

Short-acting and Long-acting Buprenorphine Therapeutic Drug Levels Following Single Subcutaneous Administration in Diabetic Yucatan Miniswine

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ABSTRACT

Sustained and controlled analgesia for animals involved in potentially painful procedures, such as surgery, is required for animal welfare and ethical considerations. Many analgesics are available to Laboratory Animal Veterinarians but the pharmacokinetic and pharmacodynamic data are not always available for every species. This is the situation for miniswine and porcine models. Standard short-acting buprenorphine HCl (BUP), an opioid, is routinely used in swine models on a BID basis (dose range 0.005-0.02 mg/kg im, sc or iv) while BUP SR (Sustained Release) is dosed at approx. 10-fold levels in large animals. The published data supporting this porcine BUP regimen or the use of Sustained Release (SR) buprenorphine (BUP SR) in swine is quite limited, thereby forcing investigators to favor on the side of caution which can be expensive. Therefore, we designed a study to assess the PK for buprenorphine analgesics in Yucatan miniswine. The diabetic Yucatan was selected because we chemically induce, place VAPS, and maintain a large herd of these animal models. Four castrated male alloxan diabetic animals weighing approximately 30 kg were used in a complete cross-over design. For standard buprenorphine HCl animals were dosed subcutaneously (left flank fold) with either 0.01 mg/kg (low-dose) or 0.02 mg/kg (high-dose), while for sustained release buprenorphine the dose was either 0.12 mg/kg (low-dose) or 0.24 mg/kg (high-dose) s.c. in left flank-fold. Washout was set at 9d before animals were redosed with another formulation. For the shorter acting buprenorphine, blood samples were collected at pre-dose, 0, 15, 30, 60, 120, 240 and 480 minutes (8 timepoints targeted). For the sustained formulation, samples were collected at pre-dose, 0, 30, 60, 90, 240 and 480 minutes, and 12h, 24h, 48h, 72h, and 96h (12 timepoints targeted). Buprenorphine was analyzed in K2EDTA plasma samples by liquid-liquid extraction and LC-MS/MS (quantitation range 50 to 5000 pg/mL). Results were reported in picograms/mL of plasma. All data were quality controlled and outliers removed before summary statistics were calculated and plotted. Results for buprenorphine high- & low-dose plasma drug profile curves showed that BUP peaked at 2192 pg/ml for the high-dose and 842 pg/mL for the low dose. Following single s.c. administration, short-acting BUP drug was onboard in plasma for 240-480 min (above 0.1 ng/mL efficacious threshold for 480 min or 8 hrs). Results for buprenorphine SR high- & low-dose plasma drug profile curves showed that BUP SR peaked at 1795.5 pg/ml at 240 min (high-dose) and peaked at 1531.8 pg/mL (low dose) at 30 min. Sustained release drug was present in plasma for 96 hrs for both high- & low-dose (above 0.1 ng/mL). In conclusion, these data suggest that these dose levels provide sufficient plasma levels of drug for analgesia (>0.1 ng/mL) for at least 8 hr (short-acting BUP) or for at least 96 hr (long-acting BUP SR). Standard pharmacokinetic parameters were calculated.

Keywords: 1) Analgesia, 2) Yucatan miniswine, 3) Buprenorphine HCl or Buprenorphine SR

INTRODUCTION

Sustained and controlled analgesia for animals involved in potentially painful procedures, such as surgery, is required for animal welfare and ethical considerations. Many analgesics are available to veterinarians but

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pharmacokinetic and pharmacodynamic data are not always available for every species. Standard buprenorphine HCl (BUP), an opioid, is routinely used in swine models on a BID basis (dose range 0.005-0.02 mg/kg im, sc or iv), while BUP SR (Sustained Release) is dosed at approx. 10-fold levels in large animals. The published data supporting this porcine regimen or the use of buprenorphine sustained release (BUP SR) in swine is quite limited, thereby forcing investigators to favor on the side of caution which can be expensive. We designed a study to assess the pK for buprenorphine analgesics in Yucatan miniswine. The diabetic Yucatan was selected because we chemically induce, place subcutaneous vascular access ports (VAPS), and maintain a large herd of these animal models.

