

Pharmacodynamics of Orally Administered Sustained-release Hydromorphone in Humans

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Background: **The disposition kinetics of hydromorphone generally necessitates oral administration every 4 h of the conventional immediate-release tablet to provide sustained pain relief. This trial examined time course and magnitude of analgesia to experimental pain after administration of sustained-release hydromorphone as compared with that after immediate-release hydromorphone or placebo.**

Methods: **Using a 4 × 4 Latin square double-blind design, 12 subjects were randomized to receive a single dose of 8, 16, and 32 mg sustained-release hydromorphone and placebo. The same subjects had received 8 mg immediate-release hydromorphone before this study. Using an electrical experimental pain paradigm, analgesic effects were assessed for up to 30 h after administration, and venous hydromorphone plasma concentrations were measured at corresponding times.**

Results: **The hydromorphone plasma concentration peaked significantly later (12.0 h [12.0–18.0] *vs.* 0.8 h [0.8–1.0]; median and interquartile range) but was maintained significantly longer at greater than 50% of peak concentration (22.7 ± 8.2 h *vs.* 1.1 ± 0.7 h; mean ± SD) after sustained-release than after immediate-release hydromorphone. Similarly, sustained-release hydromorphone produced analgesic effects that peaked significantly later (9.0 h [9.0–12.0] *vs.* 1.5 h [1.0–2.0]) but were maintained significantly longer at greater than 50% of peak analgesic effect (13.3 ± 6.3 h *vs.* 3.6 ± 1.7 h). A statistically significant linear relation between the hydromorphone plasma concentration and the analgesic effect on painful stimuli existed.**

Conclusion: **A single oral dose of a new sustained-release formulation of hydromorphone provided analgesia to experimental pain beyond 24 h of its administration.**

HYDROMORPHONE is a semisynthetic opioid analgesic derived from morphine. The equianalgesic dose ratio of morphine and hydromorphone ranges from 3:1 to 9:1 depending on the mode of administration.[1,2] Hydromorphone is an effective alternative to morphine in the treatment of opioid-responsive moderate to severe pain.[1,3] The availability of different opioids to manage pain is beneficial, because opioid rotation can reduce unacceptable side effects while preserving or improving pain relief.[2,4]

The disposition kinetics of hydromorphone generally necessitates administration every 4 h of the conventional immediate-release tablet to provide sustained pain relief.[5,6] However, multiple daily dosing is inconvenient and may result in decreased compliance, more pronounced pain, and a reduced quality of life.[7–9] Therefore, a new sustained-release formulation of hydromorphone recently was developed for the treatment of chronic pain with a single daily dose.

Oral osmotic pump systems for the sustained release of orally administered drugs have become available during the last two decades.[10–12] Figure 1 illustrates the principle configuration and mechanism of action of the OROS osmotic dosage form (ALZA Corporation, Palo Alto, CA). OROS usually is designed to release drug over a period of 24 h. The efficacy of various drugs previously requiring multiple daily dosing was preserved or increased with a single daily dose of a corresponding oral osmotic pump system.[10–12]

The primary goal of this study was to examine the time course and magnitude of analgesia to experimental pain after administration of a new sustained-release formulation of hydromorphone using OROS (hydromorphone OROS) and to compare it with that after immediate-release hydromorphone or placebo administration.

Methods

This report summarizes analgesic data obtained with an experimental pain model in human volunteers after oral administration of hydromorphone. Data were collected during five different study sessions at least 5 days apart, *i.e.*, after administration of a single dose of immediate-release hydromorphone (session 1) followed in randomized sequence by three different doses of hydromorphone OROS and placebo, respectively (sessions 2–5). Hydromorphone plasma concentrations are reported only in the context of the pharmacodynamic analysis. A detailed pharmacokinetic analysis including data from intravenous administration of hydromorphone will be the subject of a subsequent manuscript.

Clinical Protocol

The study was approved by the Institutional Review Board of Stanford University. Twelve healthy subjects (six men and six women) with a mean age of 27 yr (range, 21–34 yr) and a mean body weight of 76 kg (range, 60–88 kg) for men and 64 kg (range, 59–70 kg) for women gave written informed consent. All subjects

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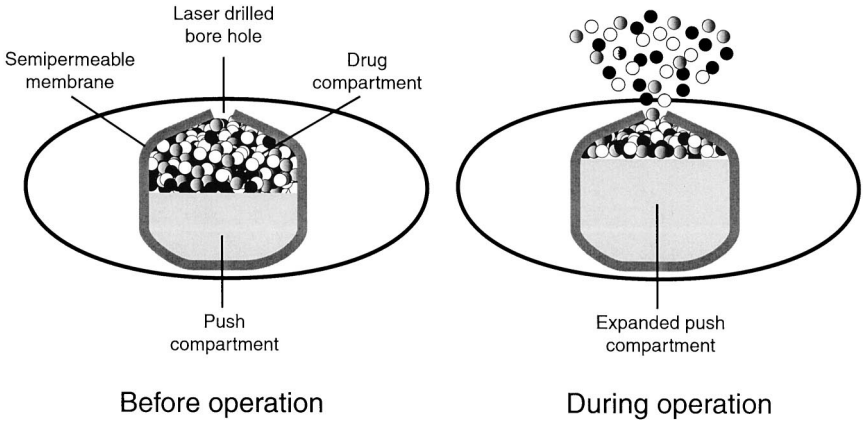

Fig. 1. The oral osmotic system before and during operation. The oral osmotic system consists of a semipermeable membrane containing a drug and an osmotic active push compartment. In the gastrointestinal tract, water enters through the semipermeable membrane and expands the push compartment, which in turn forces drug at an approximately constant rate through a laser drilled bore hole.

had a normal physical examination, electrocardiogram, routine laboratory profile, negative drug screen, and pregnancy test (women) before enrollment. No over-the-counter medication was allowed 48 h before each study day. Intake of prescription drugs or chronic medication was prohibited during and 14 days before the study except for the use of oral contraceptives. Before each study session subjects fasted overnight. On arrival at the study center, a catheter was inserted in one arm vein, and recording of vital signs was started (electrocardiogram, noninvasive arterial blood pressure, hemoglobin oxygen saturation, and respiratory rate).

