

Original Article

The INFUSE-Morphine IIB Study: Use of Recombinant Human Hyaluronidase (rHuPH20) to Enhance the Absorption of Subcutaneous Morphine in Healthy Volunteers

Jay R. Thomas, MD, PhD, Richard C. Yocum, MD, Michael F. Haller, PhD, and Jocelyne Flament, MD

Department of Supportive Care Medicine (J.R.T.), City of Hope, Duarte, California; Department of Drug Development and Medical Affairs (R.C.Y.), Rockwell Medical Technologies, Inc., Wixom, Michigan; Department of Research and Development (M.F.H.), Halozyne Therapeutics, Inc., San Diego, California, USA; and European Organisation for Research and Treatment of Cancer AISBL-IVZW (J.F.), Brussels, Belgium

Abstract

Morphine is usually given intravenously (IV) for the treatment of moderate-to-severe pain, but subcutaneous (SC) administration is a viable alternative for parenteral delivery. The pharmacokinetics of SC morphine may be enhanced by coadministration with a hyaluronidase product. In this Phase IV, double-blind, randomized, crossover study, 18 healthy adults received a single dose of 2 mg morphine SC with 150 U of recombinant human hyaluronidase (rHuPH20), SC with 0.9% normal saline, or IV on three consecutive days. The primary endpoint was time to maximum plasma morphine concentration (T_{max}) for SC injection with rHuPH20 vs. SC injection without rHuPH20. Safety and tolerability were assessed each study day, the day after the last injection, and 28 days after the last injection. After SC dosing, morphine mean T_{max} was significantly shorter with rHuPH20 than without it. Mean maximum plasma morphine concentration (C_{max}) after SC dosing was 29% greater with rHuPH20 than without rHuPH20 ($P = 0.023$), although the extent of exposure of morphine was similar. T_{max} was shortest and C_{max} was highest with IV administration. For the major active metabolite of morphine, morphine-6-glucuronide, mean T_{max} after SC morphine was significantly shorter with rHuPH20 than without rHuPH20 (a difference of approximately 17.5 minutes; $P = 0.0169$). Coadministration of morphine with rHuPH20 appeared safe and well tolerated. Compared with SC morphine alone, rHuPH20 shortens morphine T_{max} and raises C_{max} in healthy adults, without changing the extent of exposure. *J Pain Symptom Manage* 2009;38:673–682. © 2009 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.

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Deerfield, IL, and Dr. Yocum was employed by Halozyne Therapeutics, Inc. San Diego, CA.

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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

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Key Words

Recombinant human hyaluronidase, subcutaneous, morphine, hospice, pain, pharmacokinetics, interstitial, palliative care, difficult venous access, parenteral

Introduction

Parenteral morphine is usually delivered intravenously (IV) for the treatment of moderate-to-severe pain, but administration by this route may be challenging or impossible in patients presenting with difficult venous access, in uncooperative or delirious patients, or in a patient care setting that does not easily accommodate IV access (e.g., a home or a non-skilled nursing care facility). The subcutaneous (SC) route is generally preferred for patients who require parenteral morphine and for whom IV administration either is not an option or is not desired. Access via the SC route is easier than it is with IV, the number of injection sites is virtually unlimited, less skill is needed for administration, rotation of injection sites is less frequent, the risk of systemic infection is reduced, and the cost is lower.¹⁻³

Given enough time, SC morphine has been shown to be as effective as IV morphine for palliative care in cancer patients,⁴⁻⁷ and this approach avoids some potential complications and expenses associated with IV catheters.⁸⁻¹¹ However, SC injections can be limited by the low compliance of the human tissue space, unless they are augmented with a "spreading agent" such as SC hyaluronidase.³ This enzyme temporarily decreases the viscosity of the interstices, thereby reducing the barrier to the movement of molecules through the SC space.¹²

Until recently, all hyaluronidase formulations were animal-derived, but a recombinant human form, recombinant human hyaluronidase (rHuPH20), is now approved in the United States as an adjuvant to increase the absorption and dispersion of other injected drugs. It exhibits no allergenicity after single-dose, intradermal injection in humans,¹³ and it significantly enhances the dispersion of coadministered molecules in preclinical models.¹² Clinical findings indicate that rHuPH20 significantly increases the absorption of SC rehydration fluids¹⁴ and significantly enhances the pharmacokinetics (PKs) of SC morphine in

palliative care patients (see accompanying article). Case reports in hospice patients support its safety and tolerability in facilitating both SC hydration and drug administration.¹⁵ The duration of effect in the hypodermis is approximately 24 to 48 hours, which is consistent with the rapid turnover of its principal substrate, hyaluronan.³ All of these results suggest that rHuPH20 has the potential to improve drug absorption after SC drug injection in patients for whom IV drug delivery may not be practical (e.g., those with limited venous access).

