

Original Article

The INFUSE-Morphine Study: Use of Recombinant Human Hyaluronidase (rHuPH20) to Enhance the Absorption of Subcutaneously Administered Morphine in Patients with Advanced Illness

Jay R. Thomas, MD, PhD, Mark S. Wallace, MD, Richard C. Yocum, MD, Daniel E. Vaughn, PhD, Michael F. Haller, PhD, and Jocelyne Flament, MD
Department of Supportive Care Medicine (J.R.T.), City of Hope, Duarte, California; Department of Anesthesiology (M.S.W.), University of California, San Diego Center for Pain Medicine, San Diego, California; Department of Drug Development and Medical Affairs (R.C.Y.), Rockwell Medical Technologies, Inc., Wixom, Michigan; Department of Research and Development (D.E.V., M.F.H.), Halozyme Therapeutics, Inc., San Diego, California, USA; and European Organisation for Research and Treatment of Cancer AISBL-IVZW (J.F.), Brussels, Belgium

Abstract

Morphine is often administered by the subcutaneous (SC) route when venous access is difficult to achieve. Hyaluronidase temporarily increases the permeability of SC connective tissues by degrading hyaluronan and has been shown to increase the dispersion and absorption of coadministered molecules. Therefore, hyaluronidase could enhance the pharmacokinetics of subcutaneous morphine. This Phase IIIB, double-blind, randomized, placebo-controlled crossover study compared the pharmacokinetics, safety, and tolerability of morphine administered SC with and without 150 U of recombinant human hyaluronidase (rHuPH20) with those of intravenous (IV) morphine administration in 13 patients in a hospice or palliative care setting. Each patient received morphine 5 mg parenterally daily for three days by a different method each day: IV, SC plus rHuPH20, and SC plus placebo (normal saline). The primary endpoint was the time to maximum plasma concentration (T_{max}) for morphine. Concomitant SC administration of rHuPH20 enhanced the absorption rate of morphine compared with SC morphine with placebo, significantly reducing the mean T_{max} from 13.8 to 9.2 minutes, a 33% decrease ($P = 0.026$). The respective values for geometric mean maximum plasma concentration were 94.9 and 107.5 nmol/L, a 13% increase ($P = 0.024$), and the area under the plasma concentration vs. time curve values

Halozyme Therapeutics, Inc. funded the study. Baxter Healthcare Corporation supported the study with documents, database, and statistical analysis. Editorial assistance in the preparation of this manuscript was provided by Barbara J. Goldman, RPh, of Advogent and funded by Baxter.

At the time the study was conducted, Dr. Flament was employed by Baxter Healthcare Corporation, Deerfield, IL, and Dr. Yocum was employed by Halozyme Therapeutics, Inc., San Diego, CA.

Clinical Trial Registration: www.ClinicalTrials.gov, Identifier: NCT00593281.

Address correspondence to: Jay R. Thomas, MD, PhD, City of Hope, 1500 East Duarte Road, Machris 1111, Duarte, CA 91010-3000, USA. E-mail: jaythomas@coh.org

Accepted for publication: April 1, 2009.

were 7.7 and 7.2 $\mu\text{mol}\cdot\text{min}/\text{L}$ ($P = 0.23$). Morphine plus rHuPH20 appeared to be safe and well tolerated. In patients requiring opioid analgesia, SC morphine plus rHuPH20 provides pharmacokinetic characteristics that are superior to those of SC morphine alone. These positive results warrant further studies on analgesic efficacy of morphine delivered with rHuPH20. *J Pain Symptom Manage* 2009;38:663–672. © 2009 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.

Key Words

Subcutaneous, M6G, difficult venous access, parenteral, hospice, hospice care, palliative care, pain, pharmacokinetics, interstitial

Introduction

Injectable hyaluronidase products may enhance the subcutaneous (SC) absorption of coadministered medications by temporarily depolymerizing hyaluronan, a highly hydrated glycosaminoglycan, which is a major barrier to diffusion and bulk flow in the SC space. Pre-clinical pharmacology studies of a recombinant form of human hyaluronidase (rHuPH20) have shown that it enhances the dispersion and systemic bioavailability of coadministered molecules up to 200 nm in diameter.¹ The extent of drug dispersion is proportional to the concentration of hyaluronidase injected and the volume of the coinjected material. The viscosity of tissues is restored to preinjection levels within 24–48 hours after injection of hyaluronidase.^{1,2}

By facilitating the absorption of coadministered drugs, SC injection of rHuPH20 may provide an alternative method of administration that could reduce complications encountered in patients with difficult venous access (DVA), including those with catheter placement failure as a result of obesity; vein sclerosis, fragility, or collapse; or catheter malfunction. Complications that might be avoided include multiple needlesticks, catheter-related venous thrombosis, infection, port-related complications, and extravasation injury.^{3–5}