Study Session 1: Immediate-release Hydromorphone. Subjects received a single dose of 8 mg, open-label, immediate-release hydromorphone with 240 ml of water (Dilaudid, Knoll Pharmaceutical Company, Mount Olive, NJ). No other water intake was allowed from 1 h before dosing through 1 h after dosing. A meal was taken 3 h after drug intake.

Venous blood samples were obtained and vital signs recorded before and 15, 30, 45, 60, 90, 120, 180, 240, 300, and 360 min after drug intake. Experimental pain testing was performed in duplicate before and 30, 60, 120, 240, and 360 min after drug intake. Occurrence and severity of adverse events were recorded (mild = no limitation of usual activity, slight discomfort; moderate = some limitation of usual activity or significant discomfort; severe = inability to conduct usual activity or intolerable discomfort).

Study Sessions 2–5: Sustained-release Hydromorphone. Using a double-blind design, subjects were randomly allocated to receive a single dose of 8, 16, and 32 mg hydromorphone OROS (Hydromorphone SR, Knoll Pharmaceutical Company), and placebo. All subjects received all treatments but on different occasions. Dose selection was based on developing a single daily dose formulation matching the doses of the immediate-release formulation (2, 4, and 8 mg) administered every 4–6 h.

At the beginning of each study session, subjects swallowed three tablets, all containing no drug or two containing no drug and one containing 8, 16, or 32 mg hydromorphone OROS. Water intake was restricted as outlined for study session 1. Meals were taken at 3, 9, 24, and 28 h after drug intake. Venous blood samples were obtained before and 1, 2, 3, 6, 9, 12, 15, 18, 21, 24, and 30 h after drug intake. Experimental pain testing was performed in duplicate before and 3, 6, 9, 12, and 30 h after drug intake. Vital signs were recorded hourly. Adverse events were recorded as outline for study session 1.

Assay

Seven milliliters of venous blood was drawn into heparinized glass tubes, centrifuged, frozen within 1 h, and stored at −20°C. Plasma and the internal standard trideuterated hydromorphone were injected onto a SCIEX API III-Plus LC-MS-MS (PE Biosystems, Foster City, CA). The assay was linear over a range of 0.05–10.0 ng/ml. The between-day coefficient of variation ranged from 1.4 % to 11.2%. The lower limit of quantification was 0.05 ng/ml.

Experimental Pain Testing

Instrument. A constant current device (Neurometer, Neurotron Inc., Baltimore, MD) with a maximum output of 20 mA and delivering 5 Hz sine wave pulses of 3-s duration was used to administer nociceptive electrical stimuli. An aluminum–gold ring electrode was attached to the surface of the skin at the right lateral upper arm as previously described.[13]

Experimental Pain Test Algorithm. Before study participation, subjects were familiarized with the test procedure. During study sessions, subjects completed experimental pain test cycles of approximately 10-min duration at specified times. Standardized sentences emphasizing the test procedure were read to subjects before starting a test cycle. A test cycle consisted of two distinct series of electrical stimuli.

A first series was administered using an ascending staircase design. The intensity of the first stimulus varied randomly between 1.2 and 2.4 mA. The intensity of subsequent stimuli increased by 30% steps until a subject reported pain, and then by 15% steps until a subject

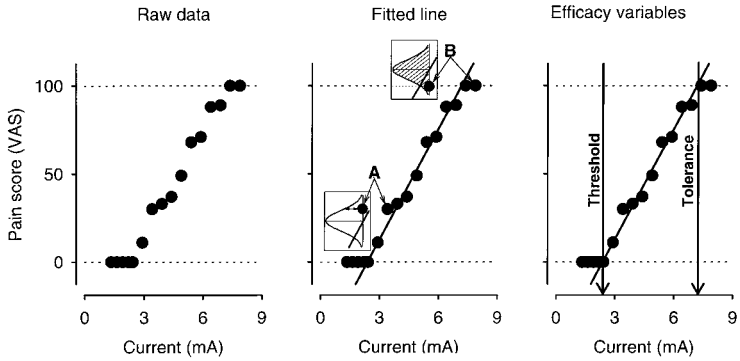

Fig. 2. The derivation of the analgesic efficacy variables is shown. (*Left*) An example of a scatter plot depicting nociceptive intensity (mA) *versus* pain intensity (visual analog scale [VAS]) as obtained in a volunteer during one pain test cycle. (*Middle*) The fitted line describing the raw data. (*Inset*, *A*) The error model used to fit a line to uncensored VAS scores between 1 and 99. The bell shaped curve reflects the error distribution. The likelihood of an error was maximized, graphically corresponding to maximizing the length of displayed arrow. (*Inset*, *B*) The error model used to fit a line to censored VAS scores of 0 and 100. The probability of the error was maximized, graphically corresponding to maximizing the shaded area (y-value > 100) under the bell-shaped curve. (*Right*) The derivation of the analgesic efficacy variables, *i.e.*, the pain threshold and the pain tolerance from the model parameters underlying the fitted line.

indicated that he or she was unable to tolerate the next stronger stimulus. The interstimulus interval was 15 s. The first series allowed estimating the pain threshold (average of highest electrical current not evoking pain and lowest electrical current evoking pain) and the pain tolerance (current evoking most painful perception tolerated).

The second series was composed of 16 stimuli evenly spaced starting 30% less than the estimated pain threshold and ending at the estimated pain tolerance. Each stimulus was administered once in random sequence. Subjects rated the magnitude of pain evoked by each stimulus on a 100-mm visual analog scale (VAS) anchored by the words "no pain" and "most intense pain tolerable." A scatter plot depicting the 16 stimulus intensities (mA) *versus* pain (VAS) resulted for each test cycle (fig. 2, plot on the left).

