Exploring Clinical and Pharmacological Effects of Nalbuphine HCl ER Tablets in Hemodialysis Subjects with Pruritus

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Introduction

- Uremic pruritus is an itch disorder associated with end-stage renal disease (ESRD) that can be severe and debilitating.
  - Uremic pruritus is associated with significant deleterious impairments of patient quality of life, including depression and disruption of sleep.
  - A 17% increase in mortality rate, attributed to sleep disturbances, is associated with moderate to severe pruritus.[1]
  - Uremic pruritus has been correlated to an imbalance between the endogenous opiate ligands beta endorphin (μ-agonist) and dynorphin A (κ-agonist).[2]
  - Itch intensity is reported to fluctuate and appears to be cyclical in some patients. However, patients with moderate to severe pruritus have a more persistent itch (daily or nearly daily).
- Nalbuphine HCl is a mixed μ-antagonist/κ-agonist opioid drug, currently only available in a parenteral formulation, and approved for the indication of the relief of moderate to severe pain.
  - Nalbuphine was shown to significantly reduce Substance-P induced itch in a mouse model.[3]
  - Nalbuphine has been shown to attenuate morphine-induced pruritus in a number of clinical studies.[4]
  - The mechanism of action suggests that it may be effective in the treatment of patients with uremic pruritus.

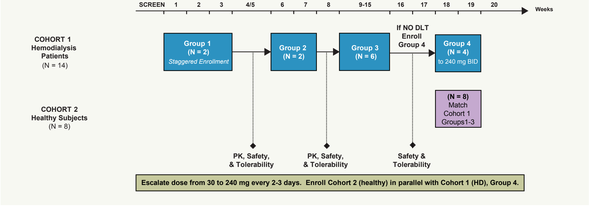
Objectives

This study was designed to:

- Assess the safety and pharmacokinetics (PK) of nalbuphine administered orally as nalbuphine HCl extended release (ER) tablets in hemodialysis (HD) patients with mild to moderate pruritus.
- Explore the clinical and pharmacological effects of nalbuphine on pruritus using a visual analog score (VAS).

Methods

Figure 1: Study Design - Open-Label, Single Site, Multiple Escalating Dose



Study Design

- All subjects received the first dose (30 mg single dose) on Day 1; dose was subsequently escalated to twice daily (BID) 30 mg, 60 mg, 120 mg, and 180 mg over 13 days except for subjects in Cohort 1, Group 4 who were dosed up to 240 mg BID over 15 days. Subjects remained at each dose level for a minimum of 4 consecutive doses.
  - Titration scheme mimics intended use in the clinic.
  - Dialysis was conducted at same time each day over 3 to 3.5 hours using a Fresenius high-flux dialyzer with polysulfone membrane.
  - The study was sponsored by Trevi Therapeutics. Institutional review board approval and signed informed consent forms were obtained prior to initiating the study.

Study Drug and Administration

- Nalbuphine HCl ER tablets (Trevi Therapeutics) were administered with food in multiples of 30-mg tablets to achieve the desired dose. For HD patients on dialysis days, the morning dose was administered no earlier than 6 hours and no later than 4 hours prior to dialysis.

Safety Assessments

- Evaluation of adverse events (AEs), clinical laboratory results, vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature), extensive oxygen saturation (SpO_2) monitoring, 12-lead electrocardiogram (ECG) measurements, and physical examination findings.

Pharmacokinetic Analyses

- Pharmacokinetic parameters were derived from plasma and dialysate nalbuphine concentration versus time data using noncompartmental analysis with WinNonlin Professional v6.2.1.

Assessment of Itch Severity

- HD patients self-reported their worst daytime and nighttime itch intensity twice a day using a VAS scale of 0-10. Average worst VAS score and change from baseline were calculated for each HD patient at each dose level.
- Changes in VAS measure of itch intensity of at least 20% in either direction were considered indicative of a change in patient-rated pruritus severity.[5]

Results

Patient Characteristics

- 24 subjects were enrolled: 15 HD patients in Cohort 1 (12 males and 3 females), of whom 13 completed the study and 2 discontinued; 9 healthy subjects in Cohort 2 (7 males and 2 females), of whom 8 completed the study and 1 discontinued. Healthy subjects were matched to HD patients for gender, body mass index, and age (**Table 1**).