In the current trial, called the INcreased Flow Using Subcutaneously-Enabled Morphine IIB (INFUSE-Morphine IIB) study, the PKs, safety, and tolerability of morphine administered SC were compared in the presence and absence of concomitant rHuPH20 in healthy adults. The SC results also were compared with those of IV morphine administration.

Methods

Study Design and Subjects

This Phase IV, double-blind, randomized study was conducted in 18 healthy male and female volunteers using a three-way crossover design. This study was approved by an institutional review board (IRB) convened at MDS Pharma Services, and all subjects provided IRB-approved written informed consent. The study was not blinded with respect to IV vs. SC morphine administration, but it was blinded with respect to SC administration with placebo vs. SC administration with rHuPH20.

Eligible subjects included healthy nonsmoking (or smokers using <10 cigarettes/day) males or nonpregnant, nonlactating females 19-65 years of age with adequate venous access in both upper extremities. Female subjects were required to use an acceptable form of contraception, to be surgically sterile for at least six months, to be postmenopausal for at least two years, or to be postmenopausal for less than two years, with a follicle-stimulating hormone level ≥ 40 mIU/mL. Subjects also were required

to refrain from using nicotine products, alcohol, and beverages containing caffeine or caffeine-like substances for 24 hours before screening, 24 hours before planned clinic admission, and four hours after their last dose of study drug.

Exclusion criteria included a history of drug or alcohol abuse; a confirmed positive result on screening or admission urine drug tests; a confirmed positive pregnancy test; a confirmed positive hepatitis B, hepatitis C, or HIV test; known hypersensitivity or history of any toxicity to morphine or naloxone; contraindication for morphine or rHuPH20; and morphine use within four days of the first study drug administration. Potential subjects also were excluded if they had a known allergy to hyaluronidase or any other ingredient in the formulation of rHuPH20; had a serum hemoglobin <12 g/dL; had signs of edema, infection, or any other lower extremity or pelvic disorder that might affect SC absorption; had made a blood donation or had experienced a significant loss of blood within 56 days of enrollment; had made a plasma donation within seven days of enrollment; or had participated in a study of any investigational drug or device within 30 days of enrollment. Also excluded were those subjects with any medical history, screening physical examination finding, or clinical laboratory result that, in the opinion of the investigator, would preclude safe participation in this study or which could adversely affect the interpretation of the study results.

Treatments

For three consecutive days, each eligible subject received a single injection of 2 mg morphine (injection volume = 0.4 mL) by one of the following methods: SC + rHuPH20 (Hyle-nex® 150 U/mL; Baxter International, Inc., Deerfield, IL), SC + placebo (saline), and IV alone. For the SC injections, 1 mL of blinded rHuPH20 150 U or saline was injected first, followed by morphine and 1 mL of 0.9% sodium chloride (saline) flush through the same catheter. The IV morphine injections were followed by 3 mL of saline flush. Thus, the total volume was 2.4 mL for each SC injection and 3.4 mL for the IV injection. The method of injection given each day was determined according to the randomization schedule shown in Fig. 1.

A 24-gauge butterfly needle was used for each SC injection. These injections were made in the abdomen approximately at the level of the umbilicus (as allowed by skin condition) and approximately 15 cm (minimum 10 cm) from the margin of the navel. The first SC injection for a given subject was made in the left side of the abdomen, and the second was made symmetrically on the right side. IV injections were made using an indwelling catheter. Subjects fasted 10 hours before and four hours after each injection.

Blood Collection for Pharmacokinetic Analysis

Blood was collected by venipuncture or from an indwelling IV catheter for PK profiling, based on plasma concentrations of morphine and its major active metabolite, morphine-6-glucuronide (M6G). Blood samples (10 mL) were drawn immediately preinjection and 1, 3, 6, 9, 12, 15, 20, 25, 30, 45, 60, 120, and 360 minutes after completion of injection. Assays for morphine and M6G were performed using a validated liquid chromatography-tandem mass spectrometry method. The analytical range for morphine and M6G was 0.25 to 50.0 ng/mL.

