

Pharmacokinetics of Hydromorphone in Dogs after Intravenous Bolus and Delivered Subcutaneously with the RxActuator Mini-Infuser® Infusion pump

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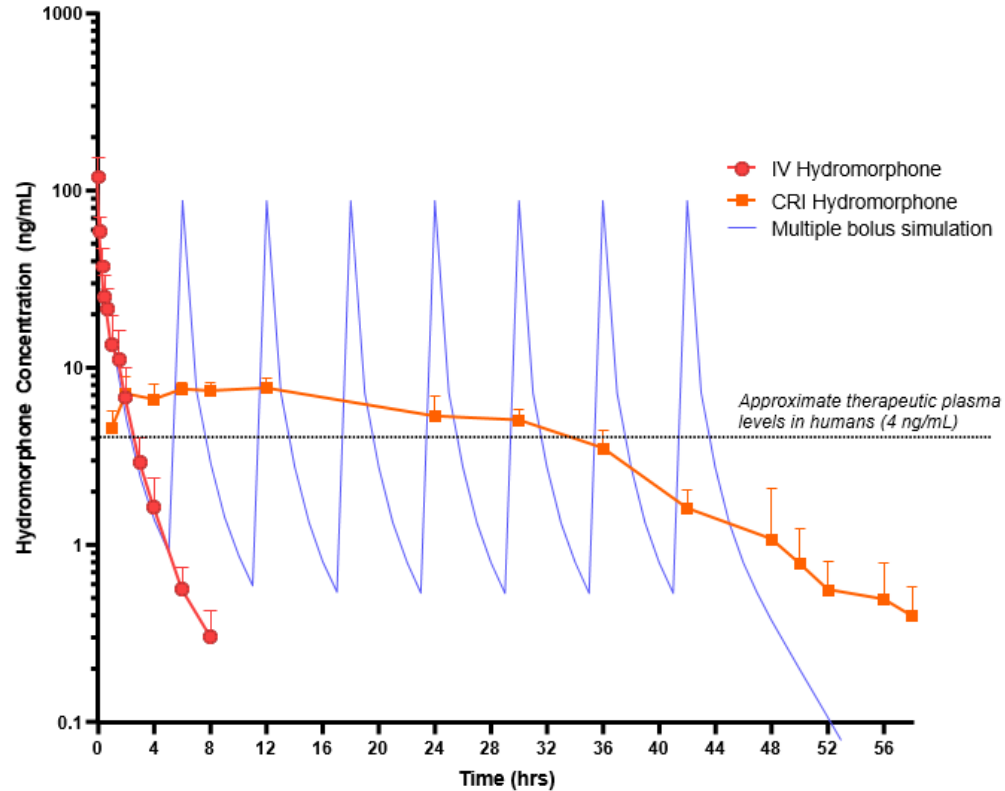
Disclosures Related to This Study

- RxActuator provided financial support and infusion pumps for this study

Hydromorphone PK and PD in Dogs

- Previous PK studies suggest dosing of 0.1 mg/kg q 2 h
- No studies have confirmed therapeutic plasma concentrations
 - Suggestion of 4 ng/mL base on human studies
- Surprisingly, no PK data on hydromorphone infusions in dogs

