Pharmacokinetics of Nalbuphine Hydrochloride Extended Release Tablets in Hemodialysis and Healthy Subjects following Multiple Escalating Oral Doses

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Abstract

Purpose: Uremic pruritus (UP) is a common and deleterious condition among dialysis patients that involves opioid receptors. In particular, mu-opioid receptor antagonism and kappa-agonism seem to have anti-pruritic effects. Thus, nalbuphine, a mixed mu-antagonist and kappa-agonist opioid may be effective in UP treatment. The objective of this Phase 1 open-label study was to evaluate nalbuphine pharmacokinetics (PK) and safety following oral administration twice-daily (BID) of nalbuphine hydrochloride extended -release (ER) tablets in hemodialysis (HD) subjects with UP and explore its effect on itch.

Methods: Fourteen HD subjects with UP and 8 matched healthy subjects were enrolled. Subjects were titrated every 2-3 days from 30 mg up to 240 mg BID over 15 days. Drug concentrations in plasma and dialysate were measured using validated LC-MS/MS assays. Non-compartmental PK analysis was performed using WinNonlin. PK modeling was performed using NONMEM. HD subjects self-reported itch intensity daily using a 0-10 Visual Analogue Score.

Results: Plasma nalbuphine concentrations reached steady state within 2-3 days with no significant accumulation for both HD and healthy subjects (R=2.7 and 1.6, respectively). In HD subjects, mean Cmax and AUC(0-12h) ranged from 13 to 83 ng/mL and 118 to 770 ng.h/mL, respectively; the mean half-life was 14 hours, compared to 10 hours in healthy subjects resulting in 2-fold higher exposure in HD than in healthy subjects. Exposure on dialysis and non-dialysis days was similar with 1% of nalbuphine dose extracted during HD. Nalbuphine PK in HD patients was well described by a one-compartment model with a dialysate compartment and provided PK parameter estimates with good precision. A decrease in itch by 2-3 points was noted. Nalbuphine was well tolerated.

Conclusions: Nalbuphine HCl ER tablets can be safely administered to HD subjects without dose adjustment up to 240 mg BID and may hold promise in treating UP. PK modeling will facilitate exposure-response analysis in efficacy studies with sparse PK sampling.

Uremic Pruritus

Uremic Pruritus (UP) is a chronic itch disease common in end-stage renal patients on hemodialysis. The disease can be a serious and severe conditions with significant impact on the patient QoL with no approved therapy in the US or EU.

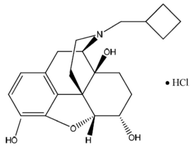
Sensation of itch is believed to work through neuroanatomical interactions with pain mediating pathways at various CNS levels

Pruritic condition has been related to a mu/kappa opioid receptor imbalance

Recent findings suggest that opiate pharmacology plays an important role in controlling itch

- Direct antagonism of mu-receptors of the cell group facilitating itch signaling since this cell group is activated by mu-receptor agonists
- Activation of independent neural circuit via opioid kappa agonist-mediated activation down regulates the cell group facilitating itch response

