Anesthesiology 2002; 97:827–36

Input Characteristics and Bioavailability after Administration of Immediate and a New Extended-release Formulation of Hydromorphone in Healthy Volunteers

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Background: **To compare the pharmacokinetics of intravenous, oral immediate-release (IR), and oral extended-release (OROS®) formulations of hydromorphone.**

Methods: **In this randomized, six-session, crossover-design study, 12 subjects received hydromorphone 8-mg intravenous, 8-mg IR oral, and 8-, 16-, and 32-mg OROS® formulations or placebo orally followed by plasma sampling for hydromorphone determination. Pharmacokinetic analysis was performed using NONMEM. Using the disposition of hydromorphone from the intravenous administration, deconvolution was used to estimate the input rate function (release rate from the gut to the blood) for the IR and OROS® formulations. A linear spline was used to describe the drug input rate function.**

Results: **The deconvolution using linear splines described the *in vivo* release characteristics of both the IR and OROS® formulations. The mean absolute bioavailability for the 8-mg OROS® formulation was significantly larger ($P = 0.025$) than for the 8-mg IR formulation: 0.24 (SD 0.059) *versus* 0.19 (SD 0.054), respectively. The bioavailability was the same for the three doses of the OROS® formulation. Predicted degree of fluctuation of plasma concentrations would be expected to be 130% and 39% for the IR and OROS® 8-mg doses, respectively.**

Conclusions: **The OROS® formulation of hydromorphone produced continued release of medication over 24 h, which should allow for once-daily oral dosing. The extended release of hydromorphone will produce less fluctuation of plasma concentrations compared with IR formulations, which should provide for more constant pain control. The *in vivo* release of hydromorphone from both IR and OROS® formulations were adequately described using a linear spline deconvolution approach. The increased bioavailability from the OROS® formulation may be related to decreased metabolism by a first-pass effect or enterohepatic recycling of hydromorphone.**

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Received from the Department of Anesthesia, Stanford University School of Medicine, Stanford, California. Submitted for publication February 22, 2001. Accepted for publication June 3, 2002. Supported by a grant from Abbott Laboratories, Abbott Park, Illinois. Presented in part at the annual meeting of the American Society of Anesthesiologists, Dallas, Texas, October 9–13, 1999. Knoll Pharmaceutical Company, North Mount Olive, New Jersey, sponsored the original study and was sold to Abbott Laboratories during preparation of the manuscript. Dr. Drover has a consulting agreement with Abbott Laboratories that is not related to this study or any of these formulations.

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IN anesthesia clinical practice, intravenous bolus and infusion is a familiar method of delivery for most drugs. The clinician knows precisely how much intravenous drug has been given and, with clinical experience and pharmacologic understanding, can predict the clinical response from the given intravenous dosing regimen. With oral administration, the amount of drug delivered systemically and the duration over which it is absorbed is difficult to assess clinically relative to intravenous administration of the same drug. With oral administration, the absorption process and underlying bioavailability issues are complex, as the rate of drug entry into the blood stream changes with time. When orally administered sustained-release products are administered, this issue becomes even more complex. Understanding the release rate profile *versus* time of an orally administered, sustained-release product is analogous to understanding the infusion rate of an intravenously administered drug. This information allows more logical use of orally administered drugs with sustained-release properties in the patient population.

Hydromorphone is a derivative of morphine that is approximately five times more potent and primarily acts by binding to μ-opioid receptors. Because of rapid elimination and redistribution of hydromorphone, oral dosing every 4 h with the conventional immediate-release (IR) tablet is required to sustain adequate plasma concentrations.[1] Sustained-release drug formulations provide more convenient dosing, improve compliance, and produce more stable plasma concentrations, which should result in a more desirable therapeutic effect.[2–5] Optimal treatment of chronic continuous pain requiring opioid analgesics is better managed with sustained plasma concentration of the opioid analgesic. A new once-daily extended-release formulation of hydromorphone has been developed for the treatment of chronic pain. Osmotic pump delivery technology for the extended release of orally administered drugs has become available during the past two decades. The OROS® system (ALZA Corporation, Mountain View, CA) previously described by Theeuwes[6] consists of a semipermeable membrane surrounding a bilayer tablet core, one layer containing the drug and the other an osmotically active component. A small hole is drilled through the membrane on the side adjacent to the drug layer. In the gastrointestinal tract, water diffuses across the membrane, and a gel-like suspension is formed in the drug layer. As the osmotic layer expands, the drug suspension

is pushed through the orifice at a near constant rate into the lumen of the gastrointestinal tract for absorption.

The goals of this study were to determine the release characteristics and bioavailability of an OROS® sustained-release hydromorphone preparation. To accurately understand the release rate of a sustained-release product, it is necessary to separate the drug absorption phase from the drug distribution and elimination phases. To do this precisely, it is necessary to first measure the distribution and elimination using the intravenous route, then in the same individual, on another occasion, to administer the oral dosage form. Mathematical data analysis can then separate the oral absorption phase of drug entry into the blood stream from concurrent distribution and elimination phases. This approach allows comparison of hydromorphone bioavailability from IR and OROS® formulations and considers the effect of sustained-release products on bioavailability. Understanding the release characteristics of the sustained-release opiate will allow more logical use of this formulation in patients with chronic pain.

Materials and Methods

Subjects

After we obtained approval from the Stanford University Institutional Review Board, 12 healthy subjects (6 men and 6 women) were enrolled after giving written informed consent. Subjects were included if they were nonsmokers and consumed the caffeine equivalent of no more than three cups of coffee per day. Prior to enrollment, all subjects had a screening physical examination, 12-lead electrocardiogram, routine laboratory profile, and drug screen. Women were required to test negative for pregnancy. The drug abuse screen and pregnancy test were confirmed negative prior to each study day. No alcohol or over-the-counter medication was allowed within 48 h prior to each study day. Prescription drugs and chronic medications were prohibited during and 14 days prior to the study except for oral contraceptives. Prior to each study session, subjects fasted overnight.

