubts about a consistent relationship between serial measures of pain intensity and pain relief occur when considering the controversy as to which measure should be used to quantify analgesic drug action. One would expect that the two measures are interchangeable if

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both are useful in terms of quantifying analgesic drug action. Nevertheless, some investigators argue that pain relief should be preferred in assessing analgesic efficacy directly in the context of a given experiment.[6,10] Others have expressed concerns about measuring pain relief because they doubt that subjects can recall the pain at the beginning of an experiment reliably enough to infer pain relief consistently.[11,12]

Using a chronic pain population the goal of the present study was to analyze whether measures of pain intensity and pain relief relate to each other consistently over time using a visual analog scale.

Methods

The analgesic data of two independent drug studies were analyzed. One study was conducted at Stanford University (Stanford, California) and explored the relationship between the plasma concentration and the analgesic efficacy of methadone in opioid-naive, chronic pain patients. The other study was conducted at the Memorial Sloan-Kettering Cancer Center (New York, New York) and explored the relationship between the plasma concentration and the analgesic efficacy of hydromorphone in cancer pain patients treated chronically with opioids. To quantify the analgesic efficacy of either drug, patients had to indicate repetitively their pain intensity *and* their pain relief on separate visual analog scales. Our analysis is confined to the data collected on the visual analog scale. The remaining data of either study have not yet been published.

Methadone Study

This study was approved by the Institutional Review Board of Stanford University. Data from eight patients (four women and four men; mean age, 55 ± 16 yr) participating in the study after having given written informed consent were analyzed. All patients suffered from chronic (> 6 months) nonmalignant pain, were opiate-naive, and abstained from any analgesic drug 24 h before the study. On the day of the study patients were carefully instructed on the use of the visual analog scale. Two different 100-mm visual analog scales were used to assess patients' pain intensity and pain relief. The phrases "no pain" and "worst pain imaginable" anchored the two ends of the visual analog pain intensity scale. The phrases "no pain relief" and "maximum pain relief" anchored the two ends of the visual analog pain relief scale. Patients indicated the magnitude of their pain intensity and pain relief by setting pencil marks relative to the verbal anchors of the respective visual analog scales.

Before drug administration, patients' baseline pain intensities were recorded. At this time the patients' pain relief was zero by default because no drug had yet been given. A computer-controlled infusion pump then targeted in a staircase pattern geometrically increasing methadone plasma concentrations.[13] Each target plasma concentration was held constant for 30 min before proceeding to the next higher plasma concentration (lowest and highest plasma concentrations explored were 20 and 640 ng/ml, respectively). The methadone infusion was stopped if the patient indicated satisfactory analgesia or unacceptable side effects. Patients' pain intensity and pain relief were recorded at 10, 20, and 30 min of holding each target methadone plasma concentration constant and at 15, 30, 60, 120, 180, 300, 420, 660, 900, and 1,200 min after stopping the methadone infusion. Vital signs (blood pressure, heart rate, respiratory rate, blood hemoglobin oxygen saturation) and adverse events were recorded.

Hydromorphone Study

This study was approved by the Institutional Review Board of the Memorial Sloan-Kettering Cancer Center. Data from seven patients (six women and one man; mean age, 53 ± 14 yr) participating in the study after having given written informed consent were analyzed. All patients suffered from chronic cancer pain, were being treated with opioids, but had abstained from analgesic drugs for at least 5 h before the study. On the day of the study patients were carefully instructed on the use of the visual analog scale as outlined for the methadone study. The phrases "least possible pain" and "worst possible pain" anchored the two ends of the visual analog pain intensity scale. The phrases "no pain relief" and "complete pain relief" anchored the two ends of the visual analog pain relief scale.