Nalbuphine HCl

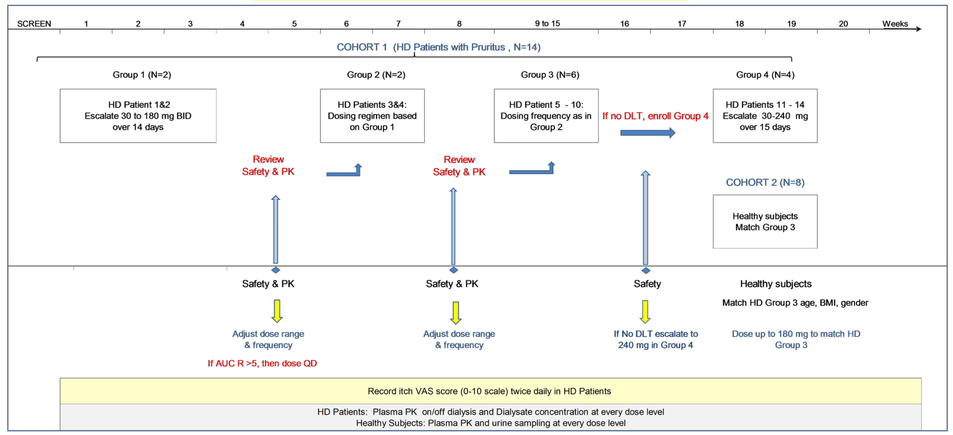


- Nalbuphine is a mixed mu-antagonist and kappa-agonist opioid drug that would be expected to relieve scratching/itch
- Currently marketed as *Nalbuphine HCl for Injection* for use in the relief of moderate to severe pain
- Nalbuphine was shown to significantly reduce Substance-P induced itch in a mouse model
- Nalbuphine is known to reduce morphine-induced itch in clinical settings
- In view of its dual agonist/antagonist mechanism of action, nalbuphine may be effective at reducing pruritus by therapeutically rebalancing the opioid receptor occupancy
- An extended release oral dosage form is currently being developed by Trevi Therapeutics for the treatment of chronic itch

Nalbuphine In Hemodialysis Patients

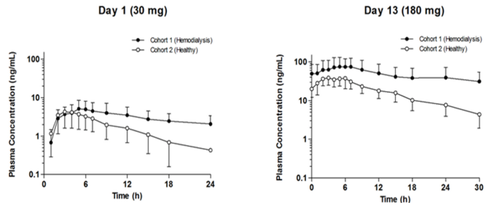
- Nalbuphine is a high extraction (perfusion-rate limited)
- Unlike other opioids, renal clearance plays minor role in disposition
- Though hepatic clearance predominates, nalbuphine plasma clearance may be impacted in HD subjects due to extraction during dialysis
- No clinical PK data is available on subjects with renal dysfunction
- Thus the need to assess its safety and PK under conditions that mimics its intended use in the target patient population
- AsC with other opioids, patients will most likely titrate to effect, hence the dose escalation regimen in this study

Phase 1 Open Label Adaptive Study Design

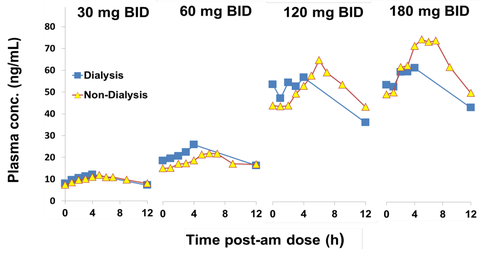


Pharmacokinetic Results

PK Profile in Hemodialysis and Healthy Subjects



PK Profile in HD subject on Dialysis and Non-Dialysis Days



Statistical Analysis of Effects of Hemodialysis on PK of Nalbuphine

Parameter	Dose (mg)	N*	Geometric Means		Statistics	
			On Dialysis (Test)	Non-Dialysis (Ref.)	% GMR* (T/R)	90% Confidence Limit
AUC_{last} (ng-h/mL)	30	11/14	86.46	94.14	91.85	81.02, 104.12
	60	10/10	188.59	159.84	117.99	103.56, 134.43
	120	10/10	418.26	442.56	94.51	83.46, 107.03
	180	13/9	567.05	599.15	94.64	82.95, 107.99
C_{max} (ng/mL)	All doses	15/14	31.04	31.39	98.9	89.73, 109.01

*Number of subjects on dialysis/non-dialysis *GMR: Geometric mean ratio

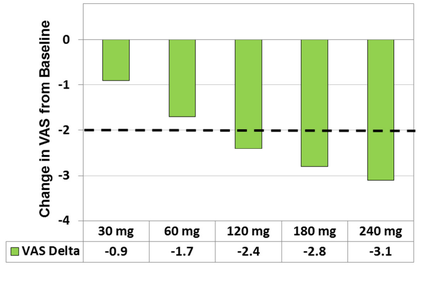
Analysis of variance performed on the natural logarithms of the parameters: For AUC_{last}, the model included hemodialysis (HD) status, dose, and HD status by dose interaction as fixed effects and subject as a random effect. For C_{max}, the model included HD status and dose as fixed effects and subject as a random effect. Point estimates and 90% confidence intervals (CIs) for differences on the log scale were exponentiated to obtain estimates for ratios of geometric means and 90% CIs of the ratios on the original scale