Morphine is commonly used to treat moderate to severe pain and is the standard against which all new analgesics are measured.⁶ Often delivered intravenously (IV), morphine is the first-line medication for patient-controlled analgesia, both postoperatively⁷ and for patients with advanced illnesses such as cancer.⁸ SC delivery of morphine does not require venous access, reduces the likelihood of

infection, precludes the need for close supervision owing to the less-invasive nature of administration,⁹ and is less costly to administer.⁸ Given sufficient time, SC-administered morphine has been shown to be as effective as IV morphine for palliative care in cancer patients.^{8,10} We hypothesized that coadministration of rHuPH20 with morphine would enhance drug absorption, thus altering SC morphine pharmacokinetics to more closely resemble the IV profile. To test this hypothesis, we designed the INcreased Flow Utilizing Subcutaneously Enabled Morphine (INFUSE Morphine) studies to determine the pharmacokinetics, safety, and tolerability of morphine administered SC, with and without rHuPH20, compared with IV morphine administration. The trial reported here was conducted in patients requiring opioid analgesia. A complementary trial of morphine pharmacokinetics in healthy volunteer participants follows.

Methods

Study Design and Patients

This Phase IIIB, double-blind, randomized, placebo-controlled study involved 13 patients in a hospice or palliative care setting. A three-way crossover design was used (IV morphine, SC morphine with placebo, and SC morphine with rHuPH20), with each patient serving as his or her control. The study was approved by the appropriate institutional review boards (IRBs). Each patient signed an IRB-approved informed consent form and was reimbursed for the cost of time spent in the study. The study was not blinded with respect to IV vs. SC morphine administration, but it was double blinded with respect to SC

administration with placebo vs. SC administration with rHuPH20.

Eligible participants were men or women at least 18 years of age who were patients of, or recruited through, San Diego Hospice and Palliative Care or the University of California at San Diego Center for Pain Medicine. All patients were receiving non-morphine opioid therapy equivalent to ≥ 60 mg oral morphine per day with acceptable tolerability. Patients on this baseline nonmorphine opioid therapy were chosen because they were considered less likely to experience an adverse reaction or intolerance to morphine, given their demonstrated tolerance to opioid therapy. Additional inclusion criteria included vital signs within the normal range, adequate venous access in both upper extremities, a negative pregnancy test within seven days of the first injection (for women of childbearing potential), life expectancy ≥ 10 days, and decision-making capacity.

Exclusion criteria included a known hypersensitivity, contraindication, or history of any toxicity to morphine or naloxone; morphine use within four days before the first study medication injection or anticipated morphine use during any of the treatment days; known allergy to hyaluronidase, bee, or vespid venom; contraindication for IV heparin lock or known hypersensitivity to heparin; hemoglobin < 10 g/dL; edema, infection, or any other lower extremity or pelvic disorder that might affect SC absorption from the thigh; any other medical condition that would present an unacceptable safety risk to the patient; and participation in a study of any investigational drug or device within 30 days of enrollment.

Treatments

Each eligible patient was to receive a single daily injection of 5 mg morphine on each of

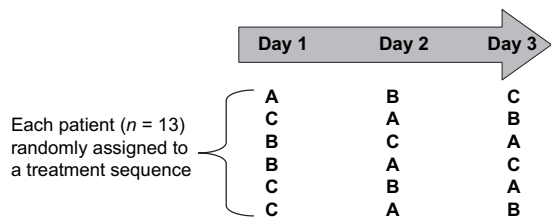


Fig. 1. Randomized sequence of injections. A, intravenous morphine; B, subcutaneous morphine with placebo; C, subcutaneous morphine with rHuPH20.

three consecutive days by one of the three following methods: IV injection (1 mL morphine sulfate 5 mg/mL); SC coinjection with rHuPH20 150 U (Hylenex[®] 150 U/mL; Baxter International, Inc., Deerfield, IL; 2 mL total volume: 1 mL morphine sulfate 5 mg/mL + 1 mL rHuPH20 150 U/mL); and SC coinjection with placebo (2 mL total volume: 1 mL morphine sulfate 5 mg/mL + 1 mL 0.9% sodium chloride). The method of injection given each day followed the order specified by a randomization schedule (Fig. 1). All injection components were drawn into a syringe attached to a 25-gauge needle, mixed, and given by slow push over 60 seconds. The first SC injection was made in the patient's left anterior thigh (midway between the anterior iliac crest and the cephalad border of the patella), and the second was made in the right thigh in a symmetrical location. The IV injection was given in a vein in the upper extremity contralateral to the upper extremity containing the IV heparin or saline lock used for blood sample collection.

