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 debilitating symptom among dialysis patients. Pruritus can occur due to a variety of mechanisms, including increased cellular turnover in the skin and autonomic nervous system upregulation, which plays a role in central neuropathic pain. Recent findings suggest that opiate pharmacology plays an important role in controlling pruritic condition has been related to a mu/kappa opioid receptor imbalance mediating pathways at various CNS levels. Sensation of itch is believed to work through neuroanatomical interactions with pain mediating pathways.

Methods: Twenty HD subjects with UP (and 10 healthy subjects were enrolled. Subjects were randomized to receive escalating doses of nalbuphine (2.5, 5, 10, 30 mg), twice daily (BID) for 3 days. Subjects were dosed during HD and at home. Safety was monitored throughout the study.

Results: Plasma nalbuphine concentrations showed steady state levels within 3 days with no significant accumulation for HD and healthy subjects. HD induced a 1.4-fold decrease in HD subjects, even after 1400-1500 mg from 3 days of therapy. HD patients had lower peak levels of nalbuphine compared to healthy subjects due to dialysis extraction.

Conclusions: Nalbuphine HD ER tablets can be safely administered in HD subjects with effective analgesic action compared to baseline as demonstrated by significant reduction in VAS and itch on a VAS scale 0 (none) to 10 (worst) in patients receiving HD therapy. Overall results promise in treating uremic pruritus without dose adjustment up to 240 mg BID and may hold promise in treating other chronic pruritic conditions in patients on HD.

Uremic Pruritus

Uremic pruritus (UP) is one of the most common and distressing symptoms among dialysis patients. Pruritus can occur due to a variety of mechanisms, including increased cellular turnover in the skin and autonomic nervous system upregulation, which plays a role in central neuropathic pain. Recent findings suggest that opiate pharmacology plays an important role in controlling UP.

PK Profile in Hemodialysis and Healthy Subjects

Mean PK Parameters in HD and Healthy Subjects

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

Nalbuphine HCI

Nalbuphine is a mixed agonist/antagonist opioid drug that is effective at treating moderate to severe chronic pain. It is available in oral, injectable, and nasal forms. Nalbuphine is indicated for the treatment of chronic pain, including neuropathic pain associated with diabetes, chronic non-cancer pain, and chronic postoperative pain.

Nalbuphine in Hemodialysis Patients

Nalbuphine is a highly biotransformed (approximately 80%) prodrug and is extensively metabolized in the liver. Nalbuphine is primarily excreted in the urine (approximately 15% of a dose) and is rapidly removed from the body by hemodialysis.

The effects of chronic kidney disease (CKD) and hemodialysis (HD) on the pharmacokinetics (PK) and pharmacodynamics (PD) of nalbuphine have been studied in several clinical trials. HD patients have lower peak levels of nalbuphine compared to healthy subjects due to dialysis extraction. Nalbuphine HCl ER tablets were well tolerated up to 240 mg BID in ESRD patients with mild to severe pruritus, on 3x week hemodialysis and dialysate Nalbuphine concentrations were also qualitatively in this study (data not shown).

Population PK Parameters of Final PK Model

Predicted Plasma Nalbuphine Concentrations in HD Patients

Nalbuphine steady state is reached in about 3 days of dosing

Conclusions

- Nalbuphine HCl ER tablets were well tolerated up to 240 mg BID.
- Nalbuphine has increased exposure on dialysis (1.4-fold decrease).
- PK of nalbuphine is reduced in a non-compartmental model with first order absorption and elimination processes.
- HA precedence of dialysis has been demonstrated in a mouse model and in clinical studies.
- Nalbuphine HCl ER tablets were well tolerated and may hold promise in treating other chronic pruritic conditions in patients on HD.

Pharmacokinetic Modelling

Schematic Representation of PK Model for Nalbuphine and M2

Predicted Plasma M3 Concentration in HD Patients

Predosed M3 steady state is reached in about 3 days of dosing

Population PK Parameters of Final PK Model

Predicted Corrected Visual Predictive Check Plots for Final PK Model

Clinical response data were collected using Visual Analogue Score. This endpoint was used to evaluate the analgesic effect of nalbuphine in the study.

Change in VAS from 1 to 7 days

Three days with no difference in VAS (0 to 10 mm) between HD and non HD groups.