Improving Effectiveness of Buprenorphine Dosing Regimen in Non-human Primates through Modeling and Simulation

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Purpose

Buprenorphine was developed as a long-acting semi-synthetic opioid analgesic for humans and has been used in laboratory and companion animal species for almost 30 years. The clinically effective dose range and administration intervals for buprenorphine in nonhuman primates (NHP) are mostly empirical and based on the assumption that therapeutic blood levels for buprenorphine in monkeys is similar to that established for humans. In addition the PK of buprenorphine administered by the most commonly used SC route has not been reported before. The aim of the current study is to use PKPD model-based simulations to guide more effective use of buprenorphine in NHP.

Methods

Adult male Cynomolgus monkeys (Macaca fascicularis) of Mauritian origin, 10.1-14.7 years of age were used. Buprenorphine PK studies (0.002 mg/kg and 0.02 mg/kg IV; 0.01 mg/kg, 0.02 mg/kg, and 0.05 mg/kg SC; brain penetration study at 0.05 mg/kg SC) were first conducted and a population PK model was developed to characterize buprenorphine disposition. Next, PD parameters describing anti-nociceptive effect of buprenorphine based on previous PKPD understanding in rat and human (Yassen 2006 & Yassen 2005) were extracted and allometry was used to derive NHP PD parameters. Subsequently, an M. fasicularis buprenorphine PKPD model describing time course of anti-nociceptive effect was constructed after integrating observed PK and prior knowledge on PD. Expected magnitude and duration of analgesic effect for some common buprenorphine dosing regimens as well as additional regimens were simulated.

Results

Following SC administration, buprenorphine was rapidly absorbed reaching maximum plasma concentrations within 1 hour. A bi-exponential decline in drug levels with a rapid distribution phase (t1/2 alpha = 0.77 hr) and a much slower elimination phase (t1/2 beta = 15.8 hr) was observed in both SC and IV PK studies. 76% of buprenorphine reaches systemic circulation after SC administration and the drug penetrates the brain and spinal cord freely. Simulation results suggest that the duration of analgesia may be insufficient towards the end of the dosing interval when some current dosing regimens (e.g. 0.02 mg/kg Q12 hr) are used. The model predicts that more frequent dosing or using a loading dose could provide more complete analgesic coverage over the duration or therapy. Several alternative dosing regimens which may improve analgesia over time are proposed.

Conclusion

This work demonstrates the utility of modeling and simulation to improve efficacy of buprenorphine analgesia in NHP through optimizing the dosing regimen.