Blood Collection and Analysis of Plasma Morphine and Morphine-6-Glucuronide

To determine the pharmacokinetic profile of morphine and its active metabolite (morphine-6-glucuronide [M6G]), 2 mL blood samples were collected immediately preinjection and at 5, 10, 15, 20, 25, 30, 45, 60, 90, 120, 180, and 240 minutes after completion of injection. A reference laboratory (MicroConstants, Inc., San Diego, CA) determined the concentrations of morphine and M6G in human plasma samples. Samples containing morphine and M6G, with their respective deuterated forms as the internal standards, were precipitated with a trichloroacetic acid solution. An aliquot of the supernatant was extracted, using solid phase extraction well plates, and analyzed by reverse-phase, high-performance liquid chromatography, using a Zorbax SB-Phenyl column maintained at 40°C. The mobile phase was nebulized, using heated nitrogen in a Z-spray source/interface, and the ionized compounds were detected, using a tandem quadrupole mass spectrometer (MS/MS). This method was validated using standardized procedures for chromatographic analytical assays. The linear range of the assay was from 1.75 to 1754.4 nmol/L. Morphine

and M6G are stable in plasma for 34 days when stored frozen at -70°C (data on file; Halozyme Therapeutics, Inc., San Diego, CA).

Pharmacokinetic Evaluation

The primary pharmacokinetic endpoint was time to maximum plasma concentration (T_{max}) for morphine. The arithmetic mean morphine T_{max} for each mode of administration was calculated as the average of the protocol-specified time points at which the plasma morphine was highest in each patient. Secondary endpoints included T_{max} for M6G, as well as maximum plasma concentration (C_{max}), area under the plasma concentration vs. time curve (AUC_{0-t}), half-life ($t_{1/2}$), and SC bioavailability relative to IV bioavailability for both morphine and M6G. The AUC_{0-t} was calculated using the trapezoidal method. Pharmacokinetic parameters included M6G because this major metabolite has analgesic activity that may be at least equal to that of the parent compound.^{11,12}

Efficacy

Efficacy was not an outcome measure in this study, which was primarily designed to measure morphine pharmacokinetics.

Safety and Tolerability

Safety and tolerability were assessed on each injection day (Days 1, 2, and 3) through physical examinations, signs and symptoms at injection sites (pain, rash, and edema), vital signs (blood pressure, heart rate, and respiratory rate), and adverse events. Injection-site edema and rash were evaluated up to four hours postinjection. Follow-up evaluations for vital signs, physical exam, injection-site rash or edema, and other adverse events were also performed the day after the last injection (Day 4), and adverse events were evaluated through 28 days after the last injection (Day 31). The patient's subjective assessment of pain at the injection site was measured five minutes after the completion of the infusion by means of a visual analogue scale with a range of 0 mm (no pain) to 100 mm (most severe pain). The presence of both edema and rash at the injection site was independently graded by the investigative site staff on a scale of 0 (none) to 4 (severe). Edema was assessed at three minutes, four hours, and 24 hours postinjection; rash was evaluated at

20 minutes, four hours, and 24 hours postinjection.

Statistical Analyses

Pharmacokinetic endpoints were evaluated for patients who had received all three methods of injection and for whom sufficient data for pharmacokinetic profiling were available. All patients who had received at least one injection of the study drug were evaluated for safety.

The primary analysis was the three pairwise comparisons of T_{max} for the SC morphine injection with rHuPH20, the SC morphine injection with placebo, and the IV morphine injection. Secondary pharmacokinetic endpoints underwent a similar analysis. A paired *t*-test (two-tailed) was used for all comparisons of pharmacokinetic variables among the treatments, with a significance level of $P \leq 0.05$. The results are reported without adjustment for potential Type 1 error.

Plasma concentrations were fit to a pharmacokinetic model by nonlinear regression analysis to minimize the sum of squared residuals among all observations of plasma concentration for a given analyte at all times and over all patients. The model chosen depended on the analyte and the route of administration. Morphine plasma levels following IV injection were fit to a two-phase exponential decay model. Morphine plasma levels following SC injection were fit to a single-compartment model. M6G plasma levels for all injections were fit to a single-compartment model with a lag time. Calculations and graphing were performed with Prism version 4.02 (GraphPad Software, Inc., San Diego, CA; www.graphpad.com). Additional statistical analysis was performed using the SAS System[®] version 9.1 (SAS Institute, Inc., Cary, NC; www.sas.com), running under Windows XP on a PC-compatible computer. Because of extremely high carryover baseline values for M6G at Days 2 and 3 for one patient, this patient's data were excluded from analyses of the M6G pharmacokinetic parameters but were included in the morphine analyses.

