Norbuprenorphine Pharmacokinetics and Pharmacodynamics: First in Man Evaluation

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Background: Buprenorphine (Bup) is a partial μ agonist, δ and κ antagonist, and nociceptin receptor agonist, with complex pharmacology. It is extensively metabolized, primarily to norbuprenorphine (norBup); both Bup and norBup undergo glucuronidation. Metabolite exposure can exceed that of Bup. NorBup, Bup-glucuronide and norBup-glucuronide are pharmacologically active. Mechanisms of Bup pharmacology in humans remain undefined. This investigation evaluated norBup clinical pharmacology, including PK, clinical effects and PD, in two first in man, IRB-approved, single-center protocols in healthy volunteers.

Methods: Protocol 1 was an open label dose-escalation (0.005-1 mg, 1 hr infusion) pilot, to evaluate dose-dependent PK and clinical effects of NorBup. Venous plasma was sampled for up to 13 hr, and urine collected for 24hr. Protocol 2 subjects received a fixed-dose 0.3 mg 1-hr infusion of NorBup. Arterial (radial) and venous plasma was sampled for 13 hr and 96 hr, respectively. Pupil diameter, respiratory rate, end-expired CO_2, and subjective self-assessment of drug effect were recorded. Response to thermal stimulus (Peltier thermode analgesia), was assessed using the methods of limits (maximal tolerated temperature) and ramp and hold method (VAS pain rating to a predetermined temperature). NorBup and NorBup-glucuronide were quantified by LCMS. Population PK modeling was performed with Phoenix 64 NMLE 7.0 using the FOCE ELS algorithm (Certara). Model parameters were assumed to be log-normally distributed across the population. Independent PK models for arterial (NorBup & NorBup-glucuronide) and venous (NorBup & NorBup-glucuronide) were tested against a minimal, comprehensive model that linked arterial and venous drug/metabolite concentrations, using recirculatory model principles, and a metabolic tanks-in-series pathway. Criteria for accepting the linked model were improvement of -2LL of at least 3.84 and reduction in AIC (Chi squared, $p<0.05$). Urine drug and metabolite concentrations were incorporated in the respective models as cumulative drug or metabolite collected at each collection time point.

Results: NorBup was well-tolerated, without adverse effects. Plasma norBup-glucuronide exceeded norBup concentrations. NorBup and norBup-glucuronide plasma AUCs, and urine excretion, were proportional to dose ($r>0.9$) throughout the entire dose range. NorBup-glucuronide was formation-rate limited. NorBup arterial concentrations were 2x venous concentrations during the infusion, and similar thereafter with venous

systematically higher. The A-V difference was well modeled with a linked 3-compartment base model and a recirculatory mixing component with a typical cardiac output of 6.5 L/min. NorBup to the glucuronide tvCl was 342 ml/min and renal tvCl of NorBup-glucuronide was 125 ml/min, based on urine collection. Non-renal clearance accounted for 91% of NorBup and 71% of NorBup-glucuronide clearances. NorBup (0.3 mg) caused mild miosis (maximum pupil diameter change 1.3 ± 0.8 mm), minimal respiratory depression (respiratory rate decreased from 16 ± 1 to 14 ± 3 and end-expired CO_2 increased from 39 ± 2 to 41 ± 2 mmHg), and was slightly anti-analgesic (maximum tolerated temperature decreased from 49 ± 1 to 48 ± 1 °C and NRS pain ratings to a preset temperature increased to 113 ± 13% of baseline). Effect (miosis) vs concentration showed hysteresis.

Conclusions: NorBup is pharmacologically active in man, shows both μ agonist and κ antagonist properties and may contribute to the pharmacologic effects of parent Bup.