METHODS

Four castrated male alloxan diabetic (db) animals weighing approximately 30 kg were used in a complete cross-over design. Buprenorphine HCl (Buprenex™ injection, 0.3 mg/mL, Reckitt Benckiser Pharmaceuticals) and Buprenorphine HCl SR 10mg/ml (SR Veterinary Technologies/ZooPharm, Windsor, CO) was obtained. For BUP, animals were dosed subcutaneously (left flank fold) with either 0.01 mg/kg (low-dose) or 0.02 mg/kg (high-dose), while for BUP SR the dose was either 0.12 mg/kg (low-dose) or 0.24 mg/kg (high-dose), also dosed s.c. in left flank-fold. Washout was set at 9d before animals were redosed with another formulation. For the BUP, blood samples were collected at pre-dose, 0, 15, 30, 60, 120, 240 and 480 minutes (8 timepoints targeted). For the BUP SR, samples were collected at pre-dose, 0, 30, 60, 90, 240 and 480 minutes, and 12h, 24h, 48h, 72h, and 96h (12 timepoints targeted). Buprenorphine was analyzed in K2EDTA plasma samples by liquid-liquid extraction and LC-MS/MS (quantitation range is 50 to 5000 pg/mL). Results were reported in picograms/mL of plasma. All analytical data were quality controlled and outliers removed before summary statistics were calculated and plotted.

Non-compartmental analysis was applied to the drug concentration – time data. Pharmacokinetic analysis was performed using Phoenix WinNonlin 6.3 (Pharsight Corporation, Mountain View, CA). Pharmacokinetic parameters were calculated separately for each individual animal using the raw data and nominal blood sampling time points. Group means were also tabulated. For PK modeling purposes, plasma drug concentrations reported as less than the lower limit of quantification were designated as 0 in the analysis data set. The following PK parameters were estimated: Cmax, Tmax, T1/2, and AUC. AUC values were determined by the method of linear trapezoidal linear interpolation.

RESULTS

Buprenorphine plasma drug profile curves showed that BUP peaked at 2192 pg/ml for the high-dose and 842 pg/mL for the low dose (Table 1 and Figure 1). Short-acting BUP drug was in plasma for 480 min (above 0.1 ng/mL efficacious threshold for 8 hrs). BUP SR plasma drug profile curves showed peaks at 1795.5 pg/ml at 240 min (high-dose) or at 1531.8 pg/mL (low dose) at 30 min (Table 2 and Figure 2). Sustained release drug was present in plasma for at least 96 hrs for both high- & low-dose (above 0.1 ng/mL). Table 3 presents pK analysis parameters by drug group (includes Cmax, Tmax, T1/2, Clast, Tlast, AUClast, AUCα, Vz/F, Cl/F, MRTlast). Of significance, the higher dose BUP SR reached

RESULTS (CONTINUED)

Tmax quicker than did the lower dose SR (5.4 vs. 9.1 hr). Two of 4 high dose SR animals exhibited considerable variability (Tmax: 1.5 & 12 hr) from the other two animals Tmax of 4 hours each.

Table 1. High vs. Low Dose SA Buprenorphine Dosed Subcutaneously In db Yucatan: Group Plasma Means (pg/mL) Over Time (N=4)

	pK Timepoint (mins)						
	predose	15 min	30 min	60 min	120 min	240 min	480 min
Mean BUP Low	76.5	474.5	842.75	695.25	502.75	397.5	352.75
Mean BUP High	130.03	1985.00	2192.00	1905.00	1128.75	821.00	428.75

Figure 1. High vs Low Dose SA Buprenorphine Dosed s.c. In db Yucatan Miniswine: Group Plasma Means Over Time (N=4)