Study Design

A three-stage (six-session), placebo-controlled, crossover study design was used. The pharmacodynamic component of this study has been previously published.[7] For the first stage, after subjects arrived at the study center, electrocardiogram and hemoglobin oxygen saturation were continuously monitored, and a catheter was inserted into a radial artery for continuous hemodynamic monitoring and to obtain blood samples for assessment of plasma drug concentration. An intravenous catheter was placed in the contralateral arm for administration of drug. After obtaining a baseline blood sample, an 8-mg zero-order infusion (0.8 mg/min) of hydromorphone was given over 10 min. Arterial blood samples for pharmacokinetic analysis were drawn at 0 (prior to dosing), 1, 3, 5, 7, 10, 11, 12, 13, 15, 17, 20, 25, 40, 55, 70, 100, 130, 190, 250, and 370 min after commencing the infusion. A second intravenous catheter was placed for sampling of later blood specimens at 370, 490, 730, 970, and 1,450 min after dosing. Simultaneous venous and arterial samples were obtained at the 370-min sample time to confirm comparability of sampling sites. In all stages of the study, the exact time of the midpoint of each sample draw was used as the time of the pharmacokinetic specimen. Meals were taken at standardized times, *i.e.*, 250 and 490 min after drug administration (coinciding blood drawings preceded the meals).

In the second stage, each subject received a single dose of 8 mg IR hydromorphone (Dilaudid®; Abbott Laboratories, Abbott Park, IL). Subjects swallowed the single tablet with a standardized amount of water (240 ml). No other water intake was allowed from 1 h prior to dosing through 1 h after dosing. Meals were taken at standardized times, *i.e.*, 180, 540, and 1440 min after drug intake (coinciding blood drawings preceded the meals). Venous blood samples were drawn immediately before drug intake and 15, 30, 45, 60, 90, 120, 180, 240, 300, 360, 480, 720, 960, and 1,440 min after drug intake.

Dosing for each of the four periods in stage 3 (sessions 3–6) was randomized and double-blind; subjects received single doses of 8, 16, and 32 mg OROS® hydromorphone (Abbott Laboratories) and placebo in a randomized sequence. A schematic representation of the OROS® release mechanism has been published.[7] A double-blind, randomized, placebo-controlled design was used to minimize bias during acquisition of pharmacodynamic data.[7] To maintain the blind, at the beginning of each study session subjects swallowed three tablets, all containing no drug (placebo period) or, alternatively, two containing no drug and one containing 8, 16, or 32 mg of the OROS® formulation of hydromorphone. Water intake was standardized as outlined for IR stage 2 sessions. Meals were taken at standardized times, *i.e.*, 3, 9, 24, 28, 33, and 48 h after drug intake (coinciding blood drawings preceded the meals). Venous blood samples were drawn before drug intake and 1, 2, 3, 6, 9, 12, 15, 18, 21, 24, 30, 36, and 48 h after drug intake.

Hydromorphone Assay

Seven-milliliter samples of blood were drawn into heparinized glass tubes and centrifuged, and plasma was frozen within 1 h. Plasma was stored in polypropylene at −20°C. Plasma (1.0 ml) and the internal standard (trideuterated hydromorphone) were extracted into organic solvent. Following centrifugation, an aliquot of the organic layer was injected onto a SCIEX API$^{III\text{-}Plus}$ LC-MS-MS (PE Biosystems, Foster City, CA) using a short high-performance liquid chromatography column. The

peak area of the m/z 286→185 product ion of hydromorphone was measured against the peak area of the m/z 289→185 product ion of the internal standard. Quantitation was performed using an x^{-1}-weighted linear least-square regression line generated from spiked plasma calibration standards. The assay was linear over a range of 0.05 to 10.0 ng/ml. The between-day coefficient of variation ranged from 1.4 to 11.2% (10 runs). The limit of quantification was 0.05 ng/ml.

Data Analysis

Plasma concentration and time data were analyzed by nonlinear regression using NONMEM version V (NONMEM Project Group, University of California, San Francisco, CA).[8] As the first step, the disposition function of hydromorphone after intravenous administration was determined for each subject. The frequency of data sampling allowed individual fits of the data for the purpose of obtaining the individual disposition parameters. One-, two-, and three-compartment mamillary models were considered for the disposition of hydromorphone. A proportional error model was used, of the form y = f (1 + eps), where y is an observation, f is the corresponding prediction, and eps represents the error, which is assumed to be normally distributed with mean zero and unknown variance (the NONMEM software estimates the unknown parameters in the function f and the error variance using maximum likelihood). Best fit of the data for each individual subject was judged based on visual assessment of the data and the value of the Hannan criteria.[9] The estimated disposition parameters for each individual were used in the next steps of deconvolution. Deconvolution describes the mathematical separation of the absorption phase from the distribution and elimination phases.

Hydromorphone IR deconvolution was initially performed using a traditional parametric approach with NONMEM, using the disposition function from the intravenous hydromorphone period of the study and assuming first-order absorption. A lag time for absorption was also considered as a component of this analysis. The deconvolution was subsequently repeated using a semiparametric approach. Instead of assuming first-order absorption, the absorption phase was described using a linear spline[10–12] to characterize the input rate function. A spline is a mathematical function that describes a smooth curve connecting a set of points (*e.g.*, breakpoints, nodes) and was chosen because a spline describes an arbitrary shape. This is described here by the following equation:

$$R(t) = \int_0^t K(\tau) \cdot I(\tau - t)dt + \varepsilon \qquad (1)$$

Equation 1 represents a causal linear time-invariant system, one that depends only on input up to and including time (t). The response of the system at time t [R(t)] is described by the convolution of the disposition function [K(t)] with the input rate function [I(t)], which is represented by a spline function. In this equation, t is time and τ is an integration variable, the parameter ϵ denotes error between the model and the data. The two constraints used in this analysis were that absorption of hydromorphone would be nonnegative and that during the period after peak absorption, the curve would be monotonically decreasing. Constraints are a method of providing information to the solution of the problem without making unnecessary assumptions. The term "spline" indicates a piece-wise polynomial function. A spline connects points corresponding to certain locations called breakpoints or nodes. There are several options for choice of breakpoints: the breakpoints were chosen at the quantiles of the observation times.[12] The flexibility of a spline increases with the number of breakpoints; thus, few breakpoints might fail to recover the correct input function, but too many might show artifacts (*e.g.*, generate unrealistic oscillations in the spline). The number of breakpoints was determined both by visual assessment of the fit as well as using the Hannan criterion.[9]