Pharmacokinetic Analysis

A noncompartmental approach was used for calculating the PK parameters. The PK parameters included 1) area under the plasma concentration curve over time from Time 0 to the last measurable concentration (AUC_{0-t}), calculated by the linear trapezoidal method, 2) maximum plasma concentration (C_{max}), 3) time to C_{max} (T_{max}), and 4) apparent first-order terminal elimination half-life ($t_{1/2}$), calculated as $0.693/kel$, where kel is the first-order terminal elimination rate calculated by linear least-squares regression analysis, using the maximum number of points in the terminal log-linear phase. Other PK parameters were also evaluated in this study: area under the plasma concentration curve over time from Time 0 to the last measurable concentration (AUC_{0-inf}), the ratio of AUC_{0-t} to AUC_{0-inf} , and the relative morphine bioavailability (F) calculated as $(\text{dose IV}/\text{dose SC}) \times (AUC_{0-inf SC}/AUC_{0-inf IV})$.

Safety and Tolerability

Safety and tolerability were assessed on each study day (Days 1, 2, and 3) through physical examinations, signs and symptoms at injection

Day 1	Day 2	Day 3
SC + rHuPH20	SC + Saline	IV
SC + rHuPH20	IV	SC + Saline
SC + Saline	SC + rHuPH20	IV
SC + Saline	IV	SC + rHuPH20
IV	SC + rHuPH20	SC + Saline
IV	SC + Saline	SC + rHuPH20

Fig. 1. Study design: six treatment sequences for administration of 2 mg morphine.

sites (e.g., pain, rash, edema), vital signs (blood pressure, heart rate, and respiratory rate), adverse events, and the need for concomitant medications. Injection site edema and rash were independently graded for each clinical sign by the investigative site staff on a 0 (none) to 4 (severe) categorical scale. Edema was assessed at three minutes, four hours, and 24 hours postinjection; rash was assessed at 20 minutes, four hours, and 24 hours postinjection. The research participant's subjective assessment of pain at the catheter site was measured five minutes after the completion of the injection by means of a validated visual analogue scale (VAS) with a range of 0 (no pain) to 100 mm (most severe pain). Follow-up evaluations for vital signs, physical examination, injection site rash or edema, and adverse events were also completed the day after the last injection (Day 4), and adverse events were evaluated 28 days after the last injection (Day 31).

Statistical Analyses

An analysis of variance (ANOVA) was performed on untransformed T_{\max} values and natural log-transformed values for AUC_{0-b} , AUC_{0-inf} , and C_{\max} . The ANOVA model included treatment (dose types), sequence, day,

and the treatment \times day interaction (carryover effect) as fixed effects with both between-subject and within-subject error terms. To model the correlation within each subject, the variance-covariance matrix structure first-order autoregressive was used. Three pair-wise comparisons were performed sequentially in the following order: SC injection with rHuPH20 vs. SC injection without rHuPH20, SC injection with rHuPH20 vs. IV injection, and SC injection without rHuPH20 vs. IV injection. The comparison of T_{\max} for SC injection with rHuPH20 vs. T_{\max} for SC without rHuPH20 was the primary analysis. All statistical tests were performed at a two-sided alpha level of 5%.

The sample size was based on the within-subject comparison of the estimated difference in the mean T_{\max} for SC injection with and without rHuPH20. The median T_{\max} of morphine injected SC without rHuPH20 is estimated to be 15 minutes.¹⁶ The coefficient of variation in PK studies generally ranges from 0.3 to 0.5, and intrasubject correlation ranges from 0.3 to 0.6. With these assumptions and a sample size of 12, the study would have a power >99% to detect a 50% decrease in T_{\max} (mean $T_{\max} \leq 7.5$ minutes for SC injection with rHuPH20). To account for possible nonevaluable subjects,

18 subjects were enrolled and treated to ensure that one additional subject was treated in each of the six possible treatment sequences.

Results

Subjects

A total of 18 subjects were enrolled; all subjects completed the study and were evaluable.

The study population included nine males and nine females. The mean age was 37.3 years (range 19–60 years), the mean weight was 75.1 kg (range 51.7–105.2 kg), and the mean height was 172.6 cm (range 152–188 cm).