Before drug administration patients' baseline pain intensity and pain relief were recorded as outlined for the methadone study. An intravenous hydromorphone infusion was then started at a constant rate of 3 mg/h. The infusion rate was decreased by 0.3 mg/h every time two consecutively recorded visual analog pain relief scores exceeded 75 (a score of 100 indicates complete pain relief). The infusion stopped after identifying the minimal infusion rate providing sustained pain relief (visual analog score exceeding 75 on four subsequent readings). The infusion rate never had to be increased during this

procedure. Patients' pain intensity and pain relief were recorded in 15-min intervals during the hydromorphone infusion, and at 2, 5, 10, 15, 30, 60, 90, 120, and 180 min after stopping the infusion. Vital signs and adverse events were recorded.

Statistical Analysis

The same analysis was performed separately for the methadone and the hydromorphone study. During both studies patients repetitively rated their pain intensity and pain relief on a visual analog scale. Thus, each patient was the source of multiple data pairs, each consisting of the simultaneously recorded pain intensity and pain relief score. Data pairs of all patients participating in the same study were analyzed individually as well as with a pooled approach.

Linear regression analysis was used to test for a relationship between the visual analog pain intensity and pain relief scores. To test for consistency over time of such a relationship the visual analog scores recorded before and after patients' experience of maximum analgesia were analyzed separately. If the relationship between the visual analog pain intensity and pain relief scores was consistent over time, the linear regression equations describing the data before and after maximum analgesia have to be similar. Maximum analgesia was defined to be present if a patient reported a pain relief that was within 10% of the highest score.

Traditional linear regression analysis assumes that the variable represented on the y axis depends on the variable on the x axis, but that the variable on the x axis is independent from the variable represented on the y axis. As a consequence linear regression analysis typically minimizes the squared error parallel to the y axis, *i.e.*, attributes all variance to the y variable. However, pain intensity and pain relief scores are interdependent, and we had to assume equal variance for both measures. As a consequence we used a linear regression model minimizing the squared error perpendicular to the regression line and not that parallel to the y axis. The 95% confidence intervals for the slope and intercept were calculated accordingly.[14] Nonoverlapping 95% confidence intervals of the slope or the intercept before and after maximum analgesia of each study were considered to reflect statistical significance.

If linear regression analysis revealed a significantly different slope or intercept between the regression lines before and after maximum analgesia a bootstrap test was performed in these data.[15] The bootstrap test is a computer-based, iterative method to measure the accuracy of a statistical estimate (*e.g.*, the slope of a linear regression line). Accuracy is measured by assessing the variability of the statistical estimate if determined in samples randomly and repetitively drawn, with replacement, from the original data points (200 random samples for this analysis). The bootstrap test does not assume that the pairs of measurement for any one patient are independent of each other. A bootstrap test confirming that linear regression parameters were significantly different excludes the possibility that such a finding was caused simply by the interdependence of data pairs repetitively collected in each patient.

A paired t test was used to compare slopes of the regression line before and after maximum analgesia. One-way repeated-measures analysis of variance and the Student-Newman-Keuls *post hoc* test were used to analyze serial measurements of the sum of pain intensity and pain relief. A P value < 0.05 was considered to be statistically significant. Data are presented as the mean and SEM unless otherwise stated.

Results

Methadone Study

Figure 1 (upper graph) shows the mean visual analog pain intensity (squares) and pain relief scores (triangles) during and after the methadone infusion. The mean pain intensity before drug administration was 59 ± 4 and decreased to 13 ± 5 at the end of the methadone infusion. Patients' pain relief before drug administration was zero and increased on average to 85 ± 6 at the end of the infusion. Note that similar pain intensity scores at the beginning and at the end of the study were associated with different pain relief scores.