Derivation of Analgesic Efficacy Variables. To compare the stimulus intensity (mA) *versus* pain (VAS) relation obtained at different times, parameters describing the relation were derived. A line was fitted to the data using the simple linear model,

$$y = a \times (x - b) \quad (1)$$

where x is the electrical current, y is the VAS-score, a is the slope of the relation, and b is the x-intercept (fig. 2, middle graph). A maximum likelihood approach was used for parameter estimation. A power model was also explored but failed to improve the fit as judged by visual inspection and the likelihood ratio test.

The fitting procedure assumed that errors (observed − predicted value) were normally distributed around the predicted value. Fitting a line to a VAS-score between 1 and 99 maximized the likelihood of observed error, *i.e.*, minimized the distance parallel to the y-axis between the fitted line and observed data point (inset graph A of the middle graph of fig. 2). Fitting a line to a VAS score equal to 0 or 100 maximized the probability of observed error, *i.e.*, maximized the distance parallel to the y-axis between the fitted line and observed data point (inset graph B of the middle graph of fig. 2). The second fitting procedure accounted for the fact that VAS scores of 0 and 100 are censored data (0 indicates a true value of approximately 0 or lower but not higher, 100 indicates a true value of approximately 100 or higher but not lower).

One analgesic efficacy variable was the pain threshold (x-intercept of the linear model denoted "b") and the pain tolerance calculated with aid of the linear model and by setting y = 100 (fig. 2, plot on the right).

Pharmacodynamic Analysis

Analgesic efficacy variables. The pain threshold and pain tolerance measured after drug administration was expressed as the percentage change from baseline (before drug). The baseline value represented 100%. Inspection of individual plots depicting plasma concentration *versus* pain threshold and pain tolerance suggested counterclockwise hysteresis for data collected after immediate-release hydromorphone but not after hydromorphone OROS administration. Therefore, individual effect site concentrations were used for further exploration of the concentration–effect relation after administration of immediate-release hydromorphone, but plasma concentrations were used in case of hydromorphone OROS. Effect site concentration and equilibration rate constant were determined using a nonparametric approach and the equilibration half-life, *i.e.*, the time necessary to achieve 50% of the plasma concentration at the effect site was calculated using standard formulas.[14]

Data obtained after administration of immediate-release hydromorphone and hydromorphone OROS were pooled separately for further evaluation of a pharmacodynamic model describing the effect site and plasma concentration *versus* effect relation, respectively. NONMEM[15] was used to explore pharmacodynamic models nested in a power model of the general form,

$$y = c + d \times x^{\lambda} \quad (2)$$

where y is the analgesic efficacy variable, x is the plasma or effect site concentration, c is the y-intercept or the effect at baseline, d is the slope of the relation, and λ is a variable exponent.[15] Model selection was based on the likelihood ratio test and visual assessment of the good-

ness of fit. A sigmoidal model was not explored because effects close to the maximum were not observed.

Vital Signs. The relation between hydromorphone plasma concentration and heart rate, arterial blood pressure, hemoglobin oxygen saturation, and respiratory rate was explored as outlined for the analgesic efficacy variables.

Statistics

Results of summary statistics are expressed as mean and SD for data passing the normality test (Kolmogorov-Smirnov) or alternatively as median and interquartile range. Parameters of linear equations are expressed as mean and corresponding 95% confidence interval.

To compare the magnitude of observed analgesic effect after administration of 8, 16, and 32 mg hydromorphone OROS and placebo, individual area under the curves (AUCs) depicting the time *versus* the percentage change of the pain tolerance were calculated. Four AUCs resulted per subject, one for each treatment. A one-way repeated-measure analysis of variance (ANOVA) tested for significant differences among treatments. For treatments significantly different from placebo, a one-way repeated-measure ANOVA tested if analgesic effects measured at different times after drug administration differed significantly from baseline. The Student-Newman-Keuls test was used for *post hoc* analysis. Outlined procedure rather than a two-way repeated-measure ANOVA was used because raw data did not pass the normality and equal variance test. AUCs were only determined for pain tolerance data because no significant relation existed between the hydromorphone plasma concentration and the pain threshold after hydromorphone OROS administration.

Areas under the curve depicting the electrical pain tolerance *versus* time for sessions 2–5 were compared among each other to test for the presence of an order effect (ANOVA on ranks). During each session, an equal number of subjects received each treatment, *i.e.*, the total dose of hydromorphone administered during each session remained constant. An order effect should manifest itself by AUCs that are increasing or decreasing with subsequent study sessions.

The electrical pain tolerance measured before drug administration was compared among study sessions to test for the presence of changing baseline conditions (one-way repeated-measure ANOVA on ranks). The Student-Newman-Keuls test was used for *post hoc* analysis.

To explore the fact that a significant relation between hydromorphone plasma concentration and pain tolerance but not pain threshold was detected, omega squared statistics were used.[16] Omega squared (ω^2) estimates the fraction of the overall variability of the effect measure that can be attributed to the fact that subjects received different treatments. It has been suggested that $0.01 < \omega^2 < 0.06$, $0.06 < \omega^2 < 0.15$, and $\omega^2 > 0.15$ indicate a small, medium, and large treatment effect, respectively.[16]

To compare plasma concentration *versus* time profiles observed after administration of immediate-release hydromorphone and hydromorphone OROS, the following parameters were determined: peak plasma concentration, time to achieve peak plasma concentration, first and last time plasma concentration was greater than 50% of measured peak concentration, and the length of time the plasma concentration remained at greater than 50% of the peak concentration. To compare analgesic effect *versus* time profiles observed after administration of immediate-release hydromorphone and hydromorphone OROS, the following parameters were determined: peak pain tolerance, time to achieve peak pain tolerance, first and last time pain tolerance was greater than 50% of peak pain tolerance, and the length of time the pain tolerance remained at greater than 50% of the peak pain tolerance. Linear interpolation was used to determine first and last time 50% of a peak value was observed. A 50% level of peak plasma concentration and peak analgesic effect was used to obtain a normalized, *i.e.*, dose-independent measure quantifying how sustained the plasma concentration and the analgesic effect were after administration of the immediate or sustained-release formulation. The 50% level does not relate to the adequacy of the plasma concentration or measured analgesic effect, but to the performance of examined sustained-release formulation. Treatments were compared using one-way repeated-measure ANOVA on ranks and Student-Newman-Keuls *post hoc* test.