The sample size for this study was based on the comparison of the estimated population mean T_{max} between the SC morphine injection with placebo (estimated to be 30 minutes)¹³ and the SC morphine injection with rHuPH20. If the mean $T_{\text{max}} \pm$ standard deviation (SD) with placebo is 30 ± 10 minutes,

Table 1
Demographic Characteristics of the Enrolled Study Population (n = 13)

Characteristic	Value
Age in years, mean (SD)	46.9 (8.8)
Gender, n (%)	
Male	5 (38)
Female	8 (62)
Race, n (%)	
White	12 (92)
Black	1 (8)
Height in cm, mean (SD)	168.3 (9.4)
Weight in kg, mean (SD)	87.7 (40.7)

using the two-sample normal distribution *t*-test (unpaired analysis for the purpose of sample size estimation), six patients would be sufficient to distinguish a mean $T_{\max} \pm$ SD with rHuPH20 of $\leq 15 \pm 5$ minutes, based on statistical significance for a two-sided Type 1 error of 0.05% at 80% power ($P \leq 0.047$). To account for the possibility of a larger SD or a smaller reduction in T_{\max} , this study was designed to enroll up to 12 evaluable patients.

Results

Patients

A total of 13 patients were enrolled. One patient did not complete the series of injections and withdrew after receiving only the IV

injection. This withdrawal was not because of an adverse event or a drug-related toxicity. Data from 12 evaluable patients were used for the pharmacokinetic analysis; data from all 13 enrolled patients were included in the analyses of safety and tolerability. Table 1 presents their demographic characteristics. Patients had multiple comorbid conditions, and polypharmacy was common across various therapeutic categories, including analgesics, oncology agents, antidepressants, anticonvulsants, gastrointestinal agents, and cardiovascular drugs.

Pharmacokinetics

Morphine. The addition of rHuPH20 to SC morphine injection significantly reduced T_{\max} and significantly increased C_{\max} compared with SC morphine injection with placebo. As shown in Fig. 2, the mean T_{\max} values for morphine after IV injection, SC injection with rHuPH20, and SC injection with placebo were 5.4 (95% confidence interval [CI] 4.50–6.33), 9.2 (95% CI 5.63–12.71), and 13.8 (95% CI 10.40–17.10) minutes, respectively ($P = 0.026$ for SC morphine injection with rHuPH20 vs. without rHuPH20, $P = 0.0002$ for IV morphine injection vs. SC morphine injection with placebo, $P = 0.056$ for IV morphine injection vs.

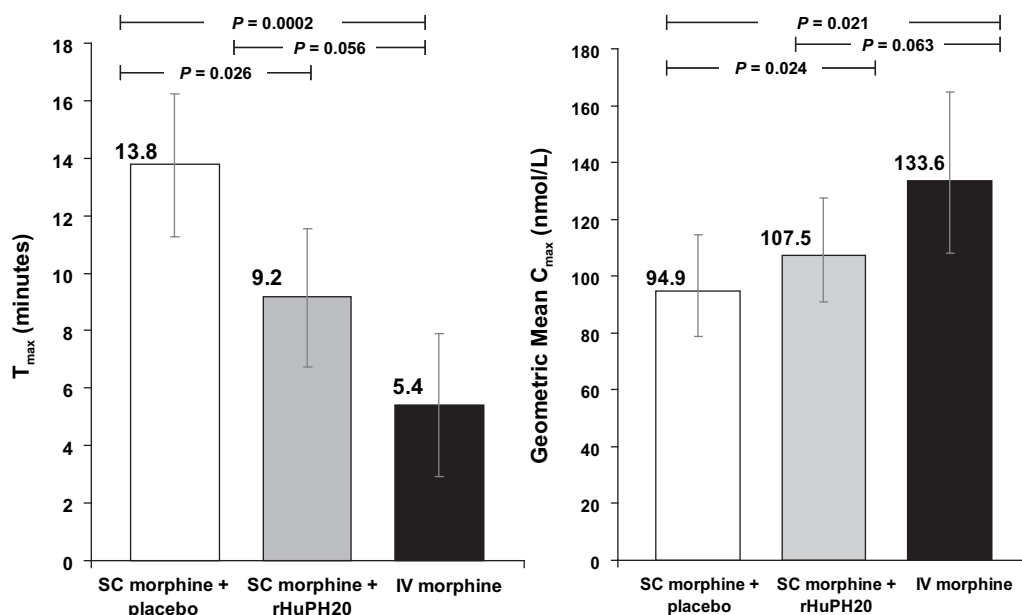


Fig. 2. T_{\max} (mean \pm SD) and C_{\max} (geometric mean \pm DS) of morphine for each administration method.