The OROS® release function was also characterized in the same fashion. The breakpoints were chosen at the quantiles of the observation times. The model selection was based on the visual inspection of the residual error plots and the value of the Hannan criteria.[9] For a comparison analysis, the IR formulation was considered the reference and the OROS® formulation the test compound. Bioavailability was calculated using the area under the input rate function curve as determined by the linear spline analysis performed with NONMEM. For validation of the area under the input rate function curve, the area under the curve (AUC) was also calculated from observed concentrations *versus* time by the log-linear trapezoidal rule. Statistical comparison of bioavailability data was performed using analysis of variance on the logarithmically transformed data.[13]

To gain a clinical impression of the mean behavior of the concentration profile of hydromorphone after dosing with 8-mg IR and OROS® formulations, a simulation was performed with repeating doses of each formulation, to a maximum of eight doses, which assures attainment of steady state. This calculation is only an estimation and is based on the following assumptions: (1) the pharmacokinetics in a patient population are similar to this volunteer population; (2) hydromorphone terminal phase of the elimination curve is accurately estimated; and (3) multiple doses do not change the pharmacokinetics of hydromorphone. Simulation was performed using NONMEM for both 8-mg IR and 8-mg OROS® hydromorphone formulations. A simulation considering

Table 1. Bioavailability Data

	Bioavailability	
Subject	IR	OROS®
1	0.15	0.186
2	0.246	0.381
3	0.197	0.252
4	0.131	0.214
5	0.264	0.313
6	0.214	0.203
7	0.153	0.263
8	0.214	0.248
9	0.157	0.231
10	0.106	0.184
11	0.274	0.241
12	0.161	0.177
Mean	0.189	0.241
SD	0.054	0.059

Bioavailability was calculated using the area under the input rate function curve.

IR = immediate release; OROS® = oral extended-release formulation.

interindividual variability was not performed because of limited information obtained from the small study population (12 subjects). IR was simulated based on every 8-h dosing intervals and OROS® based on every 24-h dosing interval, which may be reasonable clinical use projections for these two formulations. A total daily dose of 48 mg was used such that each formulation would be simulated based on the same total daily dose. At steady state, the degree of plasma concentration fluctuation (DF) was estimated for both formulations as follows:

$$DF = \frac{(C_{max} - C_{min})*100}{C_{avg}} \quad (2)$$

where C_{max} is the maximum predicted plasma concentration, C_{min} is the minimum predicted plasma concentration, and C_{avg} is the average predicted plasma concentration at steady state.

Results

Twelve subjects (6 male, 6 female), aged 21–34 yr, were enrolled in the study. All subjects completed all study sessions (table 1 web enhancement; additional information is available on the ANESTHESIOLOGY Web site at http://www.anesthesiology.org). The side effects, as reported previously,[7] were consistent with those associated with opioid analgesics, the most common of which were nausea, pruritus, and lightheadedness. After the intravenous administration of 8 mg hydromorphone, no subjects had loss of consciousness, apnea, or a hemoglobin oxygen saturation less than 90%.

Stage 1: Intravenous Hydromorphone

Each individual subject's plasma concentration-*versus*-time data were fit separately using NONMEM and were best described using a three-compartment model ($P < 0.001$, in respect to a two-compartment model) with first-order elimination from the central compartment. Raw plasma concentration-*versus*-time data for intravenous hydromorphone is presented graphically in figure 1. The individual parameters of the disposition function are available (table 2 web enhancement; additional information is available on the ANESTHESIOLOGY Web site at http://www.anesthesiology.org). The unit disposition functions obtained from the three-compartment model for the 12 subjects are available (fig. 1 web enhancement; additional information is available on the ANESTHESIOLOGY Web site at http://www.anesthesiology.org). These data were then used as the individual disposition function for further deconvolution of data from the oral dosage forms using NONMEM.

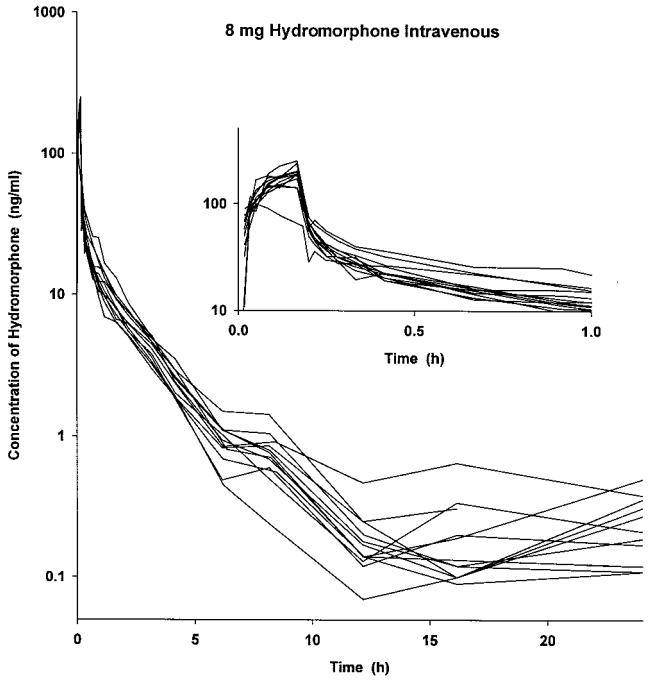

Fig. 1. Measured hydromorphone concentrations from each of the 12 subjects *versus* time after intravenous infusion of 8 mg hydromorphone given over 10 min. The insert expands the first 1 h.