One-way repeated-measure ANOVA on ranks and Dunnett's *post hoc* analysis tested for a significant difference in the incidence of side effects between active treatments and placebo. A P value less than 0.05 was considered statistically significant.

Results

Subjects

All 12 subjects completed the investigation according to the protocol. Oral contraceptives taken by five women were the only ongoing drug therapy during the study.

Pharmacodynamic Analysis

Model Parameters. The parameters of the linear model describing the stimulus intensity (mA) *versus* pain (VAS) relation at baseline were 2.8 ± 1.3 mA for the x-intercept and 16.2 (interquartile range, 11.2–25.3) for the slope. Baseline pain tolerance did not change significantly over the course of the study.

Analgesic Efficacy Variables: Immediate-release Hydromorphone. Counterclockwise hysteresis was present between the hydromorphone plasma concentra-

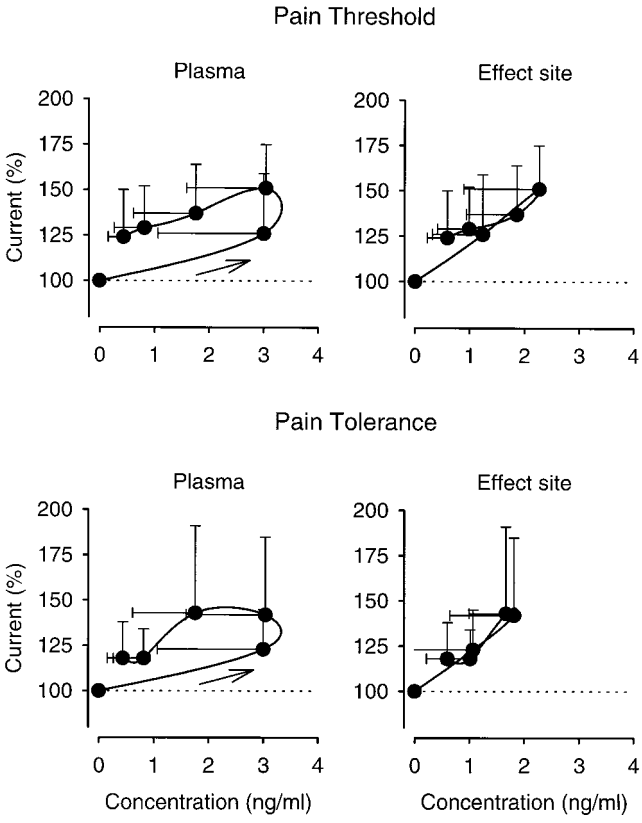

Fig. 3. Counterclockwise hysteresis was present if plotting the mean (± SD) plasma concentration measured after administration of immediate-release hydromorphone *versus* the mean (± SD) percentage increase of the pain threshold (*top left*) and the pain tolerance (*bottom left*), respectively. The solid line and arrow depict the counterclockwise hysteresis loop indicating an equilibration delay between hydromorphone plasma and effect site concentrations. Calculating the equilibration rate constant and the corresponding effect site concentration of hydromorphone by minimizing the area circumscribed by the hysteresis loop revealed the underlying concentration *versus* effect relation between hydromorphone and the pain threshold (*top right*) and the pain tolerance (*bottom right*), respectively.

tion and the pain threshold and the pain tolerance, respectively (fig. 3). The median equilibration half-life between plasma and the effect site was 18 min (1–42 min) and 38 min (8–66 min) for the pain threshold and the pain tolerance, respectively. The following significant linear relation was found between the hydromorphone effect site concentration (Ce [ng/ml]) and the percentage increase of the pain threshold (Pthr [%]) from baseline (corresponding to 100%),

$$\text{Pthr} = 122.4(\pm 11.0) + 8.0(\pm 6.6) \times \text{Ce} \quad (3)$$

Numbers in parentheses indicate corresponding 95% confidence intervals. Similarly, a significant linear relation was found between the hydromorphone effect site concentration (Ce) and the percentage increase of the pain tolerance (Ptol) from baseline,

$$\text{Ptol} = 115.5(\pm 13.9) + 10.7(\pm 9.0) \times \text{Ce} \quad (4)$$

Analgesic Efficacy Variables: Sustained-release Hydromorphone. The average analgesic efficacy of hydromorphone OROS did not change over the course of the different study sessions. There was no significant relation between the hydromorphone plasma concentration and the percentage increase of the pain threshold from baseline (fig. 4, upper graph). However, a significant linear relation existed between the hydromorphone plasma concentration (Cp) and the percentage increase of the pain tolerance (Ptol) from baseline (fig. 4, lower graph),

$$\text{Ptol} = 107.0(\pm 4.8) + 16.5(\pm 8.0) \times \text{Cp} \quad (5)$$

Numbers in parentheses indicate corresponding 95% confidence intervals. Pharmacodynamic models with a variable exponent did not improve the goodness of fit. Despite a lacking relation between the pain threshold and the hydromorphone plasma concentration, the percentage increase in pain threshold and pain tolerance correlated significantly (Pearson correlation coefficient = 0.53; $P < 0.001$).

Omega squared (ω^2), *i.e.*, the fraction of the overall variability of the pain threshold and the pain tolerance that could be attributed to the fact that subjects received different treatments (three doses of sustained-release hydromorphone and placebo) was 0.07 and 0.15, respectively. In other words, the magnitude of the analgesic treatment effect was small to medium and medium to large when assessing the pain threshold and pain tolerance, respectively.