SC morphine injection with rHuPH20). The median T_{max} value for the IV injection was five minutes (range 5–10); for the SC injection with rHuPH20, it also was five minutes (range 5–20), whereas for the SC injection with placebo, it was 15 minutes (range 5–25). The respective values for the geometric mean C_{max} were 133.6 nmol/L (95% CI 108.2–165.0), 107.5 nmol/L (95% CI 90.8–127.4), and 94.9 nmol/L (95% CI 78.8–114.5; $P=0.024$ for SC morphine injection with rHuPH20 vs. without rHuPH20, $P=0.021$ for IV morphine injection vs. SC morphine injection with placebo, $P=0.063$ for IV morphine injection vs. SC morphine injection with rHuPH20; Fig. 2). Fig. 3 shows the morphine plasma concentration curve for the three injection conditions during the four-hour observation period. Fig. 4 shows a detailed view of the curve during the first 30 minutes.

Based on the sampling time points used, no significant differences were observed in either the four-hour total drug exposure (AUC_{0-t}) or the bioavailability of SC-administered morphine, when administered with or without rHuPH20. Although the AUC_{0-t} differed significantly between the IV injection and each of the two SC injections, bioavailability was similar for all the three methods of administration. The geometric mean AUC_{0-t} values for morphine after IV injection, SC injection with rHuPH20, and SC injection with placebo were $5.7 \mu\text{mol}\cdot\text{min}/\text{L}$ (95% CI 4.5–7.1), $7.2 \mu\text{mol}\cdot\text{min}/\text{L}$ (95% CI 6.1–8.6), and $7.7 \mu\text{mol}\cdot\text{min}/\text{L}$ (95% CI 6.8–8.8), respectively (Fig. 5; $P=0.23$ for SC injection with rHuPH20 vs. without rHuPH20, $P=0.004$ for

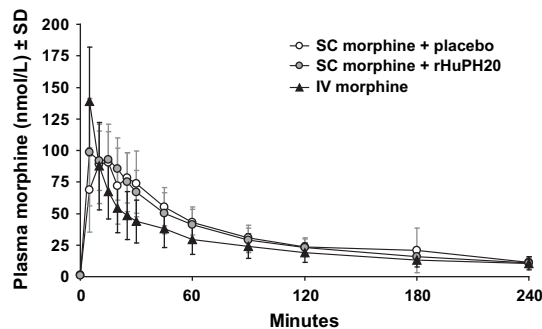


Fig. 3. Pharmacokinetic curves for morphine plasma concentration over four hours postinjection (population means \pm SDs) for each administration method.

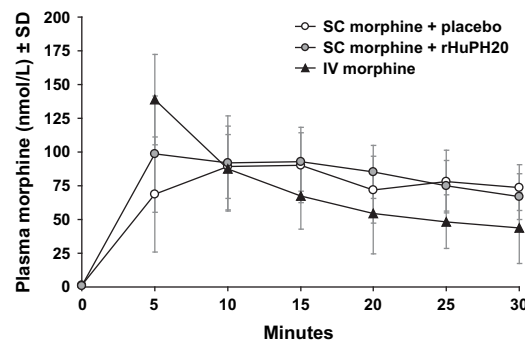


Fig. 4. Pharmacokinetic curves for morphine plasma concentration over the first 30 minutes postinjection (population means \pm SDs) for each administration method.

IV injection vs. SC injection with placebo, $P=0.005$ for IV injection vs. SC injection with rHuPH20). The bioavailability for SC morphine with and without rHuPH20 was similar to that of IV morphine (as the reference, defined as 100%): 96% and 103%, respectively. The elimination $t_{1/2}$ values for the SC with rHuPH20 and SC with placebo injections were 48 and 56 minutes, respectively.

Morphine-6-Glucuronide. The results for the major active metabolite of morphine generally followed those for the parent drug (Table 2). The T_{max} values were significantly longer after each SC injection vs. the IV injection, whereas C_{max} values were slightly lower with each SC injection vs. the IV injection. The AUC_{0-t} was greater with IV than with each SC injection, but the difference between IV and SC with rHuPH20 was not statistically significant. There

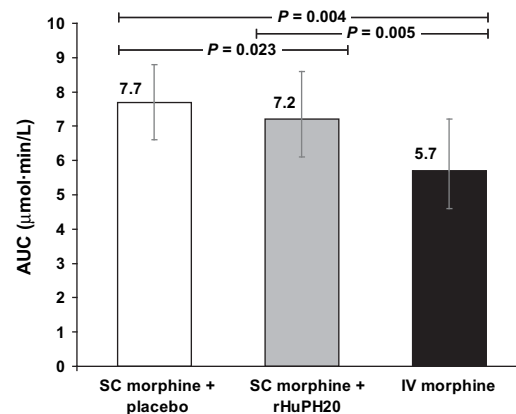


Fig. 5. Morphine AUC_{0-t} (geometric mean \pm DS) for each administration method.