Mean PK Parameters in HD and Healthy Subjects

Parameter	Cohort 1^ Hemodialysis Patients		Cohort 2* Healthy Subjects	
	30 mg QD	180 mg BID	30 mg QD	180 mg BID
	Day 1	Day 13	Day 1	Day 13
AUC_{inf} (ng.h/mL)	142.5 (33.28)	2635.38 (2038.01)	49.53 (30.04)	588.4 (214.08)
AUC_{last} (ng-h/mL)	73.43 (41.81)	1457.74 (1016.26)	40.55 (22.96)	529.85 (179.93)
AUC_{tau} (ng.h/mL)	43.2 (24.97)	760.87 (538.28)	31.53 (16.93)	351.15 (118.21)
Accumulation Ratio	2.7	--	1.6	--
C_{max} (ng/mL)	6.28 (3.36)	82.78 (55.81)	5.2 (2.78)	44.21 (14.54)
T_{max} (h)	5 1.0 - 18	5 2.0 - 7.1	3 2.0 - 5.0	4 2.0 - 6.0
$T_{1/2}$ (h)	10.49 (2.22)	14.23 (3.24)	6.81 (2.79)	8.58 (2.05)
CL/F (L/h)	219.61 (52.11)	441.67 (418.15)	915.22 (619.35)	592.93 (299.48)
Vd/F (L)	3248.81 (656.59)	9009.49 (12387.85)	7731.48 (3872.63)	7276.04 (4285.51)
$\%A_{sm}$	0.95 (0.69)	1.11 (0.85)	--	--
CL_D (L/h)	7.60 (1.30)	7.32 (1.04)	--	--
%Fe	--	--	0.68 (0.41)	0.85 (0.35)
CL_R (L/h)	--	--	4.21 (1.52)	4.34 (0.95)

Subjects were titrated every 3-4 days from 30 mg QD on Day 1 to 30 mg BID then 60 mg BID, 120 mg BID and finally 180 mg BID over a 14 day period. Data shown for Day 1 and Day 13 only.
*^Cohort 1 N = 9 and 15 at 30 mg and 180 mg, respectively except for AUCinf, Cl/F, T1/2, and V/F where N=4. *Cohort 2 N= 7-9*
Accumulation ratio: Mean AUCtau Day 4/Mean AUCtau Day 1; CL_D:Dialysate clearance; CL_R: Renal clearance

Effect of Nalbuphine on VAS
Clinically significant drop in VAS (>2-points) within 7-10 days



Study Information

Male (19) and female (5) subjects with an average age of 47 years and a BMI of 29

- ESRD patients with mild to severe pruritus, on 3x week hemodialysis and
- Age, BMI, and gender matched healthy subjects

Subjects received a single 30 mg dose on Day 1. Doses were subsequently escalated to twice daily (BID) 30 mg, 60 mg, 120 mg, 180 mg over 13 days or to 240 mg BID over 15 days. On the last treatment day, subjects received a single 180-mg. Subjects remained at each dose level for 2-3 days (minimum 4 consecutive doses). Subjects remained in clinic and safety monitored over the duration of the study

In HD patients, dialysis was conducted at same time each day on Days -1, 3, 5, 7, 10, 12, 14 (and Day 17 for Group 4) over 3 hours using a high-flux dialyzer with polysulfone membrane

Blood samples on dialysis and non-dialysis day; dialysate (HD) and urine (healthy) collected at each dose level over the 6-fold dose range

This study was sponsored by Trevi Therapeutics and conducted in accordance with the Declaration of Helsinki. IRB Approval and signed Informed Consent forms were obtained prior to initiating the study.

Bioanalysis

- Nalbuphine concentrations in plasma, dialysate and urine were determined using a validated LC-MS/MS assay.
- Nalbuphine metabolites were also quantified in this study (Data not shown here)
- A representative Metabolite M3 was selected for PK modelling

Statistical analyses were performed using SAS v9.1.3 (SAS Institute Inc, Cary, NC)

Study Information

PK Data Analysis

- Non-compartmental PK analyses were performed using Phoenix WinNonlin v6.2.1 (Pharsight Corporation, St. Louis, MO)
- Population PK analyses were carried out using NONMEM v7.2 and PDx-Pop v5.2

- A one-compartment PK model with first order absorption and elimination processes was selected to describe the PK of nalbuphine. A one-compartment PK model, driven by nalbuphine in the central compartment, with first order elimination was selected to describe the PK of M3. Nalbuphine removed by dialysis is described by the dialysate compartment. Inter-individual and residual variability terms were included in the PK model Final PK model was evaluated using bootstrapping and a visual predictive check (VPC) 95% Bootstrap confidence intervals (CIs) for PK parameters derived from 1000 bootstrap datasets