Table 1: Subject Demographics

	Hemodialysis n = 15	Healthy n = 9 = 24	Overall
Age, (years)			
Mean (SD)	46.6 (10.1)	50.1 (5.1)	47.9 (8.6)
Minimum, maximum	25, 61	39, 57	25, 61
Gender, n (%)			
Female	3 (20.0)	2 (22.2)	5 (20.8)
Male	12 (80.0)	7 (77.8)	19 (79.2)
Race, n (%)			
White	4 (26.7)	5 (55.6)	9 (37.5)
Black or African American	11 (73.3)	4 (44.4)	15 (62.5)
Ethnicity, n (%)			
Hispanic or Latino	1 (6.7)	0 (0.0)	1 (4.2)
Not Hispanic or Latino	14 (93.3)	9 (100.0)	23 (95.8)
Weight, (kg)			
Mean (SD)	88.6 (19.0)	86.5 (7.6)	87.8 (15.5)
Minimum, maximum	52.0, 120.9	75.5, 96.1	52.0, 120.9
Body Mass Index, (kg/me)			
Mean (SD)	29.5 (4.6)	28.9 (2.2)	29.3 (3.9)
Minimum, maximum	21.0, 40.7	25.2, 31.1	21.0, 40.7

Pharmacokinetics

- Over the 30 mg to 180 mg dose range, exposure increased in a near dose-proportional fashion with no evidence of accumulation beyond that expected of repeat dosing.
- Overall exposure in HD patients was higher than in healthy subjects (**Figure 2**).[6]
- Nalbuphine exposure in HD patients on dialysis days and non-dialysis days was comparable (**Figure 3**).
  - Analysis of nalbuphine concentration in dialysate indicated that about 1% of the dose was removed during a standard high-flux 3-4 hour hemodialysis session over the dosing range.

Figure 2: Plasma Concentration of Nalbuphine Following a Single 30-mg and Repeat 180-mg Dose

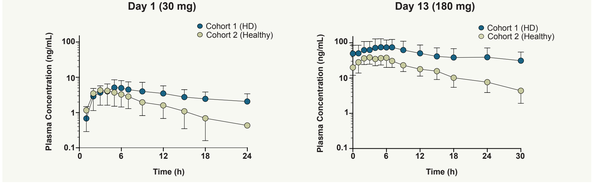
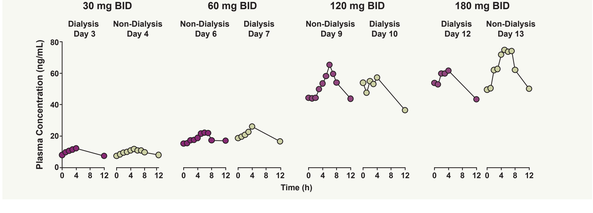


Figure 3: Nalbuphine Exposure in Hemodialysis Patients on Dialysis Days and Non-Dialysis Days



Effect on Pruritus

- Nalbuphine suppressed itch in a dose-dependent manner in 12/14 HD patients (**Figure 4**).
  - Subgroup analysis of patients with moderate or severe pruritus (VAS ≥ 4.0) showed a more pronounced change compared to all patients treated (**Figure 5A**).
- A differential treatment effect showed an increasing reduction in VAS over that for the 30-mg group at higher doses.
  - Changes in VAS at doses above 60 mg BID were greater than 2 points, compared to the 30-mg BID group (**Figure 5B**).
- The largest incremental changes occurred between 60 mg and 120 mg BID with changes in VAS greater than 2 points (equivalent to 20% change on a scale of 1-10).