Stage 2: Immediate-release Oral Hydromorphone

The disposition function from the intravenous data were fixed for each individual to estimate the IR input rate function. The raw concentration–time data used in the calculations are displayed graphically in figure 2. Although initial analysis considered a model with first-order absorption and elimination, visual inspection of the residual error plots and individual plasma concentrations indicated model misspecification. Residual error plots showing measured over predicted concentrations *versus* time were constructed for the spline input and first-order absorption models (fig. 3) to demonstrate the degree of model misspecification. Deconvolution using a

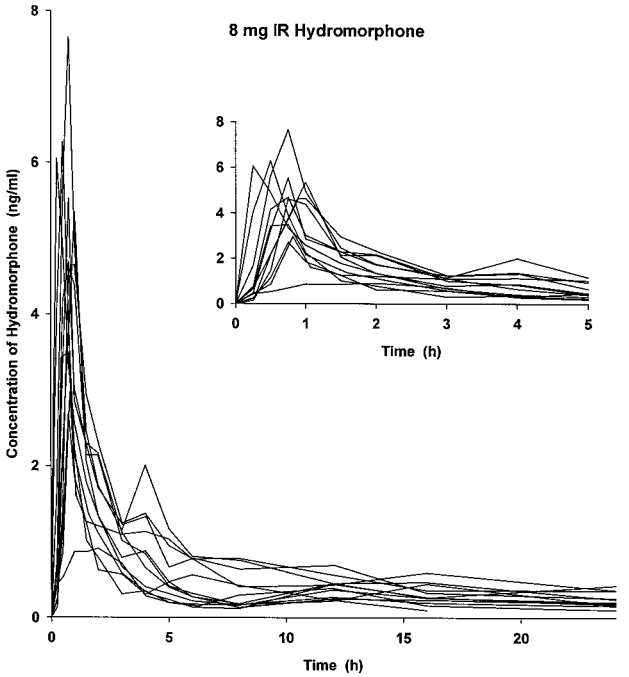

Fig. 2. Measured hydromorphone concentrations from each of 12 subjects *versus* time after oral administration of 8 mg immediate-release (IR) hydromorphone. The insert expands the first 5 h.

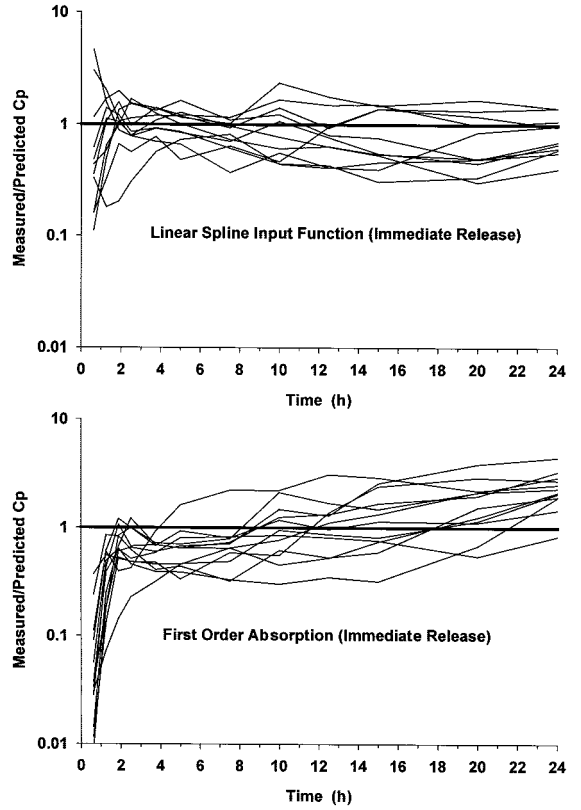

Fig. 3. Measured/predicted plasma drug concentrations from each of 12 subjects after oral administration of 8 mg immediate-release (IR) hydromorphone. The y-axis displays the ratio of measured to predicted drug concentrations for all subjects. The predicted concentrations were calculated from the pharmacokinetic model as estimated by NONMEM. The line drawn at y = 1 represents perfect prediction. (*Top*) The model using a linear spline input function; (*bottom*) data of the model assuming first-order absorption.

linear spline was then performed to estimate the input rate function. The corresponding fit resulted in a good description of the data and revealed that hydromorphone from the IR formulation is not immediately released and absorbed after dose administration. Figure 4 shows the input rate functions for each of the 12 subjects. There was an initial rapid release followed by second phase of slower hydromorphone release from the IR tablet. The mean value of the maximum rate of release was 17 mg/h (SD 10). Absolute hydromorphone bioavailability values (F) calculated from the area under the spline input rate-*versus*-time curve for each subject (mean F = 0.189 [SD 0.054]) are presented in table 1. The analogous bioavailability determined from AUC using the trapezoidal rule (mean F = 0.194 [SD 0.050]; data not shown) was 2.8% greater (not significant, $P > 0.05$) than that determined using the AUC under the spline input rate curve.

Stage 3: Oral Hydromorphone OROS® Formulation

The raw data from all subjects for each of the three doses are displayed in figure 5. Figure 6 shows the input rate functions obtained using deconvolution of the OROS® hydromorphone formulation data for each subject. The input function suggests continued release of hydromorphone from the OROS® delivery system over the sampling period, with the maximum absorption rate detected at approximately 10 h and decreasing progressively thereafter. The mean value of the maximum rate of release for the 8-mg OROS® formulations was 1.2 mg/h (SD 0.38). The bioavailability per milligram oral dose was the same for 8-, 16-, and 32-mg OROS® hydromorphone doses, indicating proportional drug release and absorption profiles with the three tablet strengths. To better display the time of peak plasma concentration and variability of the three OROS® doses, the 90% confidence limit of the parameters was calculated, and representative curves were produced. Figure 7 shows pointwise 90% confidence intervals for the OROS input and corresponding predictions. The pointwise 90% confidence intervals were obtained using the mean disposition function convolved with the 5% and 95% OROS input profiles; thus, they show the effect of variability in the input rate on drug concentrations. The bioavailability of hydromorphone from the OROS® formulation calculated from the area under the input rate-*versus*-time curve (mean F = 0.241 [SD 0.059]) for each individual is presented in table 1. Bioavailability for each individual at each dose is available (table 3 web enhancement; additional information is available on the ANESTHESIOLOGY Web site at http://www.anesthesiology.org). The hydromorphone bioavailability from the OROS® formulation cal-