Vital Signs: Immediate-release Hydromorphone. There was a significant relation between increasing hydromorphone plasma concentration and decreasing hemoglobin oxygen saturation. The lowest hemoglobin oxygen saturation measured was 95%. No significant relation was detected between the hydromorphone plasma concentration and heart rate, arterial blood pressure, or respiratory rate. The lowest respiratory rate was 8–10 breaths/min and was measured in one subject 0.5–2 h after administration of immediate-release hydromorphone. All other measurements were at least 12 breaths/min.

Vital Signs: Sustained-release Hydromorphone. There was no significant relation between the hydromorphone plasma concentration and heart rate, arterial blood pressure, hemoglobin oxygen saturation (no supplemental oxygen), or respiratory rate. The lowest hemoglobin oxygen saturation measured on one occasion 22 h after administration of 32 mg sustained-release hydromorphone was 91%. All other measurements were at least 93%. The lowest respiratory rate was 8–10 breaths/min, measured in one subject 8–14 h after administration of 16 mg sustained-release hydromorphone. All other measurements were at least 12 breaths/min.

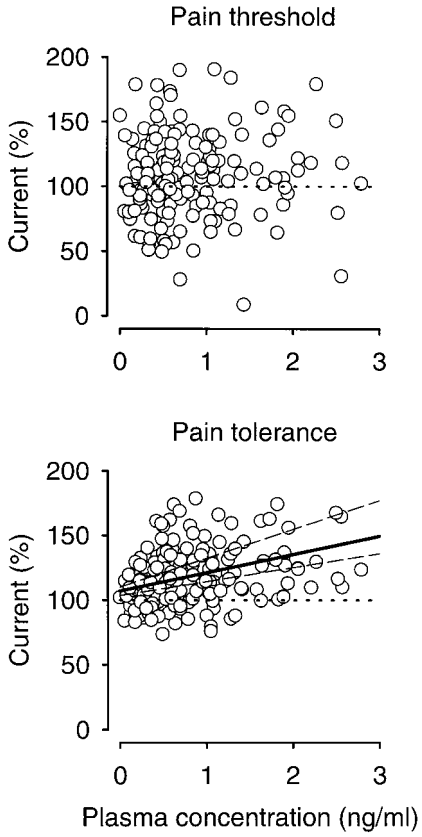

Fig. 4. (*Top*) The hydromorphone plasma concentration *versus* the percentage change of the pain threshold after administration of sustained-release hydromorphone (8, 16, and 32 mg) to 12 volunteers. There was no significant relation between the hydromorphone plasma concentration and the pain threshold. (*Bottom*) The hydromorphone plasma concentration *versus* the percentage change of the pain tolerance for the same 12 volunteers. A significant linear relation existed between increasing hydromorphone plasma concentration and pain tolerance. The relation and corresponding 95% confidence intervals are depicted by the solid and adjacent dashed lines, respectively.

Time Profile of Hydromorphone Plasma Concentration and Analgesic Effect

Plasma Concentration. Table 1 summarizes peak plasma concentration, the time to peak plasma concentration, the first and the last time 50% of peak concentration was present in plasma, and the time span that plasma concentration remained at greater than 50% of the peak concentration. Peak plasma concentration was significantly higher after administration of 8 mg immediate-release hydromorphone than after any dose of hydromorphone OROS. However, accounting for observed equilibration delay between plasma and effect site after administration of immediate-release hydromorphone, the peak effect site rather than the peak plasma concentration is relevant to relate peak concentration to peak effect. The peak effect site concentration after administration of immediate-release hydromorphone was 2.24 ± 1.19 ng/ml. This was similar to the peak concentration measured after 32 mg hydromorphone OROS but significantly higher than that measured after 8 and 16 mg hydromorphone OROS. Statistically, peak concentrations after different doses of hydromorphone OROS were dose proportional and differed significantly among each other. The time to peak plasma concentration, the first and last time 50% of peak concentration was present in plasma, and the time span that plasma concentration remained at greater than 50% of the peak concentration were all significantly shorter after immediate-release hydromorphone than after any dose of hydromorphone OROS. This was also true if considering the effect site rather than the plasma concentration in case of immediate-release hydromorphone. The time to peak effect site concentration was 2 h (1–2 h). The first and last time 50% of peak effect site concentration was present was 0.7 ± 0.4 h and 4.1 ± 1.6 h, respectively. The time span that effect site concentration remained at greater than 50% of the peak concentration was 3.4 ± 1.4 h. Different doses of hydromorphone OROS did not result in a different time to peak plasma concentration, a different first and last time 50% of the peak concentration was present in plasma, or a different time span plasma concentration was at greater than 50% of the peak concentration. Similarly, different doses of hydromorphone OROS did not result in significantly different intersubject variability of the plasma concentration. The average coefficient of variation of the plasma concentration was 43%, 43%, and 41% after administration of 8, 16, and 32 mg sustained-release hydromorphone, respectively. The bottom graphs of fig. 5 illustrate the plasma concentration *versus* time profile after administration of 8, 16, and 32 mg hydromorphone OROS, and the effect site concentration *versus* time profile after administration of 8 mg immediate-release hydromorphone, respectively.