Pharmacokinetics

Morphine. Plasma concentration curves for the three injection conditions are shown in Fig. 2,

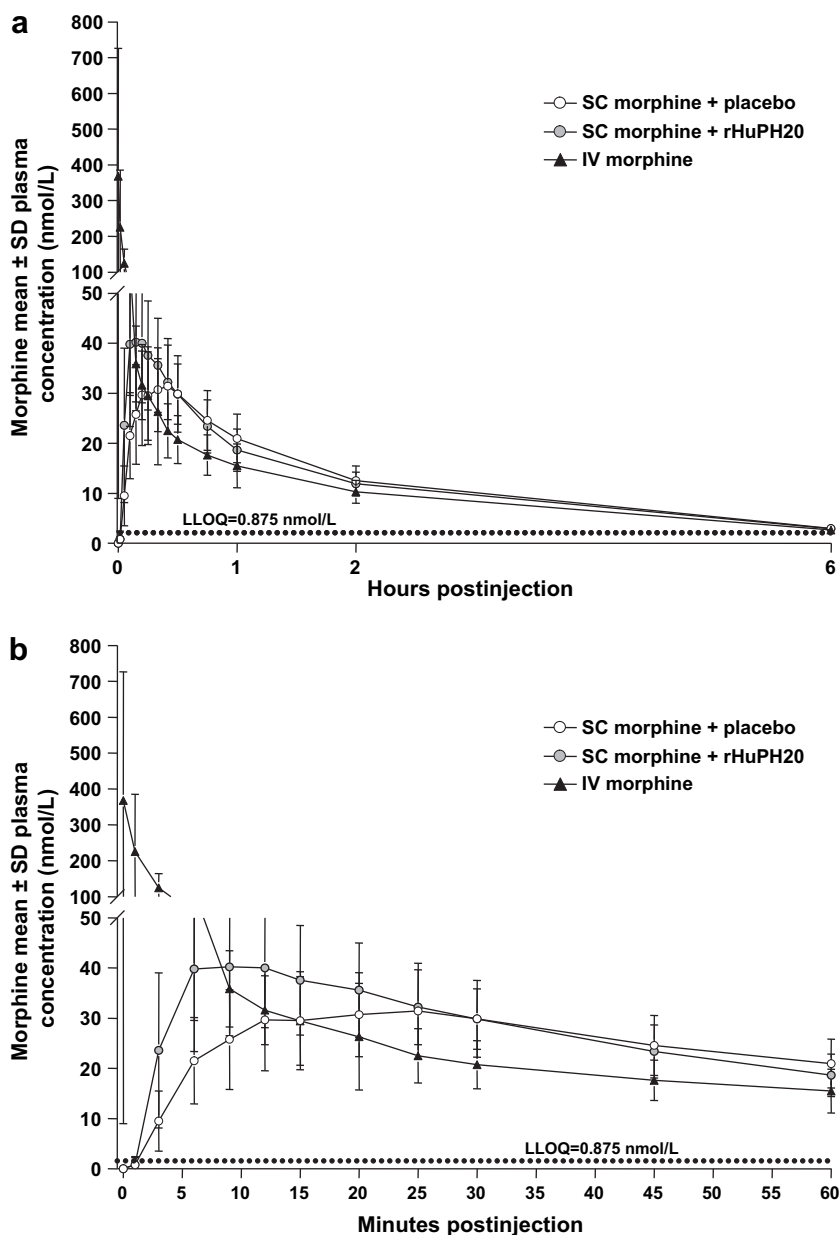


Fig. 2. a) Pharmacokinetic curves for plasma morphine concentration over six hours postinjection and b) detailed view over the first 60 minutes postinjection for each administration method. LLOQ, lower limit of quantification.

Table 1
Pharmacokinetics of Morphine

PK Parameters (N=18)	Morphine SC + rHuPH20	Morphine SC + Saline	Morphine IV
Mean T_{\max} (minutes) ^a	11.2 (95% CI: 8.7–13.6)	19.1 (95% CI: 16.1–22.1)	1.8 (95% CI: 1.1–2.6)
Geometric mean C_{\max} (nmol/L) ^b	43.1 (95% CI: 36.1–50.1)	33.5 (95% CI: 28.0–38.9)	211.1 (95% CI: 176.8–245.4)
Geometric mean AUC_{0-t} ($\mu\text{mol}\cdot\text{min}/\text{L}$) ^c	4.3 (95% CI: 4.0–4.7)	4.3 (95% CI: 3.9–4.6)	4.4 (95% CI: 4.0–4.7)
Mean elimination $t_{1/2}$ (minutes)	115 \pm 15.28	110 \pm 14.55	122 \pm 16.80
Bioavailability (%)	99	99	100

^a $P < 0.0001$ for morphine SC + rHuPH20 vs. morphine SC + saline; $P < 0.0001$ for morphine IV vs. morphine SC + rHuPH20; $P < 0.0001$ for morphine IV vs. morphine SC + saline.