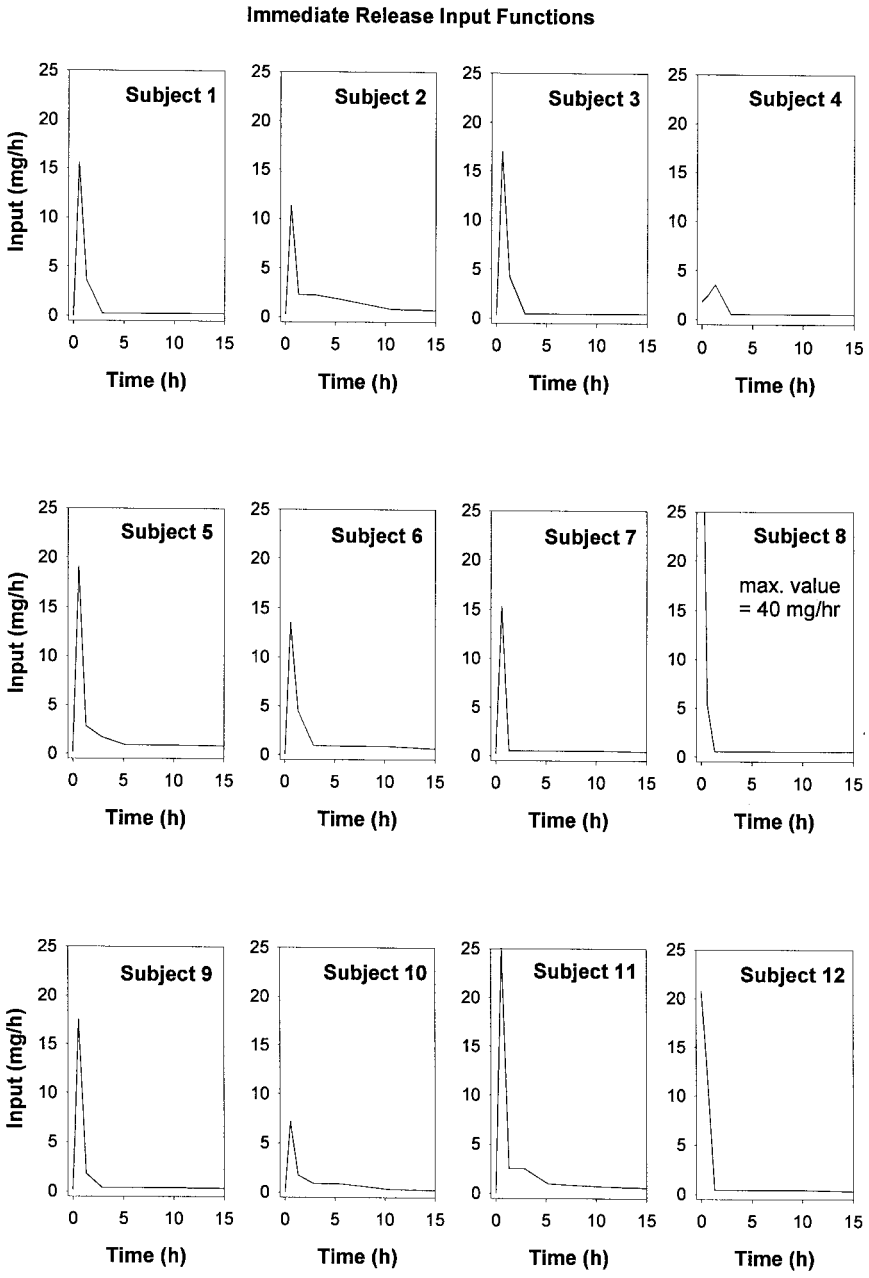

Fig. 4. Estimated individual input rate functions for 8 mg immediate-release (IR) hydromorphone for each of 12 subjects. Subject identification numbers are included in each plot.

culated using the input rate function was significantly greater than that of the IR formulation ($P = 0.025$). The analogous bioavailability determined from AUC using the trapezoidal rule (mean F = 0.251 [SD 0.073]) was 4.3% greater (not significant) than the AUC under the spline input rate curve.

Simulation of Typical Dosing of Immediate-release and OROS® Hydromorphone

Multiple dosing was simulated using the mean values from the individual fits from the NONMEM analysis for both IR (fig. 8) and OROS® (fig. 9) hydromorphone. The predicted plasma concentrations suggest that the peak plasma concentration would be almost 37% greater after an IR dose than an OROS® dose (9.2 *vs.* 6.7 ng/ml). The degree of fluctuation would be expected to be 130% for the IR and 39% for the 8-mg OROS® dose.

Discussion

Physicians use opioids to treat patients with pain conditions. In patients with moderate to severe chronic pain, ideally a steady state plasma concentration from an effective and well-tolerated dose of analgesic medication is achieved. Historically, frequent dosing with short-acting analgesic formulations has lead to continued or episodic breakthrough pain, resulting in a potential decrease in patient compliance and satisfaction.[1,14] Orally administered sustained-release opioid formulations have

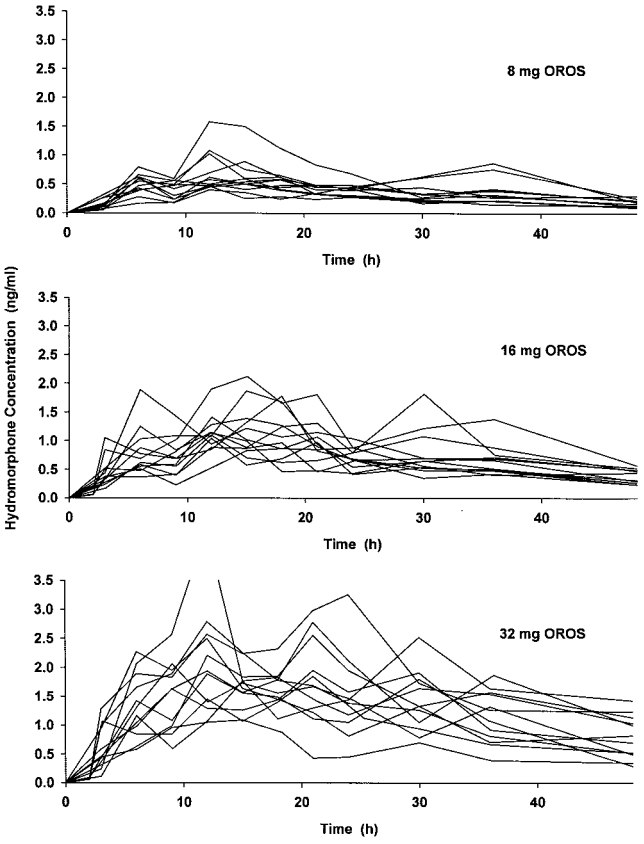

Fig. 5. Measured hydromorphone concentrations *versus* time after oral administration of 8, 16, and 32 mg of OROS® hydromorphone.