Analgesic Effect. Table 2 summarizes peak pain tolerance, the time to peak pain tolerance, the first and last time 50% of peak pain tolerance was achieved, and the time span that pain tolerance remained at greater than 50% of the peak pain tolerance. Because the AUC depicting time *versus* pain tolerance was significantly different from placebo after administration of 16 and 32 mg, but not after administration of 8 mg hydromorphone OROS, only the 16- and 32-mg doses are discussed (fig. 6). Peak percentage increase in pain tolerance was not significantly different after administration of immediate-release hydromorphone or the two doses of hydromorphone OROS. However, compared with hydromorphone OROS administration, immediate-release hydromorphone resulted in a significantly shorter time to peak pain tolerance, first and last time 50% of peak pain tolerance was achieved, and time span that the pain tolerance remained at greater than 50% of the peak pain tolerance. Pain tolerance peaked approximately six times faster after administration of immediate-release hydromorphone. Comparable analgesic effects (pain tolerance at greater than 50% of the peak pain tolerance) were pro-

Table 1. Pharmacokinetic Indices after Administration of Immediate- and Sustained-release Hydromorphone

	Peak Plasma Concentration (ng/ml)	Time to Peak Cp (h)	First-time Cp > 50% Peak (h)	Last-time Cp > 50% peak (h)	Duration Cp > 50% Peak Cp
8 mg IRH*	4.74 ± 1.76†	0.8 (0.8–1.0)‡	0.4 ± 0.2‡	1.6 ± 0.8‡	1.1 ± 0.7‡
8 mg SRH	0.77 ± 0.33†	12.0 (9.0–13.5)	5.4 ± 1.7	30.9 ± 10.6	24.2 ± 10.3
16 mg SRH	1.45 ± 0.43†	15.0 (12.0–18.0)	6.1 ± 2.3	31.5 ± 9.4	21.6 ± 8.1
32 mg SRH	2.41 ± 0.85†	16.5 (12.0–21.0)	5.5 ± 1.8	35.8 ± 6.9	26.5 ± 7.5

Data are mean ± SD or median and interquartile range. First- and last-time plasma concentration (Cp) > 50% peak indicates when at least 50% of the peak concentration was detected in plasma for the first and for the last time, respectively. Duration Cp > 50% peak Cp indicates time span that plasma concentration was greater than 50% of the peak concentration.

* Results regarding effect-site concentrations are provided in the text. † $P < 0.05$ among all treatments. ‡ $P < 0.05$, immediate-release hydromorphone (IRH) differed significantly from all other treatments, but different doses of sustained-release hydromorphone (SRH) were not significantly different among each other.

longed by a factor of approximately 4 after administration of hydromorphone OROS. The top graphs of figure 5 depict the pain tolerance *versus* time profile after administration of 8, 16, and 32 mg hydromorphone OROS, 8 mg immediate-release hydromorphone, and placebo, respectively.

Compared with baseline, a significant increase in pain tolerance was present 0.5, 1, 2, 4, and 6 h after 8 mg immediate-release hydromorphone. Pain tolerance was significantly increased from baseline at 6, 9, 12, and 30 h after 16 and 32 mg hydromorphone OROS, respectively.

Adverse Events

Table 3 summarizes the incidence and severity of various adverse events. Compared with placebo, the incidence of pruritus and nausea was significantly greater after administration of 32 mg hydromorphone OROS. No serious adverse events were observed during the study. All adverse events were of mild or moderate severity, and most resolved spontaneously. However, nausea and vomiting made intravenous administration of 4–8 mg ondansetron necessary on 3, 1, 5, and 7 occasions after administration of 8 mg immediate-release hydromorphone and 8, 16, and 32 mg hydromorphone OROS, respectively. Pruritus was treated with 25–50 mg diphenhydramine administered intravenously on two occasions each after administration of 16 and 32 mg hydromorphone OROS. Finally, headache was treated with 325–650 mg acetaminophen orally on 2, 1, 2, and 3 occasions after administration of 8 mg immediate-release hydromorphone and 8, 16, and 32 mg hydromorphone OROS, respectively. With one exception, acetaminophen was given after completion of all experimental pain tests.

Discussion

A new sustained-release hydromorphone formulation using oral osmotic pump system technology has been developed for the treatment of chronic pain with a single daily dose. Hydromorphone OROS evoked a significant dose-dependent analgesic response beginning 6 h and lasting more than 24 h of its administration. The observed analgesic response was substantially longer than that observed after a similarly effective dose of immediate-release hydromorphone.

Oral Osmotic pump systems have been successfully used for the sustained release of a variety of drugs that are quickly eliminated from the body and therefore require dosing of the conventional tablet several times a day. Pharmacokinetics reported for hydromorphone OROS are consistent with previous reports of other compounds using oral osmotic pump systems.[10,11] Plasma concentrations peaked significantly later after administration of hydromorphone OROS compared with conventional tablets, but were sustained over the 24-h interval after drug administration.

Several studies have reported equivalent or superior efficacy for compounds administered with oral osmotic pump systems if compared with corresponding conventional tablet.[10–12] Experimental pain testing reported here suggests that a single daily dose of hydromorphone OROS provides sustained analgesia closely related to measured plasma concentration. Because previous studies have demonstrated similar analgesic efficacy for equivalent doses of various immediate and controlled-release opioids in the setting of clinical pain, it is conceivable that once an effective plasma concentration is achieved, a single daily dose of hydromorphone OROS will be as efficacious as multiple daily doses of the conventional tablet.[5,17] Based on our data, a 6-h period lacking sufficient plasma concentrations to produce significant analgesia has to be expected after an initial dose of hydromorphone OROS. A possible solution to prevent a 6-h delay in the onset of analgesia may be to coadminister immediate-release hydromorphone with the first dose of hydromorphone OROS. However, with repetitive dosing of hydromorphone OROS, sustained plasma concentrations throughout the 24-h dosing interval may be expected.