Table 2
Pharmacokinetics of M6G

	Treatment		
	SC Morphine + Placebo	SC Morphine + rHuPH20	IV Morphine
Mean T_{max} (minutes) ^a	100.90 (95% CI 87.32–114.5)	111.80 (95% CI 83.19–140.4)	69.09 (95% CI 44.32–93.86)
Geometric mean C_{max} (nmol/L) ^b	31.9 (95% CI 25.7–39.5)	31.1 (95% CI 24.3–40.0)	36.0 (95% CI 29.3–44.4)
Geometric mean AUC_{0-t} ($\mu\text{mol}\cdot\text{min}/\text{L}$) ^c	5.3 (95% CI 4.3–6.6)	5.4 (95% CI 4.2–6.9)	6.3 (95% CI 5.0–7.9)
Bioavailability (%) ^b	98	96	100
Mean elimination $t_{1/2}$ (minutes) ^d	187	187	187

^a $P=0.02$ for IV morphine vs. SC morphine plus placebo, $P=0.037$ for IV morphine vs. SC morphine plus rHuPH20, and $P=0.44$ for SC morphine plus placebo vs. SC morphine plus rHuPH20.

^bNo significant differences among treatments.

^c $P=0.007$ for IV morphine vs. SC morphine plus placebo, $P=0.099$ for IV morphine vs. SC morphine plus rHuPH20, and $P=0.94$ for SC morphine plus placebo vs. SC morphine plus rHuPH20.

^dConstrained to be equal; insufficient data to resolve.

were no significant differences in bioavailability among treatments. The SC injections of morphine with and without rHuPH20 did not differ in any of the measured M6G pharmacokinetic parameters (T_{max} , C_{max} , AUC_{0-t} , and bioavailability).

Safety and Tolerability

Safety. Adverse events are summarized in Table 3. The most common adverse events, regardless of study drug relationship, were at the injection site after SC administration of morphine and were similar after administration with either rHuPH20 or placebo. Most adverse events were mild and transient; only four events were of

moderate severity (injection-site rash, erythema, and pruritus with SC morphine plus rHuPH20, and injection-site rash with SC morphine plus placebo). Non-injection-site events were uncommon for all the three regimens. Three of the four non-injection-site events (diplopia, hypotension, and dry mouth) were observed after the IV injection, and the fourth (hiccups), after the SC injection with placebo. There were no serious or severe adverse events or deaths, and no patient withdrew because of adverse events. Physical examinations and vital signs indicated no clinically relevant changes as a result of any of the treatments.

Tolerability. There were no major differences among the three injection methods with

Table 3
Treatment-Emergent Adverse Events, Regardless of Relationship to Study Drugs

Adverse Event (MedDRA ^a preferred term)	Treatment		
	SC Morphine + Placebo, ^b n (%)	SC Morphine + rHuPH20, ^b n (%)	IV Morphine, ^c n (%)
Any event	5 (41.7)	6 (50.0)	3 (23.1)
Injection-site events	5 (41.7)	6 (50.0)	0
Edema	3 (25.0)	2 (16.7)	0
Rash	3 (25.0)	2 (16.7)	0
Erythema	2 (16.7)	2 (16.7)	0
Pruritus	2 (16.7)	2 (16.7)	0
Hemorrhage	1 (8.3)	1 (8.3)	0
Irritation	0	1 (8.3)	0
Pain	0	1 (8.3)	0
Induration	1 (8.3)	0	0
Non-injection-site events	1 (8.3)	0	3 (23.1)
Diplopia	0	0	1 (7.7)
Hypotension	0	0	1 (7.7)
Hiccups	1 (8.3)	0	0
Dry mouth	0	0	1 (7.7)

^aMedDRA = Medical Dictionary of Regulatory Activities.

^bn = 12 patients.

^cn = 13 patients.