Infusions vs. Bolus Dosing



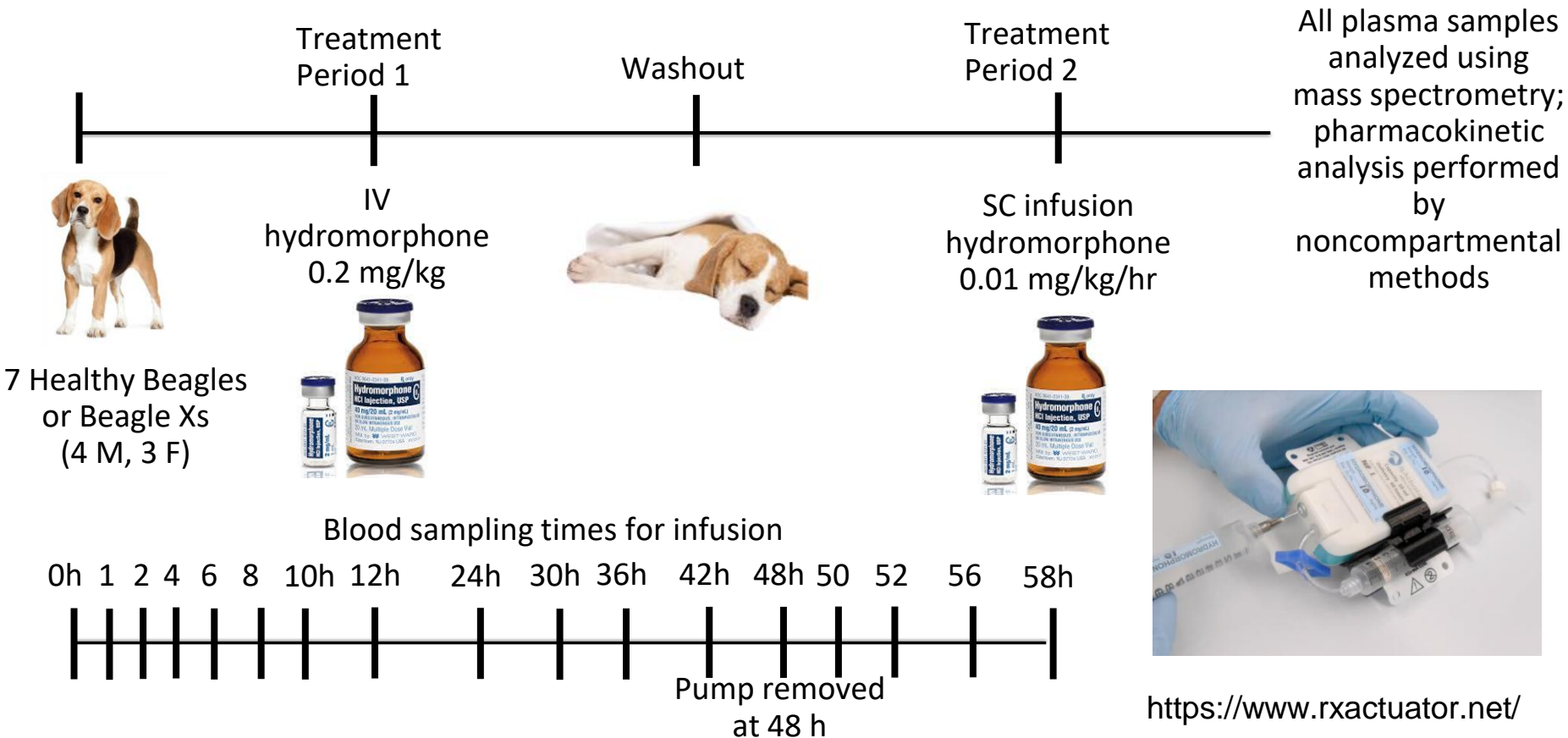
Wearable Pumps for At-Home Infusions



Study Objectives

The objective of this study was to describe the pharmacokinetics of hydromorphone in dogs following either IV bolus or subcutaneous (SC) infusion via a wearable pump

Study Design



Hydromorphone and PK Analyses

- Drug concentrations measured using ultra performance liquid chromatography with tandem mass spectrometry (UPLC-M/MS)
- PK estimates obtained with noncompartmental analysis
- Descriptive statistics utilized to present the data

Hydromorphone Concentrations in Pump

- In vitro study performed to determine if hydromorphone concentrations decrease over 48 h in the pump
- Performed in triplicate in a water bath with temperature set to 37.8 C
- 250 uL aliquot removed at same time points as study
 - Stored in cryovials at – 80 until analysis
 - Samples analyzed by HPLC/MS