Peak analgesic effects to suprathreshold stimuli lagged behind peak plasma concentrations by approximately 40 min after administration of immediate-release hydromorphone. In monkeys, maximum brain uptake of ^{11}C-hydromorphone was delayed by 10–15 min.[18] A previ-

Table 2. Pharmacodynamic Indices after Administration of Immediate- and Sustained-release Hydromorphone

	Peak Pain Tolerance (%)	Time to Peak PT (h)	First-time PT > 50% Peak (h)	Last-time PT > 50% Peak (h)	Duration PT > 50% Peak (h)
8 mg IRH	34 (23–54)	1.5 (1.0–2.0)*	0.7 ± 0.4*	4.6 ± 1.5*	3.6 ± 1.7*
8 mg SRH	NA	NA	NA	NA	NA
16 mg SRH	37 (22–64)	9.0 (6.0–10.5)	5.4 ± 2.5	20.5 ± 8.1	13.7 ± 6.3
32 mg SRH	50 (26–67)	10.5 (9.0–12.0)	7.2 ± 3.7	20.8 ± 7.7	12.9 ± 6.6

Data are mean ± SD or median and interquartile range. First- and last-time pain tolerance (PT) > 50% peak indicates when at least 50% of the peak pain tolerance was present for the first and for the last time, respectively. Duration PT > 50% peak PT indicates time span that pain tolerance was at greater than 50% of the peak PT.

* $P < 0.05$, immediate-release hydromorphone (IRH) differed significantly from other treatments, but different doses of sustained-release hydromorphone (SRH) were not significantly different among each other.

NA = not applicable because measured analgesic response after 8 mg SRH was not different from placebo.

ous study in humans reported a delay between peak plasma hydromorphone concentration and peak analgesia of 10–20 min.[18] The 40-min delay reported here must be interpreted as estimation because collection of analgesic data over time was relatively sparse. Nevertheless, the observed delay points to a relatively slow transit of hydromorphone from plasma to the effect site, *i.e.*, the central nervous system, and is similar to that described for morphine.[19,20] This is in agreement with the fact that the polarity of hydromorphone and morphine is similar at physiologic pH.[21] Generally, drug uptake into the central nervous system becomes slower with increased polarity of the compound.[22]

Administration of hydromorphone OROS resulted in a significant relation between plasma concentration and measured analgesic effect for the pain tolerance (noxious input causing maximum tolerable pain) but not the pain threshold (noxious input causing equally likely a painful or a nonpainful perception). Several studies using various experimental pain modalities and different classes of drugs support the view that measuring the pain tolerance is more suitable to detect analgesic effects than measuring the pain threshold.[13,23,24] omega-squared statistics reported here and for a previous study implies that the signal (difference between treatments) to noise (variance unrelated to treatments) ratio is superior if measuring the pain tolerance.[13] This may be explained, in part, by a superior test–retest reliability if measuring the pain tolerance rather than the pain threshold. This view is supported by our study revealing a smaller within-day (9% *vs.* 15%) and between-day (17 *vs.* 23%) coefficient of variation for measurements of the pain tolerance rather than the pain threshold at baseline.

The experimental pain model used in our study did not detect a significantly different analgesic efficacy after administration of 16 and 32 mg hydromorphone OROS. This raises the question how the precision and sensitivity of the pain model used compares with other models testing analgesic efficacy. Postoperative pain models have often been used to compare the analgesic efficacy

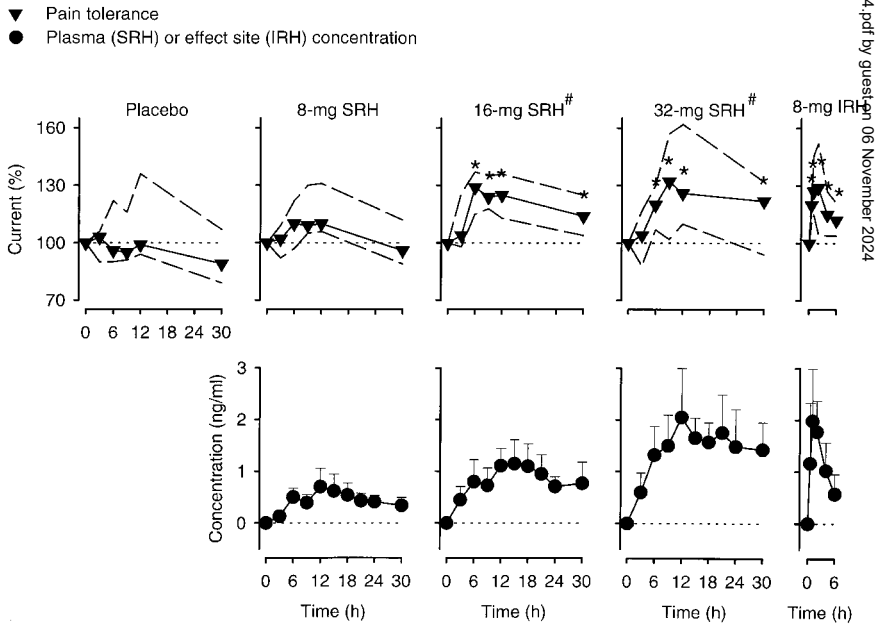

Fig. 5. (*Top*) Median percentage change (solid line) and corresponding interquartile range (dashed lines) of the pain tolerance *versus* time observed in 12 volunteers receiving sustained-release hydromorphone (SRH; 8, 16, and 32 mg), immediate-release hydromorphone (IRH; 8 mg), and placebo, respectively. Administration of 16 and 32 mg sustained-release hydromorphone resulted in a significant overall analgesic response if compared with placebo (#). An asterisk indicates times when measured analgesic response was significantly increased from baseline measurements. (*Bottom*) Mean (± SD) plasma concentration *versus* time after administration of 8, 16, and 32 mg sustained-release hydromorphone and the mean (± SD) effect site concentration *versus* time after administration of 8 mg immediate-release hydromorphone.

