Evaluation of Drug-Drug Interaction Potential of Probuphine® Implants using a Physiologically-Based Pharmacokinetic Model

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Background

Probuphine® (buprenorphine) implant, a six-month maintenance treatment for opioid-use disorder (OUD) in eligible patients is approved by the US Food and Drug Administration, Health Canada, and the European Medicines Agency. Buprenorphine (BPN) released subdermally from Probuphine implants is metabolized primarily by CYP3A4 and, to a lesser extent, by UGT1A1.[1] The potential for drug-drug-interactions (DDI) with Probuphine implants was assessed in a virtual clinical trial using a physiologically-based pharmacokinetic (PBPK) human whole body computer model, to describe drug distribution, as well as transport or disposition, using differential equations.

Objectives

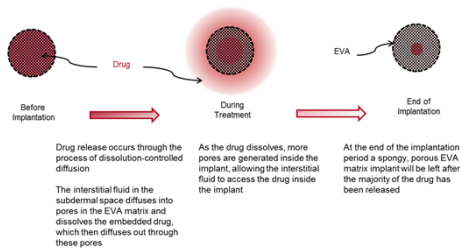
The current study applies a PBPK modelling approach to predict DDI of BPN from the approved clinical dose of 4 Probuphine implants, each containing 80 mg of BPN HCl, with co-exposure to a strong CYP inhibitor, ketoconazole (200 mg BID), or the strong CYP inducer, rifampicin (600 mg QD). Further, the potential of the UGT metabolic pathway on BPN released by Probuphine was also evaluated.

Methods

Probuphine was developed using ProNeura®, a continuous drug delivery platform. It is a solid matrix non-biodegradable implant made from a mixture of a safe co-polymer, ethylene-vinyl acetate (EVA), and BPN. Four Probuphine implants are placed subdermally in the upper arm and removed at the end of the 6 month treatment period. For continued treatment, a fresh set of implants are inserted at a different site as directed by the full prescribing information.[2] BPN is released systemically in non-fluctuating pseudo-zero-order mechanism by dissolution-controlled diffusion from the EVA matrix (Fig.1)

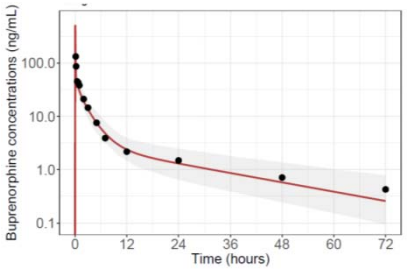
PBPK modeling was performed in three distinct steps: model development, model qualification and application.[3] Broadly, the model characterized subdermal (SD) release of BPN from Probuphine as well as intravenous (IV) BPN administration. For the model development, BPN IV data in the literature was initially employed (Fig. 2).[4] PK data for BPN SD from Phase 3 human clinical studies with Probuphine implant was used to derive the dermal absorption sub-model (Fig. 2). Models for each drug interacting with CYP3A4, ketoconazole and rifampicin, were also developed. These PBPK models were qualified against independent published data. In the final step, the qualified PBPK models were applied to predict the potential influence of ketoconazole and rifampicin on the PK of plasma BPN released by Probuphine (Fig. 3).

Figure 1. Proposed mechanism of BPN release from Probuphine implants.



PBPK Modeling Results

Figure 2. BPN concentration profiles generated over time.
Above: PBPK model validation using 16 mg IV BPN bolus injection.
Below: PBPK model validation using 4 Probuphine implants (320 mg BPN HCl).



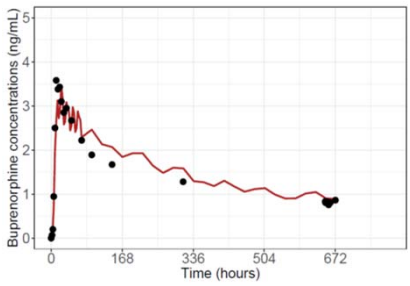
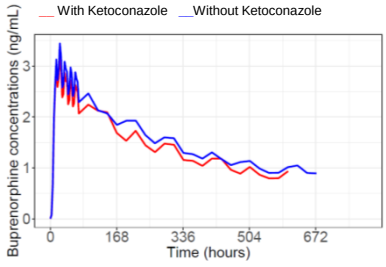
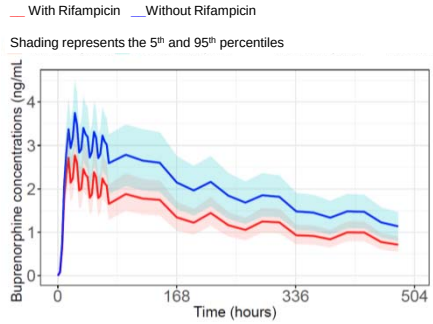


Figure 3. BPN-time profiles for 4 Probuphine implants with the strong CYP inhibitor, ketoconazole, or with the strong CYP inducer, rifampicin.
Above: PBPK Model prediction of DDI for ketoconazole + Probuphine
Below: PBPK Model prediction of DDI for rifampicin + Probuphine





Results

Ketoconazole had a negligible effect (about 10%) on BPN exposure after treatment with 4 Probuphine implants. Rifampicin reduced the BPN exposure from 4 Probuphine implants by about 25-30% (Table 1).

Table 1. PK parameters derived from the PBPK model
Above: 4 Probuphine implants -/+ 200 mg BID ketoconazole.
Below: 4 Probuphine implants -/+ 600 mg QD rifampicin.

Parameter	Probuphine Alone	Probuphine + Ketoconazole	Ratio
$AUC_{(0\text{-}610hr)}$, ng.hr/mL	869.0	897.9	1.03
C_{max}, ng/mL	3.6	3.5	0.97
	Probuphine Alone	**Probuphine + Rifampicin**	**Ratio**
$AUC_{(0\text{-}610hr)}$, ng.hr/mL	869.0	590.0	0.68
C_{max}, ng/mL	3.6	2.7	0.75

The estimated fraction of BPN metabolized via the UGT metabolic pathway is reported in the range of 8%-37%.[1] The in-vivo Km for the CYP3A4 and UGT pathways from this PBPK model, and based on published clearance values, are 13.6 uM and 22.6 uM, respectively.[3,5] This model-derived Km for UGT1A1, the relatively major contributor of BPN metabolism within the UGT pathway, translates into a requirement for very high in-vivo estimated BPN concentration (~10,000 ng/mL).

The average sustained plasma BPN concentration for Weeks 1-24 obtained from multiple Phase 3 clinical trials with 4 Probuphine implants was 0.64 ng/mL; thus making any DDI with the UGT pathway for BPN metabolism unlikely for Probuphine.

Conclusions

A reliable PBPK model for plasma BPN exposure following treatment with 4 Probuphine implants has been developed. This model was employed to predict DDI on BPN exposure following Probuphine treatment. Strong CYP3A4 inhibition negligibly increases the BPN exposure from Probuphine; while strong CYP3A4 induction is predicted to decrease BPN exposure from Probuphine by 25-30%.

The role of the UGT metabolic pathway on BPN released from Probuphine was assessed to be negligible.

References

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3. Liu et al. (2018) J Pharm. Sci.107(3):942-948.
4. Huestis et al. (2013) Drug Alc. Depend. 131(3): 258-262.
5. Chang et al. (2009) Drug Metab. Lett. 3(2):101-107.