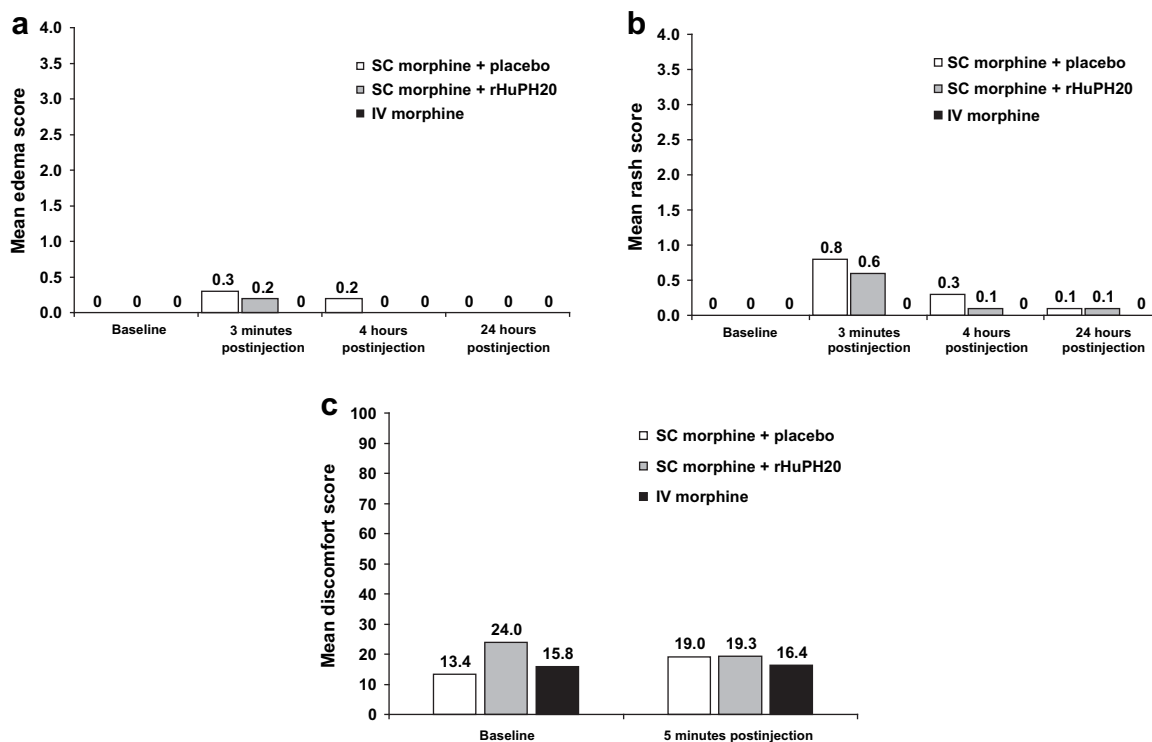


Fig. 6. Scores for severity of a) injection-site edema, (0 = none, 1 = minimal, 2 = mild, 3 = moderate, 4 = severe) b) rash (0 = none, 1 = minimal, 2 = mild, 3 = moderate, 4 = severe), and c) discomfort (0 = no discomfort, 100 = worst possible discomfort [100 mm VAS scale]).

respect to subjective assessments of edema, rash, or discomfort at the injection site at any of the time points evaluated (Fig. 6).

Discussion

In this study, coinjection of rHuPH20 with SC-administered morphine enhanced the absorption rate of morphine compared with SC coinjection of morphine with placebo. The mean T_{\max} was significantly reduced from 13.8 to 9.2 minutes, a 33% decrease. The mean T_{\max} for IV morphine was 5.4 minutes. Observed nonmodeled pharmacokinetic parameters, such as T_{\max} , C_{\max} , and AUC_{0-t} , may have been affected by the fact that the earliest pharmacokinetic sampling time point in this study was five minutes. Although the IV T_{\max} was likely limited by this fact, it is still interesting that the median T_{\max} for IV morphine and SC morphine plus rHuPH20 was five minutes for both. In fact, seven of the 12 patients had a T_{\max} of five minutes with SC morphine plus rHuPH20. Given the variability in this small study, a trial with a much larger

study population and finer time points is needed to determine how rHuPH20-enhanced SC morphine compares with IV morphine in terms of absorption and therapeutic response.

For both morphine and its active metabolite, total exposure was similar following SC morphine with and without rHuPH20. For morphine, total exposure appeared significantly greater with both SC routes than with IV, whereas for the active metabolite, there was no significant difference between either SC and the IV routes of administration. This difference in total exposure between morphine and M6G with SC vs. IV administration may be explained by the lack of sampling before five minutes, when the concentration of IV-administered morphine would have been highest. For both morphine and M6G, bioavailability was similar for all three methods of administration. Morphine administration with rHuPH20 appeared safe and was well tolerated. The apparent complete SC absorption of morphine and the ability of rHuPH20 to enhance the kinetics of this absorption are consistent with earlier findings using animal-derived preparations of SC

hyaluronidase coinjected with other agents. In a small crossover study in six volunteers, Lipschitz et al.¹³ demonstrated that the addition of hyaluronidase to radiolabeled saline increased the rate of SC absorption and led to complete absorption compared with IV delivery. Addition of hyaluronidase to an anesthetic mixture containing 2% lidocaine hydrochloride and 0.5% bupivacaine hydrochloride has also been shown to improve anesthesia,¹⁴ and T_{\max} values for bupivacaine and lidocaine have been shown to be significantly reduced when these agents are combined with hyaluronidase in patients undergoing cataract surgery.¹⁵

In previous studies comparing IV with SC morphine for management of cancer pain, efficacy was similar with the two routes, but SC titration required more time and higher doses than IV titration.^{10,16} Shortening T_{\max} and raising C_{\max} by adding rHuPH20 to SC morphine could potentially result in a quicker onset of analgesia achieved with lower doses. However, because efficacy was not measured in this study, the clinical implications of the pharmacokinetic differences among the three methods of administration cannot be determined.