In figure 2, pain intensity scores and corresponding pain relief scores of all patients are plotted against each other for data recorded before (upper left graph) and after maximum analgesia (upper right graph). The slope of the linear regression line was significantly different before and after maximum analgesia as evidenced by nonoverlapping 95% confidence intervals, −2.16 (±0.57; 95% confidence interval) and −1.05 (±0.10). The bootstrap test confirmed that the before and after slopes were genuinely different ($P < 0.01$). The y intercept of the regression line was 124.1 (±26.9; 95% confidence interval) and 100.1 (±1.6) before and after maximum analgesia, respectively. Individual slopes uniformly were steeper before than after maximum analgesia ($P < 0.01$; see right upper

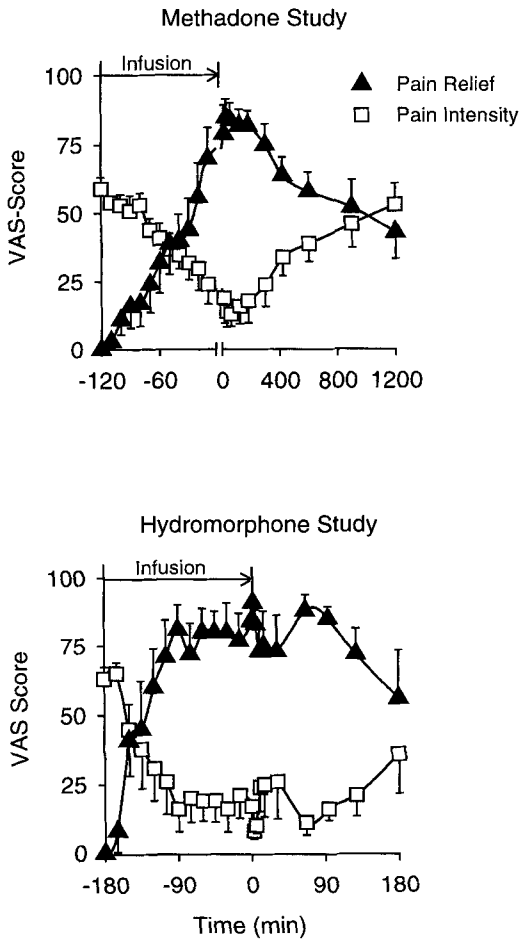

Fig. 1. Two graphs depicting the mean (± SEM) visual analog pain intensity and pain relief score during and after the intravenous infusion of methadone in eight patients with chronic nonmalignant pain (*top*) and of hydromorphone in seven patients with cancer pain (*bottom*). Patients indicating the same pain intensity before and after their experience of maximum analgesia reported a different magnitude of pain relief.

inset graph in fig. 2). The median correlation coefficients of −0.9 (−0.57 to −0.98) and −0.96 (−0.84 to −0.99) before and after maximum analgesia, respectively, indicate that the pain intensity and pain relief scores were strongly associated.

Hydromorphone Study

Figure 1 (bottom graph) shows the mean visual analog pain intensity (squares) and pain relief scores (triangles) during and after the hydromorphone infusion. The mean pain intensity before drug administration was 63 ± 4 and decreased to 8 ± 3 at the end of the hydromorphone infusion. Patients' pain relief before drug administration was zero and increased on average to 91 ± 2 at the end of the infusion. Note that similar pain intensity scores recorded early during the hydromorphone infusion and at the end of the study were associated with different pain relief scores.

In figure 2, pain intensity scores and corresponding pain relief scores of all patients are plotted against each other for data recorded before (lower left graph) and after maximum analgesia (lower right graph). The slope of the linear regression line was significantly different before and after maximum analgesia as evidenced by nonoverlapping 95% confidence intervals, −1.47 (±0.26; 95% confidence interval) and −1.09 (±0.07). The bootstrap test confirmed that the before and after slopes were genuinely different ($P < 0.01$). The y intercept of the regression line was 105.7 (±13.7; 95% confidence interval) and 99.5 (±1.7) before and after maximum analgesia, respectively. With one exception individual slopes uniformly were steeper before than after maximum analgesia ($P < 0.01$; see right lower insert graph, fig. 2). The median correlation coefficients of −0.94 (−0.78 to −0.99) and −0.91 (−0.68 to −0.99) before and after maximum analgesia, respectively, indicate that the pain intensity and pain relief scores were strongly associated.

