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

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Introduction

- Uncontrolled itching is an excitatory disorder associated with end-stage renal disease (ESRD) that can be severe and debilitating.
- Itching is a very common reason for hospitalization and a significant determinant of patient quality of life, including depression and disruption of daily activities.
- Itch intensity is recorded at baseline and repeated at least twice per day by patient-reported visual analog scale (VAS) scores in clinical practice.
- VAS is a widely recognized and validated tool for measuring patient-perceived itch intensity.
- Nalbuphine, a mu opioid receptor antagonist, has been reported to reduce itch severity in ESRD patients.

Objectives

- To assess the safety and pharmacokinetics (PK) of nalbuphine extended-release (ER) tablets in hemodialysis (HD) patients with mild to moderate pruritus.
- To explore the clinical and pharmacological effects of nalbuphine on pruritus using a visual analog score (VAS) in HD patients.

Methods

- A total of 20 subjects were randomized to 5 treatment groups: 0 mg BID (Placebo), 30 mg BID, 60 mg BID, 120 mg BID, and 180 mg BID. Each group was further divided into two subgroups for HD and non-HD patients.
- The study was a randomized, double-blind, placebo-controlled, multiple-dose, escalating-dose design.
- Dosing was administered orally as a single 30-mg dose, followed by escalating doses up to 240 mg BID.
- HD patients underwent dialysis treatments on alternate days, with the morning dose administered no earlier than 6 hours and no later than 4 hours prior to dialysis.

Patient Characteristics

- All subjects were enrolled in Cohort 1 (10 males and 3 females, of whom 13 completed the study and 2 discontinued due to dialysis). 10 males and 3 females, of whom 13 completed the study and 2 discontinued due to dialysis.
- Nalbuphine HCl was administered orally as nalbuphine HCl extended-release tablets in HD patients for 6 days (30 mg to 240 mg BID).

Pharmacokinetics

- Pharmacokinetic parameters were derived from plasma and dialysate nalbuphine concentration versus time data using noncompartmental analysis.
- Nalbuphine exposure in HD patients on dialysis days and non-dialysis days was comparable.
- Overall exposure in HD patients was higher than in healthy subjects.
- Over the 30-mg to 180-mg dose range, exposure increased in a near-dose-proportional fashion with no evidence of saturation.
- Nalbuphine does not accumulate beyond that expected of repeat dosing and is not extracted by dialysis.
- The recovery of nalbuphine in the dialysate was minimal, indicating that about 1% of the dose was removed during a dialysis treatment.

Effect on Pruritus

- Over a 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.
- Over-dose exposures in HD patients were higher than in healthy subjects.
- Nalbuphine ER tablets were compared with placebo (Figure 3).
- Nalbuphine HCl administration led to significant reductions in VAS scores.
- 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 4).
- The largest incremental changes occurred between 120 mg and 180 mg BID with changes in VAS greater than 2 points (exposure to 20% change on a scale of 1-10).

Conclusions

- Nalbuphine administered as oral nalbuphine HCl ER tablets was safe and well tolerated up to the 240 mg BID dose.
- The ability to titrate safely over a 6-fold dosing range allows individualization of dosing and treatment to reduce VAS intensity.
- Nalbuphine does not accumulate beyond that expected of repeat dosing and is not extracted by dialysis.
- Despite the widespread use of conventional antipruritic medications in this population, there were no serious findings indicating safety, PK, or PD pharmacokinetic or safety interactions.
- Exploratory investigations suggested 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 BID doses were selected for efficacy studies.
- A phase 3 efficacy study is currently being conducted in the United States and Europe to assess the safety and efficacy of nalbuphine ER tablets in hemodialysis patients with pruritus.

References


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