been developed that can provide the patient with a more convenient dosing regimen and with less variable plasma opioid concentrations than may be possible with repeated dosing of IR formulations. In this clinical investigation, we studied a once-daily oral OROS® hydromorphone formulation that produces a controlled drug release over the 24-h dosing interval. This hydromorphone preparation has been shown to provide sustained analgesia after a single daily dose in an experimental pain model.[7] The mathematical model used here effectively described the release characteristics of hydromorphone from this new sustained-release formulation. The OROS® formulation produces sustained plasma concentrations over a 24-h interval that would be consistent with expectations for effective once-daily dosing with hydromorphone.

Medications are being prepared in new formulations to make patient dosing easier and to improve drug effect, tolerance, and patient compliance. Delivering short-acting drugs in extended-release systems can produce a long-lasting effect with infrequent dosing. However, when a short-acting drug such as hydromorphone is administered in a slow-release delivery system, the drug may not appear in the circulation in a pattern that can be described effectively by the traditional sum-of-exponentials model. A first-order absorption process concurrent with appearance of drug in the sampling compartment would not be a satisfactory mathematical model when drug release, absorption, and elimination occur simultaneously and in a complex fashion. Drug input into the systemic circulation is a factor of both the release of drug from the dosage form and rate of absorption across the mucosal wall. Since hydromorphone from the OROS® formulation can be released along the entire length of the gastrointestinal tract, the absorption rate constant may not be consistent in all segments of the tract.

When the IR formulation was modeled assuming first-order absorption characteristics, there was significant model misspecification. This would suggest that even drugs that are considered IR might have a delayed-release component because of the inherent composition of the formulation. The spline method of deconvolution also showed a degree of model misspecification (fig. 3) but was the superior model when compared with a first-order absorption model, with or without a lag time. Compressed tablet formulations have been shown to have more variable release characteristics than formulations using an "effervescent" system.[15] Effervescent or liquid formulations might be most appropriately described as IR and show good mathematical fit to a first-order absorption model.

The intravenous form of a drug may not always be available or safe to administer to human subjects. While it may be tempting to use "known" pharmacokinetic parameter estimates from an "IR" formulation in the deconvolution of a sustained-release formulation, those assumptions may not always be appropriate. In the current study, when data from the IR formulation were used to provide parameters (*e.g.*, Ka) for the deconvolution of the OROS® formulation of hydromorphone, the erroneous impression that the OROS® formulation had nonlinear kinetics was concluded (data not shown). The current spline input curves describe a convolution of the release characteristics of hydromorphone from the OROS® formulation and the resultant Ka. If an accurate Ka could have been calculated from the IR deconvolution, a further deconvolution calculation could have allowed exact determination of the *in vivo* release profile of hydromorphone from the OROS® formulation. However, the IR kinetics could not be adequately described by a first-order absorption constant, and it was therefore not possible to completely characterize the *in vivo* release profile from this extended-release formulation.

The absorption of hydromorphone for 24 h from the OROS® formulation may be partially explained by the presence of enterohepatic cycling of hydromorphone. As has been described for morphine, unchanged drug is excreted in the bile and reabsorbed across the intestinal wall into the systemic circulation. This can give the appearance of continued release from an oral formulation and produce a calculation of a greater bioavailability than an IR formulation.[16–18]