Relationship between Pain Intensity and Pain Relief Scores

In the methadone (fig. 2, top graphs) and the hydromorphone (fig. 2, bottom graphs) studies the relationship between the visual analog pain intensity and pain relief scores was different before and after maximum analgesia. Comparing the methadone with the hydromorphone study by visual inspection of figure 2, the relationship between the pain intensity and pain relief scores recorded before maximum analgesia seems to be different (top and bottom graphs on the left). However, the relationship between the pain intensity and pain relief scores after maximum analgesia looks almost identical (top and bottom graphs on the right), which may suggest that the relationship between the pain intensity and pain relief scores was of a more universal character after maximum analgesia but was variable between the two studies for measurements obtained before maximum analgesia.

After maximum analgesia the linear regression analysis of pain intensity *versus* pain relief scores revealed a regression line with a slope of about −1 and a y intercept of about 100 (fig. 2, top and bottom graphs on the right). This suggests that the visual analog pain intensity

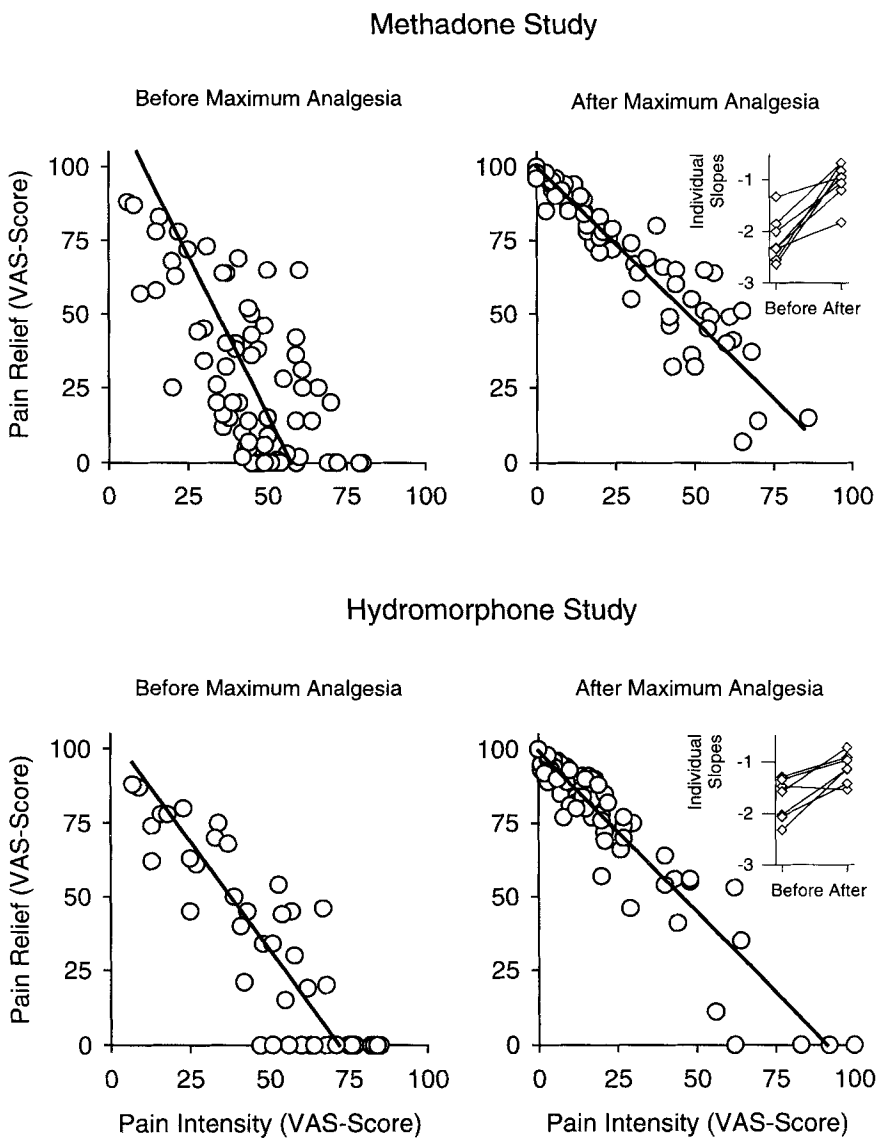

Fig. 2. (*Top*) Two graphs depicting pooled visual analog pain intensity *versus* pain relief scores recorded before (*left*) and after (*right*) maximum analgesia in the methadone study. The slope of the linear regression line characterizing pooled data before (−2.16 ± 0.57; 95% confidence interval) and after (−1.05 ± 0.1) maximum analgesia changed significantly. Individual slopes uniformly were significantly steeper before than after maximum analgesia ($P < 0.01$; *inset*). The relationship between pain intensity and pain relief scores before and after maximum analgesia had changed systematically. (*Bottom*) Two graphs depicting pooled visual analog pain intensity *versus* pain relief scores