Figure 4: Effect of Nalbuphine on VAS Score in Hemodialysis Patients

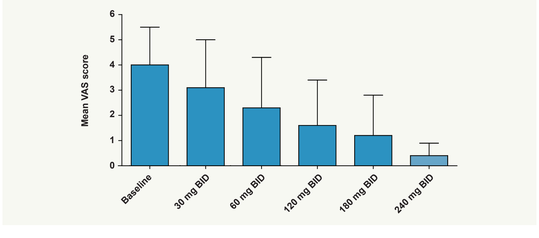
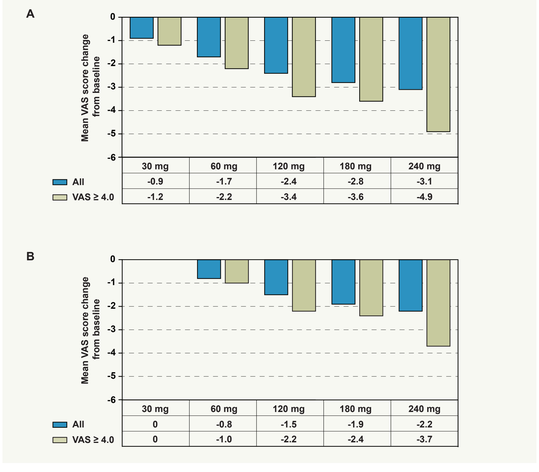


Figure 5: Difference in VAS Change from Baseline (A) or 30 mg BID (B) for All Patients and Patients With VAS ≥ 4.0 as a Function of Nalbuphine ER Dose



A

	30 mg	60 mg	120 mg	180 mg	240 mg
All	-0.9	-1.7	-2.4	-2.8	-3.1
VAS ≥ 4.0	-1.2	-2.2	-3.4	-3.6	-4.9

B

	30 mg	60 mg	120 mg	180 mg	240 mg
All	0	-0.8	-1.5	-1.9	-2.2
VAS ≥ 4.0	0	-1.0	-2.2	-2.4	-3.7

Safety

- Nalbuphine was well tolerated in all subjects. The most commonly reported treatment emergent AEs (TEAEs) were gastrointestinal and nervous system disorders (**Table 2**).
- As expected with a drug in the opioid drug class, a significant percentage of total AEs occurred at the beginning of dosing with a marked dissipation of reported AEs with time despite escalating the dose over a 6-fold range.
- There were no apparent treatment-related trends in clinical laboratory assessments, vital sign, SpO_2 measurements, ECG results, or physical examination findings.

Table 2: Number of HD Subjects with TEAEs as a Function of Dose and AE Grade

	30 mg n = 15		60 mg n = 14		120 mg n = 14		180 mg n = 13		240 mg n = 4	
Preferred Term	Grade 1	Grade 2	Grade 1	Grade 2	Grade 1	Grade 2	Grade 1	Grade 2	Grade 1	Grade 2
Nausea	8	-	-	1	-	1	1	3	-	-
Somnolence	2	-	1	-	-	1	-	1	-	-
Constipation	-	-	-	2	-	-	-	-	-	-
Dizziness	-	-	1	-	-	-	-	-	-	-
Headaches	2	-	-	-	-	-	1	1	-	-
Euphoria	2	-	-	-	-	-	-	-	-	-
Abnormal Dreams	1	-	2	-	1	-	-	-	-	-
Confusional State	-	-	-	-	1	-	1	-	-	-
Pruritus	-	-	2	-	1	-	-	-	-	-
Vertigo	-	-	-	-	-	-	-	-	-	1

Conclusions

- Nalbuphine administered as oral nalbuphine HCl ER tablets was safe and well tolerated up to the 240 mg BID dose tested in HD patients.
- The ability to titrate safely over a 6-fold dosing range allows individualization of dosing and “treatment to effect” drug management.
- Nalbuphine does not accumulate beyond that expected of repeat dosing and is not extracted by dialysis thus dose adjustment around dialysis is not necessary.
- Despite the extensive use of concomitant medications in this population, there were no obvious findings indicating safety, PK, or pharmacodynamics adverse drug interactions
- Exploratory investigations suggest that nalbuphine HCl ER tablets may be effective in reducing pruritus in HD patients, with particular benefit at doses of 60 mg BID or higher.
  - Reductions in VAS measures of itch severity appeared to be a function of increasing nalbuphine dose
- Based on safety and effect on VAS, the 60 mg and 120 mg doses were selected for efficacy studies.
- A clinical efficacy study is currently being conducted in the United States and Europe to assess the safety and antipruritic efficacy with nalbuphine HCl ER tablets in hemodialysis patients with uremic pruritus. The n for this study is expected to be 360 patients.

References

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