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 is a chronic debilitating and distressing condition affecting 80% of dialysis patients. The disease can be a serious and severe condition with significant impact on the patient quality of life. The objective of this study was to evaluate the pharmacokinetics (PK) of Nalbuphine HCl extended release tablets in hemodialysis (HD) patients and compare it with healthy subjects (HS).

Methods: In this open-label single-center, randomized, double-blind, dose escalation study, 10 male and 10 female healthy subjects and 5 male dialysis patients were enrolled. After an overnight fast, a single dose of escalating doses ranging from 30 mg up to 240 mg BID over 15 days was self-administered. Plasma and urine samples were collected and were analyzed for nalbuphine. The final PK model provided reasonable estimates of PK parameters with good precision. A decrease of 20% or 2 points (out of 10) considered clinically significant.

Results: Significant differences were observed in the HD group compared to the HS group. The mean half-life was 14 hours, compared to 10 hours in healthy subjects. Exposure on HD days was similar with 1% of nalbuphine dose extracted during dialysis.

Conclusions: Nalbuphine HCl ER tablets can be safely administered to HD patients without dose adjustment up to 240 mg BID and may hold promise in treating UP. PK modeling showed that dialysis had minimal effect on nalbuphine (1% dose extracted). Nalbuphine was shown to significantly reduce Substance P induced itch in a mouse model.

Study Information

Drug (Nalbuphine HCl) subjects with an average age of 37 years and a BMI of 26.

- 130 HD patients with severe itch (visual analog score [VAS] > 7) were included in the target patient population.

- A one-compartment PK model with first order absorption and elimination processes was selected to describe the PK of nalbuphine. A two-compartment PK model, driven by nalbuphine in the central compartment and M3 in the peripheral compartment, with direct mechanisms of action was selected to describe the PK of M3.

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