recorded before (*left*) and after (*right*) maximum analgesia in the hydromorphone study. The slope of the linear regression line characterizing pooled data before (−1.47 ± 0.26; 95% confidence interval) and after (−1.09 ± 0.07) maximum analgesia changed significantly. Individual slopes uniformly were steeper before than after maximum analgesia ($P < 0.01$; *inset*) with one exception. The relationship between pain intensity and pain relief scores before and after maximum analgesia had changed systematically.

and pain relief scale had become used as reversed scales that share the same interval size and scale range. A numerical decrease in pain intensity was now accompanied by a similar numerical increase in pain relief, and a 0 on one scale had become the same as 100 (maximum scale value) on the other scale. Figure 3 explores this relationship graphically over time for the methadone (top graph) and the hydromorphone (bottom graph) studies. The mean sum of corresponding pain intensity and pain relief scores was plotted *versus* time. This sum should be about 100 (maximum value on either scale) if the pain intensity and pain relief scales were used as reversed scales sharing the same interval size and scale range. Before maximum analgesia the sum of the pain intensity and pain relief scores initially was equal to the mean pain intensity score (pain relief at that time was 0 by default) and then gradually increased to about 100 as maximum analgesia was achieved. However, after maximum analgesia the sum of the pain intensity and pain relief scores remained close to 100 despite decreasing pain relief and increasing pain intensity (fig. 3, dotted lines). The pain intensity and pain relief scales were used as reversed scales sharing the same interval size and scale range after, but not before maximum analgesia. Visually this is reflected by the near perfect mirror picture of the dotted lines depicting the mean pain intensity and pain