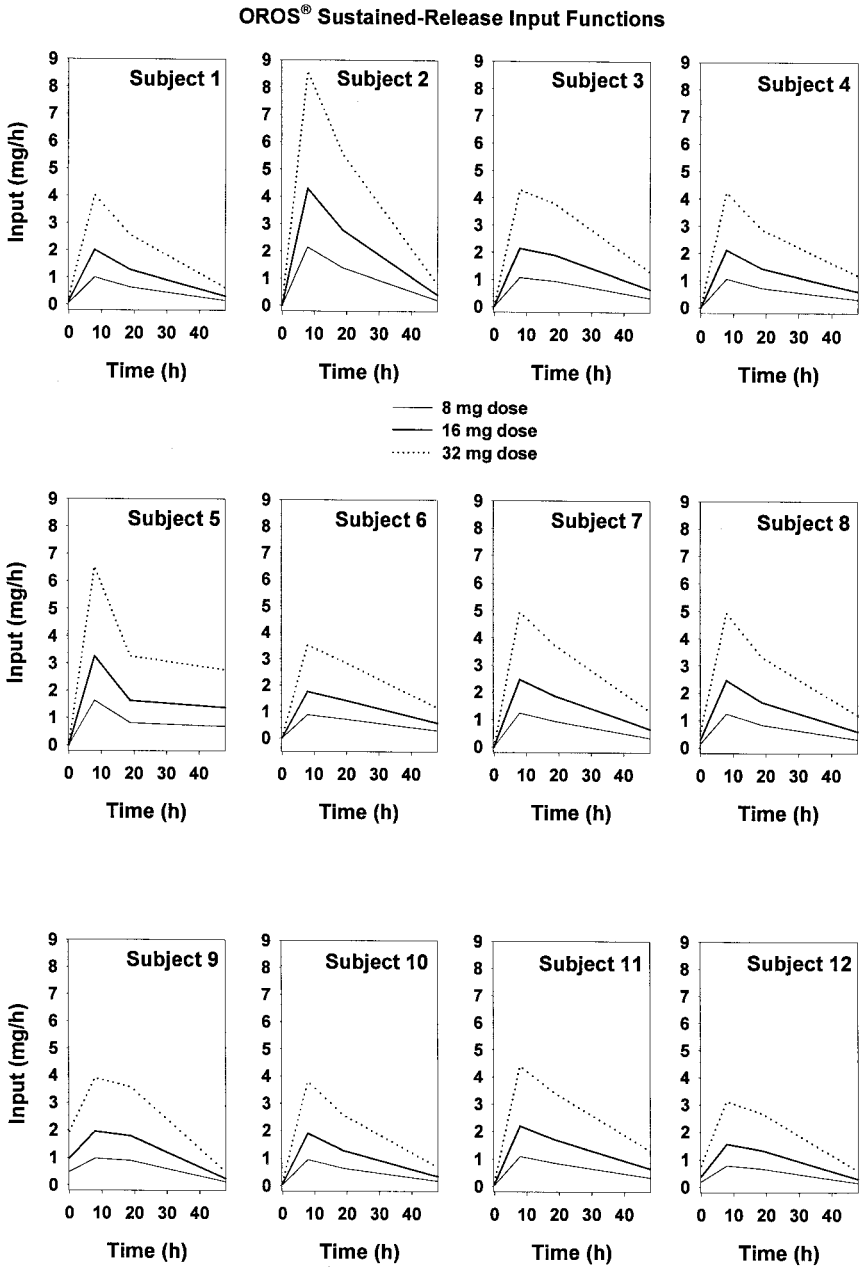

Fig. 6. Estimated individual input rate functions for 8 (lowest line), 16 (middle line), and 32 mg (upper line) OROS® formulation of hydromorphone for each subject. Subject identification numbers are included in each plot.

The bioavailability of hydromorphone from other oral formulations in humans has been reported previously.[19–21] The greater bioavailability reported previously cannot be explained by this study. Previous studies in humans have used shorter sampling periods than our study. This sampling difference may account for a different pharmacokinetic model and might lead to incorrect estimation of the AUC. Also, previous studies used a radioimmunoassay method of quantitation of hydromorphone that was less specific for the parent drug and may have detected glucuronide metabolites. The absolute bioavailability of hydromorphone implies a significant amount of first-pass metabolism by the liver. Rapidly released drugs that are absorbed from the duodenum enter the mesenteric vessels and are transported to the liver, where they may undergo extensive metabolism before entering the rest of the system; this has been termed the "first-pass effect." The OROS® hydromorphone formulation had a greater bioavailability than the IR form. This might be explained by the release and absorption of hydromorphone from the OROS® formulation in the colon and rectum, thus avoiding or decreasing the amount of the first-pass effect. Similarly, the OROS® formulation of oxybutynin has been found to have a greater bioavailability than the IR oxybutynin formulation, and a difference in first-pass metabolism was postulated as the likely cause for this greater bioavailability.[2] Conversely, the extended-release formulations may contain undelivered drug at the time of dosage form excretion in the stool. This would be expected to

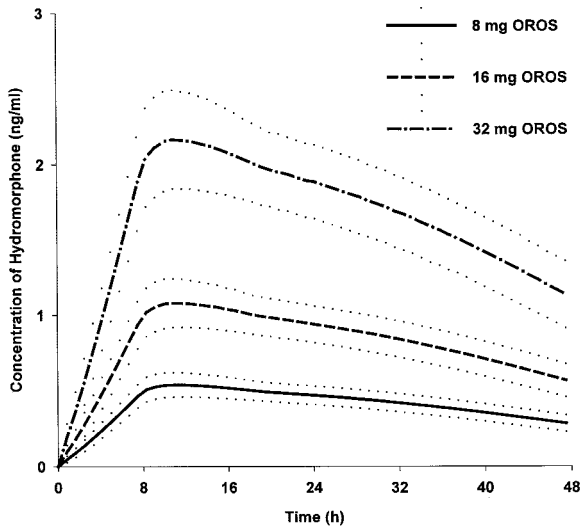

Fig. 7. Simulated curves of the 8-, 16-, and 32-mg OROS® doses of hydromorphone. The dotted lines above and below each mean dose curve represents the area of the 90% confidence interval as calculated from the parameter estimates.

decrease relative bioavailability. In addition, the long period of release noted for this formulation (24–48 h) might be considered longer than most patient's normal gastrointestinal tract transit time.

Two possible reasons for this apparently long release period exist. First, hydromorphone, like most opioids, delays gastric motility and produces constipation; thus, OROS® may reside in the gastrointestinal tract longer than other medications. Second, decreased sampling frequency during the 24–48 h postdose period would produce model error in predicting final release characteristics from the formulation. This error results in an inability to accurately determine whether plasma concentrations at the later sampling points are a result of continued release or final disposition of the drug; more intense sampling during this interval may have improved prediction of plasma concentrations.

The characteristics of the IR and OROS® formulations were simulated mathematically to gain an impression of

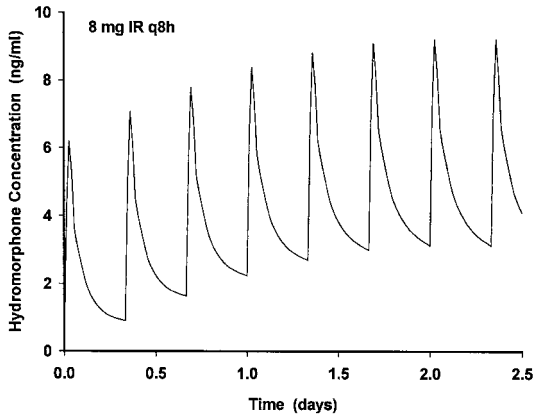

Fig. 8. Simulation of repeated doses of hydromorphone immediate-release (IR; 16 mg) given orally every 8 h.