Results and Side Effects

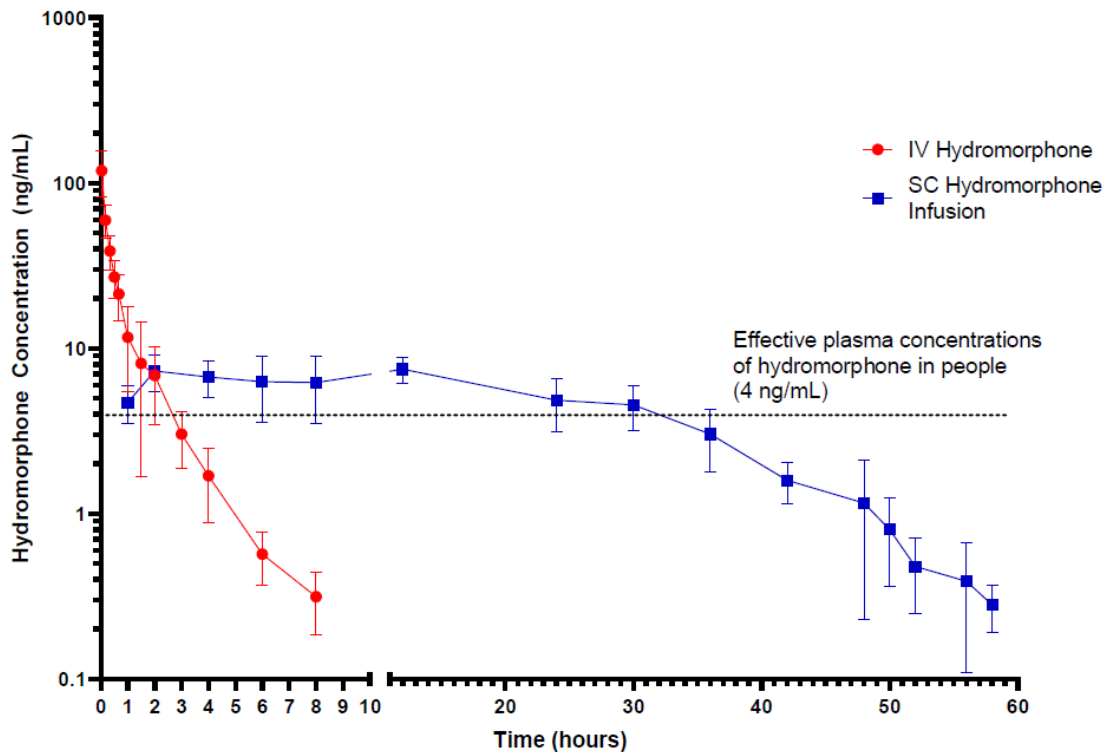
- All dogs completed the study
- GI side effects subjectively noted in both groups
 - Decreased appetite, hypersalivation and nausea noted as early as 1 h post infusion initiation
 - Lasted between 30 h and 42 h in the infusion group
 - No treatments were administered, but canned food was offered
- Sedation subjectively observed at 1 h post infusion initiation, occurring up to 12h

Pump Performance and Hydromorphone Concentrations

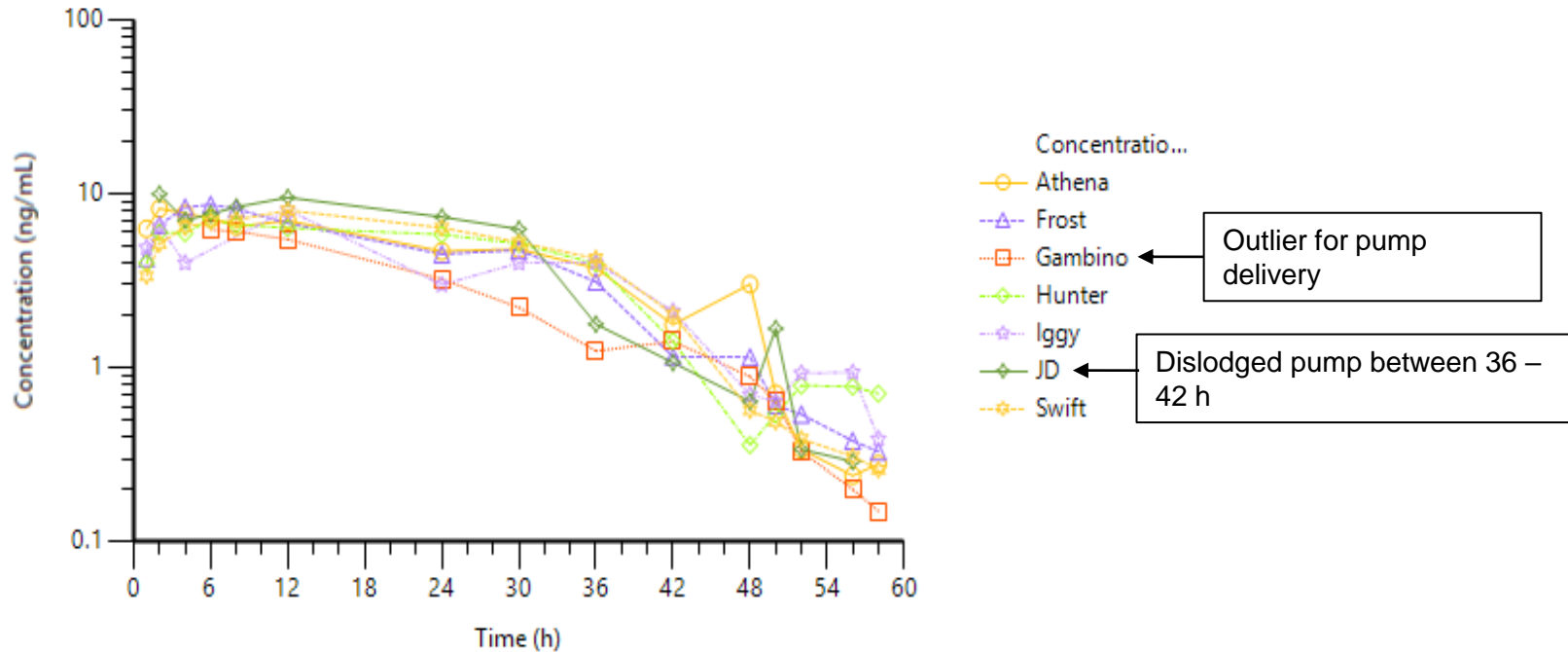
- Mean +/- SD volume remaining in pump at 48 hr = 710 (+/- 1466) μL
 - If outlier (4300 μL) removed: 112 +/- 74 μL
- One pump dislodged at 42 h time point
- Hydromorphone concentrations remained stable over time based on in vitro study