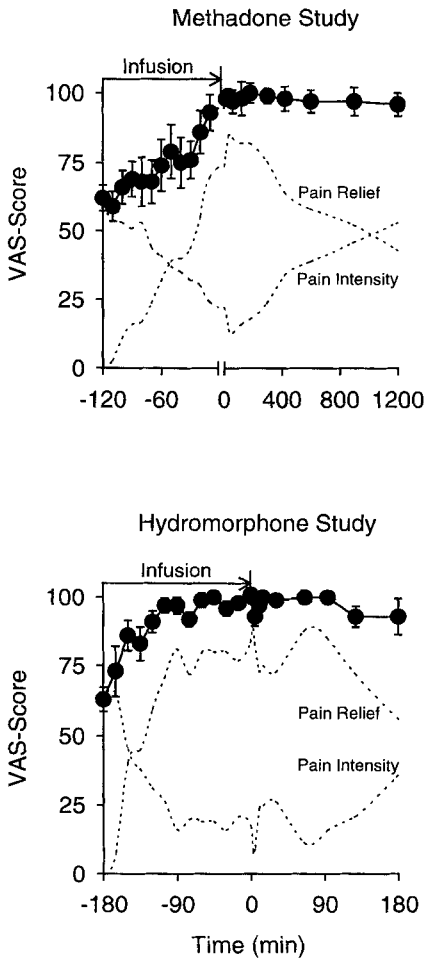

Fig. 3. Two graphs depicting the mean (± SEM) sum of corresponding visual analog pain intensity and pain relief scores (*filled circles*) during and after the intravenous infusion of methadone (*top*) and of hydromorphone (*bottom*). The sum before maximum analgesia started at the initial value of the pain intensity score and gradually increased to about 100, *i.e.*, the maximum value on either visual analog scale. However, the sum remained at about 100 after maximum analgesia despite decreasing pain relief and increasing pain intensity scores (*dotted lines*). After but not before maximum analgesia, the visual analog pain intensity and pain relief scales were used as reversed scales sharing the same interval size and scale range. This is reflected by the dotted lines depicting the mean pain intensity and pain relief scores *versus* time. The two lines reveal a near perfect mirror picture after but not before maximum analgesia.

relief scores *versus* time after but not before maximum analgesia (fig. 3).

All pair-wise comparisons of the sum of the pain intensity and pain relief scores showed significant differences in the methadone study (any sum for data collected between −120 and −40 min *versus* data collected between −20 and 1,200 min) and the hydromorphone study (any sum for data collected between −180 and −150 min *versus* data collected between −120 and 180 min).

Discussion

The present analysis tested whether the relationship between the visual analog pain intensity and pain relief scales was consistent over time. This is relevant if serial measurements obtained on either scale are used to determine the pharmacodynamics of an analgesic drug. Measures of pain intensity and pain relief only depict a similar time course of analgesic drug action if used consistently over time. Analysis of two independent analgesic drug studies during which pain intensity and pain relief were assessed repetitively on a visual analog scale revealed the same result. The relationship between the visual analog pain intensity and pain relief scales changed during the time course of both drug studies. Patients reporting the same pain intensity before and after experiencing maximum analgesia reported a different amount of pain relief. A troublesome consequence is the fact that the duration of action of both opioids appears to be greater if pain relief rather than pain intensity scores are considered.

The inconsistent relationship between the visual analog pain intensity and pain relief scales raises the question as to which of the two scales is more likely to reveal a true measurement of analgesic drug action. To address this question some theoretical considerations are necessary. Pain intensity and pain relief scales yield some important differences. Using the pain intensity scale, patients estimate their actual magnitude of pain in relation to the worst pain (or alternative wording) they can imagine. Pain intensity is judged in the context of an overall pain experience. Therefore, pain intensity scores do vary between subjects at the beginning of an experiment. To avoid the "problem" of various pain intensity scores at the beginning of an experiment, the pain relief scale has been proposed. Pain relief at the beginning of an experiment is zero by definition. Consequently and contrary to the pain intensity scale, the response range is the same for all subjects. In theory, the pain relief scale provides standardized conditions and assesses analgesic drug action strictly within the context of an experiment. Therefore, the pain relief scale has been advocated as the preferred scale to assess analgesic drug action, particularly in highly quantitative studies such as pharmacokinetic and pharmacodynamic drug studies.[6,10]

Another theoretical advantage pointed out for the pain relief scale is the notion that analgesia could be assessed directly.[6,10] However, this seems questionable in considering how subjects estimate their pain relief. In contrast to pain, which is directly perceived, we do not perceive analgesia but rather infer it by comparing an existing pain to a reference pain usually present at the beginning of an experiment. If we accept that pain relief is a rational construct, it becomes evident that the use of the pain relief scale is dependent on estimating the magnitude of pain. Because of this dependency it is likely that inconsistent ratings of pain intensity would have been carried over to ratings of the pain relief. If so, an inconsistent use of the pain intensity scale would hardly have changed the relationship between pain intensity and pain relief scale. However, the use of a pain intensity scale is *not* dependent on the assessment of pain relief. Therefore, inconsistent ratings of pain relief are not carried over to ratings of pain intensity. Consequently, the changing relationship between the visual analog pain intensity and pain relief scales can readily be explained by an inconsistent use of the pain relief scale.