^b $P = 0.022$ for morphine SC + rHuPH20 vs. morphine SC + saline; $P < 0.0001$ for morphine IV vs. morphine SC + rHuPH20; $P < 0.0001$ for morphine IV vs. morphine SC + saline.

^cNo significant differences among treatments.

and PK parameters are summarized in Table 1. The mean T_{\max} for SC morphine was 11.2 minutes (95% confidence interval [CI] 8.7–13.6 minutes) with rHuPH20 and 19.1 minutes (95% CI 16.1–22.1 minutes) without rHuPH20. The ANOVA comparison shows that T_{\max} occurred approximately 8 minutes earlier when SC morphine was administered with rHuPH20 than without it ($P < 0.0001$). As expected, mean T_{\max} was shortest with IV injection (1.8 minutes [95% CI 1.1–2.6 minutes], $P < 0.001$ vs. each SC regimen) and occurred most frequently at the first postdose sample. Median T_{\max} was 10.5 minutes (range 6.0–25.0 minutes) for SC morphine with rHuPH20, 20.0 minutes (range 12.0–30.0 minutes) for SC morphine with saline,

and 1.0 minute (range 1.0–6.0 minutes) for IV morphine.

After SC injection of morphine with rHuPH20, the geometric mean C_{\max} of 43.1 nmol/L (95% CI 36.1–50.1) was 29% greater than that for SC injection with saline, which was 33.5 nmol/L (95% CI 28.0–38.9; $P = 0.023$). As expected, the highest mean C_{\max} value was observed after IV injection: 211.1 nmol/L (95% CI 176.8–245.4). The extent of exposure (AUC_{0-t}) for morphine was consistent across all three treatments, with geometric mean values of 4.3 or 4.4 $\mu\text{mol}\cdot\text{min}/\text{L}$. All 95% CI values for each treatment were within the range of 3.9–4.7 $\mu\text{mol}\cdot\text{min}/\text{L}$. Mean values for both $t_{1/2}$ and relative

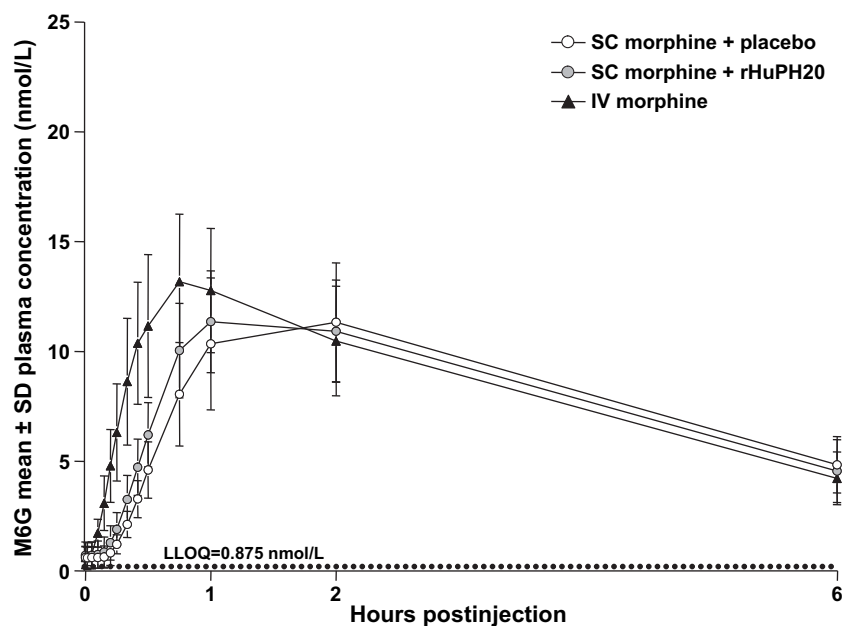


Fig. 3. Pharmacokinetic curves for M6G plasma concentration over the first six hours postinjection for each administration method. LLOQ, lower limit of quantification.