Plasma Concentration vs. Time Results

Mean (SD) IV and SC Infusion Hydromorphone
n = 7 dogs



Individual Infusion Concentration vs. Time Results



PK Results Presented as Median (Range)

Parameter	IV	SC Infusion
Clearance ($\text{mL min}^{-1} \text{kg}^{-1}$)	56.45 (47.07-88.10)	N/A
Volume of distribution at steady state (L/kg)	4.01 (2.57-7.70)	N/A
Area under the curve ($\text{hr} \cdot \text{ng mL}^{-1}$)	59.05 (37.84-70.82)	244.22 (152.55-282.72)
Terminal half-life (hr)	1.47 (1.34-2.04)	7.35 (3.25-16.07)
Cmax (ng mL^{-1})	N/A	8.08 (6.21-9.97)
Tmax (hr)	N/A	6.00 (2.00-12.00)

Comparison with Previous Studies

Study/Author	Kukanich et al, 2008	Guedes et al., 2008	Smith et al., 2008	Messenger et al., 2021
Dose and Route	0.1 and 0.5 mg/kg IV (and SC)	0.1 and 0.2 mg/kg, IV	0.5 mg/kg liposome formulation, IV	0.2 mg/kg, IV
Breed	4 Beagles	3 Beagles and 2 Mixed breed dogs	8 Male Beagles	5 Beagles, 2 BeagleX
PK Analysis	NCA	Compartmental	NCA	NCA
Clearance mL/min/kg	106; 60	68; 74.7	128	56
Vdss (L/kg)	4.2; 4.4	2.4; 7.2	8.6	4.0
AUC (hr*ng mL ⁻¹)	13.9; 122.5	26; 46	63	59
Half life (min)	34.2; 60	58; 53	67	88
Comments	Suggested CRI of 0.03 mg/kg/hr			

Limitations

- Crossover not randomized
- Lack of an IV infusion crossover
- Homogenous study population
- Sampling $>3 T_{1/2}$'s following infusion



Future Studies

- Pharmacokinetics of IV hydromorphone infusion
- Determine the context-sensitive half-time of hydromorphone in dogs
- Consider TCI study

Conclusions

- RxActuator Mini-Infuser® pump delivered a consistent rate of hydromorphone over approximately 48 hours with plasma concentrations exceeding those associated with analgesia (approximately 4 ng mL^{-1})
- Larger studies in clinical patients are warranted to further determine the analgesic effects of hydromorphone delivered as a subcutaneous infusion at 0.01 mg/kg/hr

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