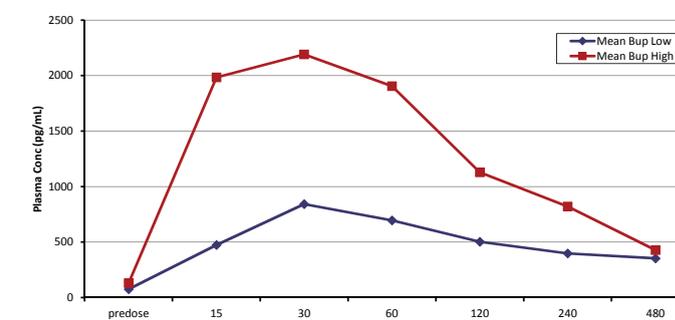
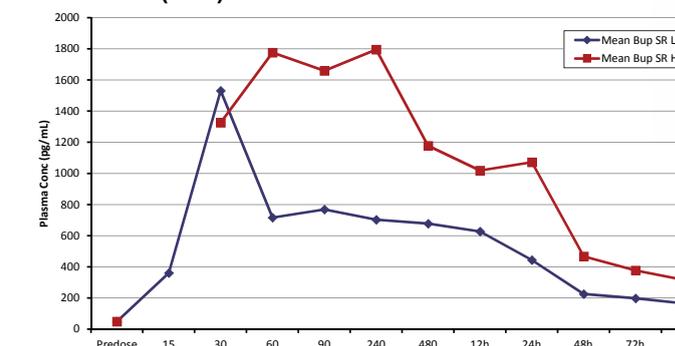


Table 2. High vs. Low Dose Buprenorphine SR Dosed Subcutaneously In db Yucatan: Group Plasma Means (pg/mL) Over Time (N=4)

	pK Timepoint (mins)											
	Pre dose	15 min	30 min	60 min	90 min	240 min	480 min	12h	24h	48h	72h	96h
Mean BUP Low	49	360.5	1531.75	716.75	768.75	703.25	677.75	627	443.75	225.25	198	162.75
Mean BUP High	49		1327	1776.25	1659.5	1795.5	1177.5	1019.25	1072.75	468	377.75	311.5

Figure 2. High vs. Low Dose Buprenorphine SR Dosed s.c. In db Yucatan Miniswine: Group Plasma Means Over Time (N=4)



RESULTS (CONTINUED)

Table 3. Buprenorphine PK Parameters in Yucatan Miniswine: Group Mean Data (N=4)

Group	Cmax (pg/mL)	Tmax (hr)	T1/2 (hr)	Clast (pg/mL)	Tlast (hr)	AUClast (hr*pg/mL)	AUCα (hr*pg/mL)	Vz/F (mL/kg)	Cl/F (mL/hr/kg)	MRTlast (hr)
1- BUP Low Dose	843	0.5	4.1	353	8	3090	4570	15689	2560	3.5
2- BUP Hi Dose	2390	0.6	3.1	429	8	8110	11300	7966	1780	2.9
3- BUP SR Low Dose	1920	9.1	111.8	163	96	35300	61000	320707	2020	31.8
4- BUP SR Hi Dose	2090	5.4	89.3	312	96	66100	108000	271588	2250	33.8

DISCUSSION

The 2-way crossover design used in this pharmacokinetic protocol added balance in that all animals received all combinations of drugs (treatments). Short-acting buprenorphine was present in plasma above the reported human minimally effective concentration for analgesia (0.1 ng/mL, Evans & Easthope, 2003) for at least 8 hrs for both high- & low-dose groups. Sustained release buprenorphine was also present in plasma above the reported human minimally effective concentration for analgesia for at least 96 hrs for both high- & low-dose groups. Our study clearly illustrate that these dose levels in miniswine provide sufficient plasma levels of drug for putative analgesia (>0.1 ng/mL) for at least 8 hr (short-acting BUP) or for at least 96 hr (long-acting BUP SR) periods in Yucatan miniswine. These findings are consistent with clinical in house experience on post-surgical analgesia at this CRO.

The group mean pK parameter for Tmax suggested that the higher dose BUP SR reached Tmax earlier than did the lower dose SR (5.4 vs. 9.1 hr). Two of 4 high dose SR animals exhibited considerable variability (Tmax: 1.5 & 12 hr) from the other two animals Tmax of 4 hours each.

CONCLUSION

In conclusion, these data show that these dose levels provide sufficient plasma levels of drug for analgesia (>0.1 ng/mL) for at least 8 hr (short-acting BUP) or for at least 96 hr (long-acting BUP SR). This is consistent with manufacturer's notice that buprenorphine SR provides analgesia for 72 hours in large laboratory species and also consistent with post-surgical clinical analgesia assessments in our miniswine.

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