- Steady state simulations of concentrations of nalbuphine and M3 following escalating repeated oral doses of nalbuphine HCl ER tablets in ESRD patients receiving HD therapy were carried out in using the parameter estimates obtained from the final PK model

Analysis of VAS Itch Measurements

- Subjects indicated their worst itch on a VAS scale 0 (none) to 10 (worst)
- VAS score obtained twice a day AM and PM daily during study
- Baseline VAS recorded pre-treatment
- Evaluate average of AM & PM VAS score as a function of dose
- Change of 20% or 2 points (out of 10) considered clinically significant

Pharmacokinetic Modelling

Schematic Representation of PK Model for Nalbuphine and M3

V2/F: apparent volume of distribution of nalbuphine;
V3/F is apparent volume of distribution of M3;
k12: first order absorption rate constant of nalbuphine;
k24: first order hemodialysis rate constant of nalbuphine;
k23: first order formation rate constant of M3;
k30: first order elimination rate constant of M3.

Population PK Parameters of Final PK Model

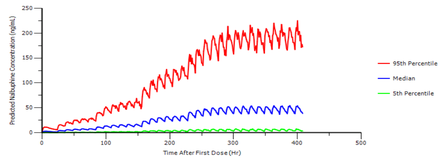
Parameters (units)	NONMEM Estimates			Bootstrap Results	
	PK Parameter Estimates	RSE	Inter-individual Variability[1]	Bootstrap Estimates	95% Bootstrap CI Lower - Upper
K12 (h^{-1})	0.457	18.10%	50.40%	0.561	0.313 - 0.712
CLM3 (L/h)	291	32.10%	86.6% (Fixed)	306	169 - 536
CLDN (L/h)	6.94	7.41%	Not estimated	6.87	5.83 - 7.89
V2 (L)	6520	27.60%	77.5% (Fixed)	6795	4100 - 11400
V3 (L)	150 (Fixed)	Not estimated	89.4% (Fixed)	Not estimated	Not estimated
CLM3O (L/h)	71.7	8.62%	25.80%	72.1	59.6 - 84.9

Abbreviations: RSE = relative standard error; CI = confidence interval; CV = coefficient of variation
[1] The magnitude of inter-individual variability was presented as CV%.
Note: The proportional error residual variability had associated CV of 27.7%.

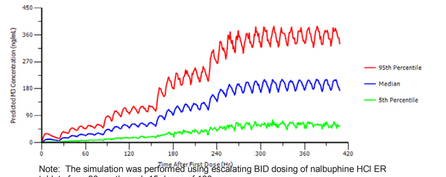
Prediction-Corrected Visual Predictive Check Plots for Final PK Model

- Inter-individual variability for the absorption rate constant (K12) and the clearance of plasma M3 (CLM3O) was estimated to be 50.4% and 25.8%, respectively
- The final PK model provided reasonable estimates of PK parameters with good precision despite the limited number of subjects
- Model evaluation using bootstrapping and prediction-corrected VPC demonstrated that the NONMEM estimates were relatively reliable and the final PK model was able to reproduce nalbuphine and M3 concentrations over time for HD patients

Predicted Plasma Nalbuphine Concentrations in HD Patients
Nalbuphine Steady state is reached in about 3 days of dosing



Predicted Plasma M3 Concentration in HD Patients
M3 Steady state is reached in about 3 days of dosing



Note: The simulation was performed using escalating BID dosing of nalbuphine HCl ER tablets from 30 mg through 15 doses of 180 mg

Conclusions

- Nalbuphine HCl ER tablets were well tolerated up to 240 mg BID
- Dialysis had minimal effect on nalbuphine (1% dose extracted). Thus dose adjustment around dialysis is not required
- PK of nalbuphine followed a one-compartment model with first order absorption and elimination in HD patients
- PK model for M3, which was driven by nalbuphine in the central compart ment, with first order elimination, and a dialysate compartment for nalbuphine was appropriate for describing M3 concentrations in plasma and nalbuphine concentration in dialysate
- Following BID dosing, steady state level of nalbuphine and M3 was reached within 3 days of dosing
- No further drug accumulation is anticipated beyond 3 days of repeat dosing
- PK modeling will facilitate exposure-response analysis in efficacy studies with sparse PK sampling

Overall nalbuphine HCl ER tablets can be safely administered to HD subjects without dose adjustment up to 240 mg BID and may hold promise in treating uremic pruritus

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