If we postulate that the visual analog pain relief scale was used inconsistently, how can we explain this? The initial relationship between the pain intensity and pain relief scale was determined by the pain intensity present at the beginning of an experiment and the pain relief score being set to zero at that time. In essence, "no pain relief" was equivalent to the magnitude of the particular pain present at the beginning of an experiment. Consequently, different pain intensity scores at the beginning of the methadone and the hydromorphone study resulted in a different relationship between the pain intensity and pain relief scale. However, after maximum analgesia the same and presumably more universal relationship was found in both drug studies. The pain relief scale now resembled a reversed pain intensity scale; *i.e.*, the verbal anchor "no pain relief" matched the anchor "worst pain imaginable" on the pain intensity scale. Patients appeared to have switched from the *pain present at the beginning of the experiment* to the *worst pain imaginable* when inferring the magnitude of pain relief. Such a switch can explain the kind of relationship between the pain intensity and pain relief scale found at the beginning and during the time course of both drug studies.

A remaining question is why patients might have switched their reference pain to infer pain relief. In this context it is interesting that patients on average switched at the time they experienced maximum analgesia. This suggests that the scaling task during the time of increasing analgesia, *i.e.*, moving on the pain intensity scale toward "no pain" (or alternative wording) and on the pain relief scale toward "complete pain relief," was performed consistently by inferring pain relief from the pain present at the beginning of the experiment. However, after maximum analgesia, moving on the pain intensity scale toward "worst pain imaginable" and on the pain relief scale toward "no pain relief" made patients reinterpret the meaning of "no pain relief." Patients challenged on their interpretation of "no pain relief" seem to have switched from a somewhat arbitrary reference pain defined by experimental conditions to a more inherent reference pain, *i.e.*, their "worst pain imaginable." In fact, previous concerns about the pain relief scale were mainly directed toward subjects' ability to reliably recall the magnitude of pain they experienced at the beginning of an experiment.[9,11,12]

The changing relationship between the visual analog pain intensity and pain relief scale could also result from a learning effect. During the drug studies patients might have become aware of the reversed character of the two scales. Consequently, they could have started to set a mark as far from the left end of one visual analog scale as they did from the right end of the other scale. Doing so, patients would have identified a way to ensure they were using the two scales consistently. However, such "consistent" scaling would no longer include a "true" evaluation of the pain relief. Mechanically, patients would have set a mark on the pain relief scale to reflect in reversed fashion the setting on the pain intensity scale. However, inspection of the linear regression plots depicting corresponding pain intensity and pain relief scores after maximum analgesia reveals a weaker association between the two measures as analgesia decreases. If a learning effect was the main reason for the changing relationship between the pain intensity and pain relief scale, the strength of association would be expected to remain approximately constant.

Our analysis might not have revealed a changing relationship between the pain intensity and pain relief scale if normalized pain intensity scores had been used. Normalization of pain intensity scores has been suggested to eliminate intersubject variability of the starting pain intensity and of the response range on the pain intensity scale.[16] However, after performing such an analysis the results were consistent with presented findings for nonnormalized data (analysis not shown).

Our analysis implies limitations for the use of the visual analog pain relief scale to characterize the time course of

analgesic drug action. Used in combination with a visual analog pain intensity scale, the resulting pain relief scores seem to have changed their quantitative meaning: The same pain relief score before and after maximum analgesia was related to a different pain intensity. In theory, the pain relief scale allows assessing analgesic drug action under standardized conditions; *i.e.*, every subject starts at zero and responds on the same range of the scale. However, if a visual analog pain intensity score (0-100) decreases from 75 to 0 or from 25 to 0 in response to a drug this may well indicate a different efficacy. Nevertheless, in both circumstances the same score of 100 would result if using the pain relief scale. This suggests that standardizing the scaling method for different baseline conditions distorts results rather than increasing their accuracy.