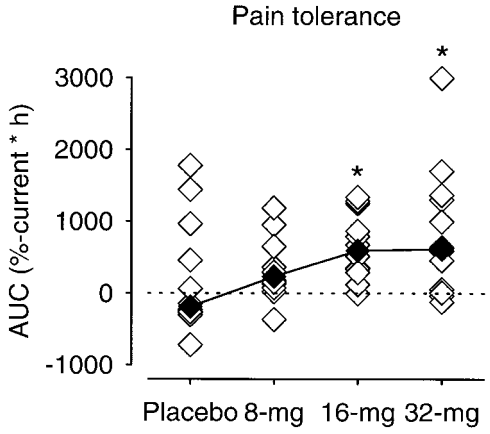

Fig. 6. White diamonds depict the individual areas under the curve (AUC; electrical pain tolerance *versus* time), and black diamonds the median area under the curve after administration of 8, 16, and 32 mg hydromorphone oral osmotic system and placebo, respectively. An asterisk indicates a significant difference from placebo administration.

of different doses of an orally administered opioid. However, despite the fact that these studies enrolled a larger number of patients than that enrolled in our study, they could not consistently demonstrate increased analgesic efficacy if doubling or even tripling the dose.[25–27] This suggests that the precision and sensitivity of our experimental pain model is at least equivalent to that of a postoperative pain model.

The difficulty of differentiating the analgesic efficacy among various doses of an orally administered opioid may result from significant intersubject pharmacokinetic and pharmacodynamic variability, less than desirable precision inherent to any pain assay, and the fact that many doses studied may constitute the low or the high end of the dose *versus* effect relation. The latter seems relevant because the dose *versus* effect relation is S-shaped for most drugs. Therefore, the gain in effect is much smaller and harder to detect if a low rather than a midsized dose is doubled.

Currently, a sustained-release hydromorphone formulation different from hydromorphone OROS is commercially available. This formulation has a pharmacokinetic and pharmacodynamic profile that allows safe and effective pain control if administered every 12 h.[6,28] However, the plasma concentration after administration of hydromorphone OROS was sustained approximately three times longer if compared with the alternative formulation.[28] Hydromorphone OROS likely needs less frequent dosing than the alternative formulation.

There are a variety of other opioids including morphine, oxycodone, and tramadol that are available as sustained-release formulations.[17,29,30] Most of these formulations allow safe and effective pain control if administered every 12 h. One formulation containing morphine was given once a day to patients with cancer pain and provided adequate pain control without the need for rescue medication in approximately 50% of the patients.[31] This formulation had pronounced sustained-release characteristics, with plasma concentrations remaining above 50% of the peak concentration for approximately 12 h.[31] By comparison, administration of hydromorphone OROS resulted in plasma concentrations that were similarly sustained for approximately 24 h. Contrasting with most sustained-release opioid formulations, a single daily dose of hydromorphone OROS may allow safe and adequate pain control and a decreased need for rescue medication.

The incidence of side effects after administration of hydromorphone OROS was dose-related. During clinical analgesic trials of opioids, a fraction of patients commonly withdrew because of disturbing opioid side effects.[5,6,32] However, studies comparing sustained- and immediate-release formulations of various opioids or among different release formulations of the same opioid did not find significant differences in the severity and incidence of side effects.[5,6,32,33] One study reported an increased therapeutic window in patients controlling the rate of a continuous intravenous infusion rather than the number of intravenous bolus injections of morphine.[34] More data are needed to establish if the thera-

Table 3. Incidence of Adverse Events after Administration of Immediate- and Sustained-release Hydromorphone, and Placebo

	Placebo	8 mg IRH	8 mg SRH	16 mg SRH	32 mg SRH
Lightheadedness	1	7 (2)	4	4 (1)	5 (1)
Drowsiness	—	2	2	2 (1)	2 (1)
Euphoria	—	2	1	—	2 (1)
Headache	—	2	2 (1)	6 (2)	7 (2)
Dry mouth	—	2	1	1	1
Nausea	1	4 (2)	1	5 (2)	9 (3)*
Vomiting	—	1	—	1	3 (1)
Pruritus	1	3	1	5 (1)	9 (3)*
Urinary retention	—	—	1	3	3

Side effects were of mild severity until noted differently by the number in parentheses, indicating the incidence that a particular side effect was of moderate severity.

* $P < 0.05$, 32 mg SRH *versus* placebo.

IRH = immediate-release hydromorphone; SRH = sustained-release hydromorphone.

peutic window between long-term administration of immediate- and sustained-release opioids differs in a relevant way.

Compliance with taking a medication is inversely related to the dosing frequency, particularly if three or more daily doses are required.[8] This was even found to be true in patients suffering from seizure disorders or chronic pain, conditions where noncompliance may result in immediate harm or increased suffering.[7,9] Cancer pain patients on controlled release morphine were more compliant, experienced less pain, and rated their quality of life higher than patients on immediate-release tablets.[9]

The development of tolerance, *i.e.*, a need to increase the dose to maintain an effect, may be different if a drug is administered as an immediate- or a sustained-release formulation.[35,36] One study suggested that more pronounced tolerance to the analgesic effects of morphine developed in patients receiving a continuous infusion rather than intermittent intramuscular bolus injections.[37] However, another study reported that, although analgesic effects were preserved, nausea and constipation became less prominent in the course of a treatment with controlled-release morphine.[9] Further investigation is needed to clarify if administration of immediate- and sustained-release opioids produce differential tolerance to analgesic and nonanalgesic effects.

Variation in gastrointestinal transit time could alter the release and absorption profile of hydromorphone OROS. No data regarding hydromorphone OROS are yet available. However, food intake and altered gastrointestinal transit time did not affect the release rate of radio-labeled markers from an oral osmotic pump system.[38] The release and absorption rate of metoprolol and oxprenolol using oral osmotic pump system technology were approximately constant along the entire gastrointestinal tract.[39,40] However, an inverse relation between the residual amount of drug recovered from excreted oral osmotic pump system and the gastrointestinal transit time has been reported.[41] Reduced systemic drug uptake can result if the gastrointestinal transit time is considerably shorter than the duration of drug release from an oral osmotic pump system.

In summary, hydromorphone OROS may become a valuable addition to other sustained-release formulations containing opioids. The presented data obtained in human volunteers using experimental pain provide strong evidence that a single daily dose of hydromorphone OROS may be effective in the treatment of opioid responsive chronic pain. Clinical studies are needed to substantiate and expand the findings presented here.

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