Morphine response has been shown to vary among patients, with wide variations in doses required to achieve analgesia with both the IV and the SC routes.¹⁰ Because doses are not generally individualized in pharmacokinetic studies, patients who were previously stabilized on effective individualized regimens of nonmorphine opioid therapy, and had thus demonstrated opioid tolerance, were selected for this pharmacokinetic study. Similar to other such studies, this study was not designed to evaluate analgesic efficacy. Future studies are needed to clarify differences in analgesic response among these methods of administration, using individualized doses that have been titrated to achieve optimal response.

In conclusion, the results from this pharmacokinetic and safety study suggest that, in patients requiring opioid analgesia, including those for whom IV administration is not feasible or practical, morphine SC coinjected with rHuPH20 provides pharmacokinetic characteristics superior to those of SC morphine without rHuPH20. These positive pharmacokinetic and safety results warrant further studies to determine the clinical benefit of faster absorption of morphine delivered SC with rHuPH20.

Acknowledgments

The authors acknowledge the following individuals and organizations for their contributions: Quest Diagnostics, Inc. (Van Nuys, CA) for clinical laboratory services; MicroConstants, Inc. (San Diego, CA) for bioanalytical pharmacokinetic services; and Linda Heiner, RN (Halozyme Therapeutics, Inc., San Diego, CA), for overseeing the conduct of the trial.

References

1. Bookbinder LH, Hofer A, Haller MF, et al. A recombinant human enzyme for enhanced interstitial transport of therapeutics. *J Control Release* 2006;114:230–241.
2. Frost GI. Recombinant human hyaluronidase (rHuPH20): an enabling platform for subcutaneous drug and fluid administration. *Expert Opin Drug Deliv* 2007;4:427–440.
3. Grune F, Schrappe M, Basten J, et al. Phlebitis rate and time kinetics of short peripheral intravenous catheters. *Infection* 2004;32:30–32.
4. Kurul S, Saip P, Aydin T. Totally implantable venous-access ports: local problems and extravasation injury. *Lancet Oncol* 2002;3:684–692.
5. Monreal M, Davant E. Thrombotic complications of central venous catheters in cancer patients. *Acta Haematol* 2001;106:69–72.
6. Lugo RA, Kern SE. Clinical pharmacokinetics of morphine. *J Pain Palliat Care Pharmacother* 2002;16:5–18.
7. Momeni M, Crucitti M, De Kock M. Patient-controlled analgesia in the management of postoperative pain. *Drugs* 2006;66:2321–2337.
8. Koshy RC, Kuriakose R, Sebastian P, Koshy C. Continuous morphine infusions for cancer pain in resource-scarce environments: comparison of the subcutaneous and intravenous routes of administration. *J Pain Palliat Care Pharmacother* 2005;19:27–33.
9. Hanks GW, de Conno F, Cherny N, et al. Morphine and alternative opioids in cancer pain: the EAPC recommendations. *Br J Cancer* 2001;84:587–593.
10. Elsner F, Radbruch L, Loick G, Gartner J, Sabatowski R. Intravenous versus subcutaneous morphine titration in patients with persisting exacerbation of cancer pain. *J Palliat Med* 2005;8:743–750.
11. Kilpatrick GJ, Smith TW. Morphine-6-glucuronide: actions and mechanisms. *Med Res Rev* 2005;25:521–544.
12. Hanna MH, Elliott KM, Fung M. Randomized, double-blind study of the analgesic efficacy of morphine-6-glucuronide versus morphine sulfate for

postoperative pain in major surgery. *Anesthesiology* 2005;102:815–821.

13. Lipschitz S, Campbell AJ, Roberts MS, et al. Subcutaneous fluid administration in elderly subjects: validation of an under-used technique. *J Am Geriatr Soc* 1991;39:6–9.

14. Morsman CD, Holden R. The effects of adrenaline, hyaluronidase and age on peribulbar anaesthesia. *Eye* 1992;6(Pt 3):290–292.

15. Nathan N, Benrhaiem M, Lotfi H, et al. The role of hyaluronidase on lidocaine and bupivacaine pharmacokinetics after peribulbar blockade. *Anesth Analg* 1996;82:1060–1064.

16. Nelson KA, Glare PA, Walsh D, Groh ES. A prospective, within-patient, crossover study of continuous intravenous and subcutaneous morphine for chronic cancer pain. *J Pain Symptom Manage* 1997;13:262–267.