Table 2
Pharmacokinetics of M6G

PK Parameters ($n = 18$) ^a	Morphine SC + rHuPH20	Morphine SC + Saline	Morphine IV
Mean T_{\max} (minutes) ^b	79.2 (95% CI: 64.3–94.0)	96.7 (95% CI: 81.7–111.6)	53.4 (95% CI: 44.5–62.3)
Geometric mean C_{\max} (nmol/L) ^c	10.9 (95% CI: 9.8–12.0)	10.7 (95% CI: 9.6–11.8)	12.6 (95% CI: 11.3–13.8)
Geometric mean AUC_{0-t} ($\mu\text{mol}\cdot\text{min}/\text{L}$) ^d	2.7 (95% CI: 2.5–2.9)	2.7 (95% CI: 2.5–2.9)	2.8 (95% CI: 2.6–3.1)
Mean elimination $t_{1/2}$ (minutes)	176 \pm 26.15 ($n = 12$)	175 \pm 30.36 ($n = 7$)	183 \pm 30.45 ($n = 17$)

^aFor some subjects, $t_{1/2}$ could not be estimated.

^b $P = 0.0169$ for morphine SC + rHuPH20 vs. morphine SC + saline; $P = 0.0008$ for morphine IV vs. morphine SC + rHuPH20; $P < 0.0001$ for morphine IV vs. morphine SC + saline.

^cNo significant difference between morphine SC + rHuPH20 vs. morphine SC + saline; $P = 0.0006$ for morphine IV vs. morphine SC + rHuPH20; $P = 0.0001$ for morphine IV vs. morphine SC + saline.

^dNo significant difference between morphine SC + rHuPH20 vs. morphine SC + saline; $P = 0.039$ for morphine IV vs. morphine SC + rHuPH20; $P = 0.032$ for morphine IV vs. morphine SC + saline.

bioavailability (F) also were similar across treatments, ranging from 1.83 to 2.03 hours and 99.2%–100.0% (by definition for IV administration), respectively.

Morphine-6-Glucuronide. The results for the major active metabolite of morphine generally were similar to those for morphine (Fig. 3, Table 2). M6G appeared rapidly in plasma after both SC and IV morphine administration. After SC administration, the mean T_{\max} for M6G was 79.2 minutes with rHuPH20 and 96.7 minutes without rHuPH20. The ANOVA comparison indicated that M6G T_{\max} occurred

about 17.5 minutes earlier with rHuPH20 than without it ($P = 0.0169$). After IV morphine administration, the mean T_{\max} was 53.4 minutes. Median T_{\max} values were 60 minutes after SC administration with rHuPH20 and 120 minutes without rHuPH20, compared with 45 minutes after IV administration. The geometric mean peak M6G plasma concentrations (C_{\max}) were similar after morphine SC injection with or without rHuPH20 (10.9 and 10.7 nmol/L, respectively) and close to the value for IV administration (12.6 nmol/L). The geometric mean AUC_{0-t} values were similar for all three treatments: 2.7 to

Table 3
Number of Subjects with Adverse Events (All Causality)

Adverse Event ^a	Morphine SC + rHuPH20, n (%)	Morphine SC + Saline, n (%)	Morphine IV, n (%)
Any adverse event	16 (88.9)	15 (83.3)	9 (50.0)
Injection site events	16 (88.9)	15 (83.3)	1 (5.6)
Injection site rash	11 (61.1)	11 (61.1)	0
Injection site pruritus	8 (44.4)	2 (11.1)	0
Injection site edema	6 (33.3)	3 (16.7)	0
Injection/infusion site erythema	4 (22.2)	4 (22.2)	1 (5.6)
Injection site bruising	0	1 (5.6)	0
Vessel puncture site bruise	0	1 (5.6)	0
Noninjection site events	3 (16.7)	3 (16.7)	8 (44.4)
Headache	1 (5.6)	0	2 (11.1)
Dizziness	1 (5.6)	2 (11.1)	0
Nausea	1 (5.6)	1 (5.6)	1 (5.6)
Eye pain	1 (5.6)	0	0
Ocular hyperemia	1 (5.6)	0	0
Dysgeusia	0	0	1 (5.6)
Paresthesia	0	0	1 (5.6)
Sensory disturbance	0	0	1 (5.6)
Tremor	0	0	1 (5.6)
Sensation of heaviness	0	1 (5.6)	2 (11.1)
Back pain	0	0	1 (5.6)
Musculoskeletal stiffness	0	0	1 (5.6)
Abdominal pain upper	0	0	1 (5.6)
Pallor	0	0	1 (5.6)
Hyperhidrosis	0	0	1 (5.6)

^aAdverse events are classified according to MedDRA version 9.0 (MedDRA MSSO, Chantilly, VA; www.meddramsso.com) preferred terms.