There are some limitations to our study and data interpretation. The number of subjects studied was small, and all patients suffered either from chronic nonmalignant or cancer pain. In addition, all patients suffered from moderate or severe but not maximal pain at the beginning of the experiments and experienced substantial analgesia. Within these constraints our analysis points to the possibility that the use of the visual analog pain relief scale may generally be problematic in terms of quantifying the time course of analgesic drug action. However, studies including a larger number of patients suffering from various pain conditions are needed to allow such a broad conclusion.

In summary, our analysis suggests that the visual analog pain relief scale might have some shortcomings and does not offer proven advantage compared with the visual analog pain intensity scale to quantify analgesic drug action over time. We therefore suggest that pain intensity be assessed if using a visual analog scale to characterize the time course of analgesic drug action.

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References

1. Craig KD: Clinical pain measurement from the perspective of the human laboratory, Issues in Pain Measurement. Edited by Chapman CR, Loeser JD. New York, Raven Press, 1989, pp 433-41

2. Sriwatanakul K, Lasagna L, Cox C: Evaluation of current clinical trial methodology in analgesimetry based on experts' opinions and analysis of several analgesic studies. Clin Pharmacol Ther 1983; 34: 277-83

3. Price DD: Psychological and Neural Mechanisms of Pain. New York, Raven Press, 1988, pp 18-49

4. Price DD, Bush FM, Long S, Harkins SW: A comparison of pain measurement characteristics of mechanical visual analogue and simple numerical rating scales. Pain 1994; 56:217-26

5. Littman GS, Walker BR, Schneider BE: Reassessment of verbal and visual analog ratings in analgesic studies. Clin Pharmacol Ther 1985; 38:16-23

6. Wallenstain SL: The VAS relief scale and other analgesic measures: Carryover effect in parallel and crossover studies, The Design of Analgesic Clinical Trials. Edited by Max MB, Portenoy RK, Laska EM. New York, Raven Press, 1991, pp 97-104

7. Jensen MP, Turner JA, Romano JM: What is the maximum number of levels needed in pain intensity measurement? Pain 1994; 58:387-92

8. Inturrisi CE: Pharmacokinetic considerations in analgesic study design, The Design of Analgesic Clinical Trials. Edited by Max MB, Portenoy RK, Laska EM. New York, Raven Press, 1991, pp 533-58

9. Max MB, Laska EM: Single-dose analgesic comparisons, The Design of Analgesic Trials. Edited by Max MB, Portenoy RK, Laska EM. New York, Raven Press, 1991, pp 55-96

10. Huskisson EC: Measurement of pain. Lancet 1974; 2:1127-31

11. Dundee JW, Loan WB: Assessment of analgesic drugs. Pharmacol Ther 1983; 12(Suppl):79-88

12. Mackie A: Further thoughts on analgesia and pain relief, Issues in Pain Measurement. Edited by Chapman CR, Loeser JD. New York, Raven Press, 1989, pp 183-5

13. Shafer SL, Siegel LC, Cooke JE, Scott JC: Testing computer-controlled infusion pumps by simulation. ANESTHESIOLOGY 1988; 68: 261-6

14. Fuller WA: Measurement Error Models. New York, Jon Wiley & Sons, 1987, pp 31-6

15. Efron B, Tibshirani RJ: An Introduction to the Bootstrap. New York, Chapman & Hall, 1993, pp 168-219

16. Laska EM, Sunshine A, Zighelboim I, Roure C, Marrero I, Wanderling J, Olson N: Effect of caffeine on acetaminophen analgesia. Clin Pharmacol Ther 1983; 33:498-509