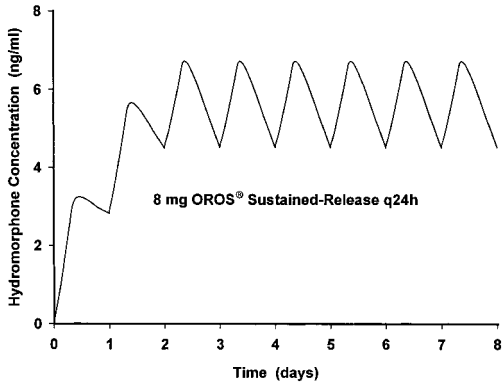

Fig. 9. Simulation of repeated doses of hydromorphone OROS® (48 mg) given orally every 24 h.

what plasma concentrations would be produced when these two different dosage forms are used clinically. The IR formulation may be expected to produce a greater peak concentration of an equivalent dose from the OROS® formulation. The degree of fluctuation of plasma hydromorphone is projected to be far greater with the IR (130%) than the OROS® (39%) formulation, even with the more frequent dosing of the IR formulation. Since the degree of fluctuation is considerably larger with the IR formulation, clinically it may translate to more side effects from greater peak plasma concentrations or a greater likelihood for breakthrough pain between scheduled doses of medication. From the simulation, although the extended-release formulation showed very slow release and delayed time to peak plasma concentration, by the third dose (third day) the peak plasma concentration would be expected to be 95% of the steady state peak. This is useful clinical information for adjusting dosage with the OROS® formulation. Dose adjustments with this extended-release formulation at 3-day intervals appear reasonable. Steady state plasma concentrations are likely attained after 3 days, providing the clinician with adequate information to evaluate and balance efficacy with tolerability before considering further titration.

In summary, hydromorphone when given intravenously was best described by a three-compartment pharmacokinetic model. The release of drug from IR hydromorphone was better described by a spline function than a first-order absorption model. The OROS® hydromorphone formulation showed an extended-release profile with much less peak-to-trough variation than the IR formulation. The bioavailability of hydromorphone from the OROS® formulation appeared greater than from the IR formulation, which may be a result of a difference in first-pass effect. Overall, the extended-release profile of hydromorphone from the OROS® formulation appears suitable for true once-daily oral dosing.

The authors thank Lawrence Saidman, M.D. (Professor, Department of Anesthesia, Stanford School of Medicine, Stanford, California), Tom Valente, M.D. (Abbott Laboratories, Abbott Park, Illinois), and Ralph Doyle, B.A. (Abbott Laboratories, Mt. Olive, New Jersey) for reviewing the manuscript.

References

1. Bruera E, Sloan P, Mount B, Scott J, Suarez-Almazor M: A randomized, double-blind, double-dummy, crossover trial comparing the safety and efficacy of oral sustained-release hydromorphone with immediate-release hydromorphone in patients with cancer pain. Canadian Palliative Care Clinical Trials Group. J Clin Oncol 1996; 14:1713–7
2. Gupta SK, Sathyan G: Pharmacokinetics of an oral once-a-day controlled-release oxybutynin formulation compared with immediate-release oxybutynin. J Clin Pharmacol 1999; 39:289–96
3. Gupta SK, Shah JC, Hwang SS: Pharmacokinetic and pharmacodynamic characterization of OROS and immediate-release amitriptyline. Br J Clin Pharmacol 1999; 48:71–8
4. Kendall MJ, Maxwell SR, Sandberg A, Westergren G: Controlled release metoprolol: Clinical pharmacokinetic and therapeutic implications. Clin Pharmacokinet 1991; 21:319–30
5. Greenberg RN: Overview of patient compliance with medication dosing: A literature review. Clin Ther 1984; 6:592–9
6. Theeuwes F: Elementary osmotic pump. J Pharm Sci 1975; 64:1987–91
7. Angst MS, Drover DR, Lotsch J, Ramaswamy B, Naidu S, Wada DR, Stanski DR: Pharmacodynamics of orally administered sustained-release hydromorphone in humans. ANESTHESIOLOGY 2001; 94:63–73
8. NONMEM Project Group: NONMEM's Users Guide. Edited by Beal S, Sheiner L. San Francisco, University of California San Francisco, 1998
9. Hannan E: Rational transfer function approximation. Stat Sci 1987; 2:135–61
10. Park K, Verotta D, Gupta SK, Sheiner LB: Passive versus electrotransport-facilitated transdermal absorption of ketorolac. Clin Pharmacol Ther 1998; 63: 303–15
11. DeBoor C: A Practical Guide to Splines. New York, Springer-Verlag, 1978
12. Verotta D: Concepts, properties, and applications of linear systems to describe distribution, identify input, and control endogenous substances and drugs in biological systems. Crit Rev Biomed Eng 1996; 24:73–139
13. Steinijans VW, Diletti E: Statistical analysis of bioavailability studies: Parametric and nonparametric confidence intervals. Eur J Clin Pharmacol 1983; 24:127–36
14. Hays H, Hagen N, Thirlwell M, Dhaliwal H, Babul N, Harsanyi Z, Darke AC: Comparative clinical efficacy and safety of immediate release and controlled release hydromorphone for chronic severe cancer pain. Cancer 1994; 74:1808–16
15. Lotsch J, Kettenmann B, Renner B, Drover D, Brune K, Geisslinger G, Kobal G: Population pharmacokinetics of fast release oral diclofenac in healthy volunteers: Relation to pharmacodynamics in an experimental pain model. Pharm Res 2000; 17:77–84
16. Westerling D, Frigren L, Hoglund P: Morphine pharmacokinetics and effects on salivation and continuous reaction times in healthy volunteers. Ther Drug Monit 1993; 15:364–74
17. Poulain P, Hoskin PJ, Hanks GW, O AO, Walker VA, Johnston A, Turner P, Aherne GW: Relative bioavailability of controlled release morphine tablets (MST continus) in cancer patients. Br J Anaesth 1988; 61:569–74
18. Hasselstrom J, Sawe J: Morphine pharmacokinetics and metabolism in humans: Enterohepatic cycling and relative contribution of metabolites to active opioid concentrations. Clin Pharmacokinet 1993; 24:344–54
19. Vallner JJ, Stewart JT, Kotzan JA, Kirsten EB, Honigberg IL: Pharmacokinetics and bioavailability of hydromorphone following intravenous and oral administration to human subjects. J Clin Pharmacol 1981; 21:152–6
20. Parab PV, Ritschel WA, Coyle DE, Gregg RV, Denson DD: Pharmacokinetics of hydromorphone after intravenous, peroral and rectal administration to human subjects. Biopharm Drug Dispos 1988; 9:187–99
21. Ritschel WA, Parab PV, Denson DD, Coyle DE, Gregg RV: Absolute bioavailability of hydromorphone after peroral and rectal administration in humans: Saliva/plasma ratio and clinical effects. J Clin Pharmacol 1987; 27:647–53