2.8 $\mu\text{mol}\cdot\text{min}/\text{L}$. For both C_{max} and AUC, the differences between IV administration and each SC administration were small but statistically significant ($P < 0.05$).

Safety and Tolerability

Safety. Sixteen (88.9%) of 18 subjects experienced at least one adverse event (Table 3). All adverse events were mild or moderate in severity, and there were no serious or severe adverse events or deaths. Systemic, noninjection site adverse events occurred more often after IV morphine (44.4%) than after SC morphine administered with or without rHuPH20 (16.7% for each treatment). There were no substantial differences with respect to the overall incidence of injection site events for SC morphine injection with or without rHuPH20 (88.9% vs. 83.3%). The incidence of individual injection site events was similar for SC injections with or without rHuPH20, with the exception of pruritus (44.4% with rHuPH20 vs. 11.1% without) and edema (33.3% with rHuPH20 vs. 16.7% without). The pruritus generally began within five minutes of injection and usually lasted less than one hour. Physical examinations and vital signs indicated no meaningful changes as a result of any of the treatments.

Tolerability. There were no meaningful differences among injection conditions with respect to subjects' assessments of the level of discomfort

at the catheter site as measured by VAS. Across all three treatments, the mean VAS scores were similar at baseline and five minutes after the end of the injections (less than 6 out of a possible range of 0–100 mm) (Fig. 4).

Subjective assessments of injection site edema and rash (graded on a scale of 0–4) are summarized in Fig. 5. After SC morphine administration with rHuPH20, two subjects (11.1%) had minimal edema at 0.05 hours and two subjects (11.1%) had minimal edema at four hours. Mild edema was observed in two subjects (11.1%) at 0.05 hour. By comparison, after SC morphine administration without rHuPH20, two subjects experienced minimal edema at 0.05 hour. No other subjects exhibited edema at any time point. At 0.33 hours after injection, minimal to mild rash was noted in nine subjects (50%) after SC administration with rHuPH20 vs. 11 subjects (61%) after SC administration without rHuPH20. Moderate rash was observed in two subjects (11.1%) after SC administration with rHuPH20 and in no subjects after SC administration without rHuPH20.

Discussion

In this study, concomitant SC administration of rHuPH20 and morphine enhanced the absorption of morphine compared with SC coadministration with saline, significantly reducing the T_{max} by 8 minutes, a 42% improvement,

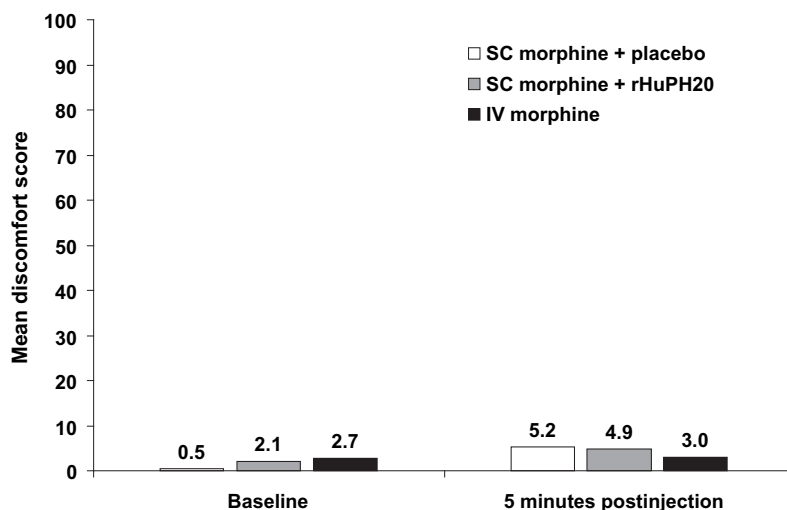


Fig. 4. Mean subjective discomfort at injection site at baseline and five minutes. 0 = no discomfort, 100 = worst possible discomfort (100 mm VAS scale).

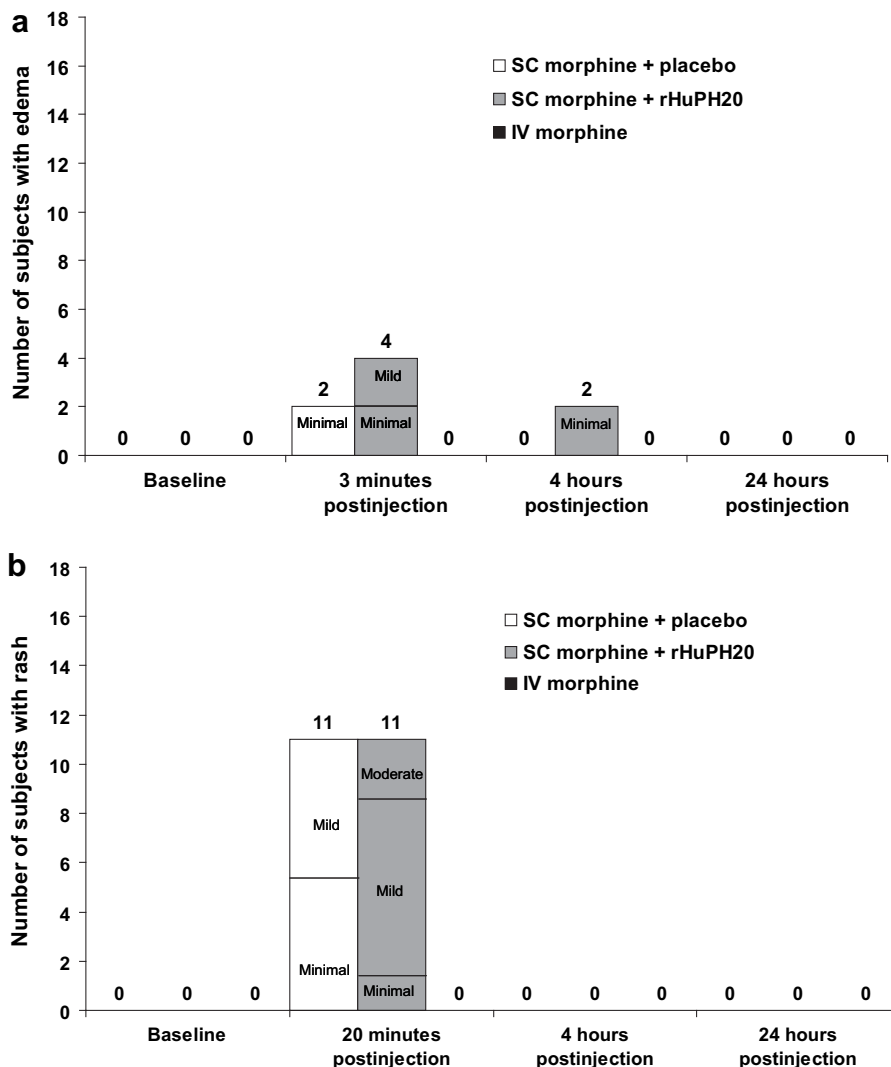


Fig. 5. a) Edema and b) rash assessments.

and increasing the C_{max} by 28.6%. This finding raises the possibility that rHuPH20 may enhance the onset of analgesia from SC morphine. Given the small sample size and variability in this study, a larger study of patients with pain will be required to determine the true magnitude of the difference in onset of analgesia and whether these PK findings are clinically relevant. SC administration of morphine with or without rHuPH20 provided total systemic drug exposure for morphine and its active metabolite that was comparable to that observed with IV administration. SC administration of morphine with or without rHuPH20 was well tolerated and was associated with fewer systemic adverse events than was IV morphine.

The apparent complete SC absorption of morphine and the ability of rHuPH20 to enhance the kinetics of this absorption are consistent with earlier studies of animal-derived hyaluronidase preparations injected with other agents. The addition of animal-derived hyaluronidase to anesthetics used for ophthalmic anesthesia has been shown to improve drug absorption and pain control.^{17–20} Similar to the present study, the addition of hyaluronidase did not significantly change AUC or $t_{1/2}$.²⁰

In conclusion, the results of this randomized, double-blind, crossover study in healthy volunteers indicate that SC morphine plus rHuPH20 provides PK characteristics superior to those of SC morphine alone, including

a shorter T_{\max} and a higher C_{\max} . SC morphine appears safe and is well tolerated, with a lower risk of systemic adverse events than IV morphine. These positive PK and safety results suggest that, in patients requiring parenteral morphine, including those for whom IV administration is not feasible, SC morphine plus rHuPH20 may offer preferable PKs over SC morphine alone, leading to a potentially more rapid analgesic effect. The timing and extent of pain relief with and without rHuPH20 warrant further evaluation.

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