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Oxandrolone Coadministration Does Not Alter Plasma Propranolol Concentrations in Severely Burned Pediatric Patients

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The systemic impact of severe burn injury results in a variety of disorders that require therapeutic intervention. Propranolol, a nonselective β_1, β_2-adrenergic receptor antagonist, reduces resting heart rate and cardiac work caused by elevated circulating catecholamines. Oxandrolone, a testosterone mimetic, promotes protein synthesis and anabolism to counter muscle wasting. Coadministration of these drugs is expected to synergistically improve patient outcomes. Testosterone administration is known to alter β-adrenergic receptor-mediated signaling. Here, we determined whether the coadministration of oxandrolone alters plasma propranolol concentrations. Ninety-two pediatric patients with burns covering ≥30% of the TBSA were enrolled in this institutional review board-approved study and randomized to receive propranolol (n = 49) or oxandrolone + propranolol (n = 43). Plasma propranolol concentrations were determined following two dosing strategies: Q6 (liquid formulation; n = 86) and Q24 (extended-release capsule; n = 22). Samples were drawn before drug administration and at regular intervals throughout the next two dosing periods. Heart rate and blood pressure were recorded throughout the study. Propranolol half-life was 3.3 hours for the Q6 drug dosing frequency ($P < .0001$) and 11.2 hours for the Q24 strategy ($P < .0001$). Percentage of predicted heart rate declined by 2.8% for each doubling of the propranolol concentration in the Q6 dosing schedule ($P < .0001$). Percentage of predicted heart rate declined by 2.5% for each doubling of propranolol concentration on the Q24 dosing schedule ($P < .0001$). Maximum and minimum propranolol plasma concentrations were similar with either dosing regimen. The addition of oxandrolone did not affect any of the measured parameters. Oxandrolone coadministration does not alter propranolol's plasma concentration, half-life, or effect on heart rate. This study is registered at clincialtrials.gov: NCT00675714. (J Burn Care Res 2017;38:243–250)

Severe burn injury is associated with cardiac perturbations, skeletal muscle wasting, and decreased lean body mass, which contribute to morbidity and mortality. Numerous studies investigating the hypermetabolic response after severe burn injury and relevant therapeutic interventions have been published during the past 30 years (reviewed in 1, 2). Two of the most promising therapeutic interventions to mitigate this hypermetabolic hypercatabolic response are propranolol (PROP) and oxandrolone. PROP is a β_1, β_2-adrenergic receptor antagonist that improves cardiac outcomes in severely burned pediatric patients.[3,4] In addition to having cardiac effects, long-term PROP administration in children with massive burns reduces skeletal muscle catabolism and lipolysis.[4] More rapid wound healing and

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decreased blood loss have also been noted following PROP treatment in severely burned adults.[5]

Administration of oxandrolone, a testosterone mimetic with reduced hepatotoxicity and virilization, increases anabolism in the severely burned as evidenced by increases in lean body mass, strength, and bone mineral content.[6–8] Oxandrolone also improves lung function and reduces resting energy expenditure in this patient population.[8,9] For the past several years, a clinical trial has been underway at our institution to determine whether coadministration of PROP and oxandrolone will further improve outcomes in severely burned pediatric patients. We have recently reported that oxandrolone and PROP coadministration blunts growth arrest after severe burn injury.[10]

While the cardiac effects of PROP are well known, there is little information regarding the effect of oxandrolone on the myocardium. Clinical data regarding the effect of testosterone on the heart are controversial, with some studies reporting that androgen administration is detrimental and others reporting that it is cardioprotective. Exogenous androgen administration has been implicated in prothrombotic, prohypertrophic signaling (reviewed in 11). In addition, there is a solid body of basic science research indicating that testosterone modulates β-adrenergic receptor signaling. For example, studies in isolated cardiomyocytes demonstrate that testosterone administration significantly increases β-adrenergic receptor expression after testosterone treatment.[12] Alterations in the β-adrenergic receptor signaling system were also seen after testosterone treatment in an animal model of heart failure.[13]

We have previously reported plasma PROP kinetics in severely burned children treated solely with PROP.[3] Given the previously mentioned data regarding the effect of androgen administration on β-adrenergic receptor expression and signaling, we hypothesized that oxandrolone may also modulate β-adrenergic receptor signaling. Thus, the aim of the present study was to determine whether oxandrolone coadministration alters PROP plasma concentrations.

METHODS

Patients

The University of Texas Medical Branch (Galveston, TX) Institutional Review Board approved this study. Informed written consent and/or assent were obtained from the subject and their legal guardian before enrollment in the study.

Between January 2012 and June 2015, 530 patients were admitted to our institution, 250 of whom consented to participate in research protocols. Ninety-two

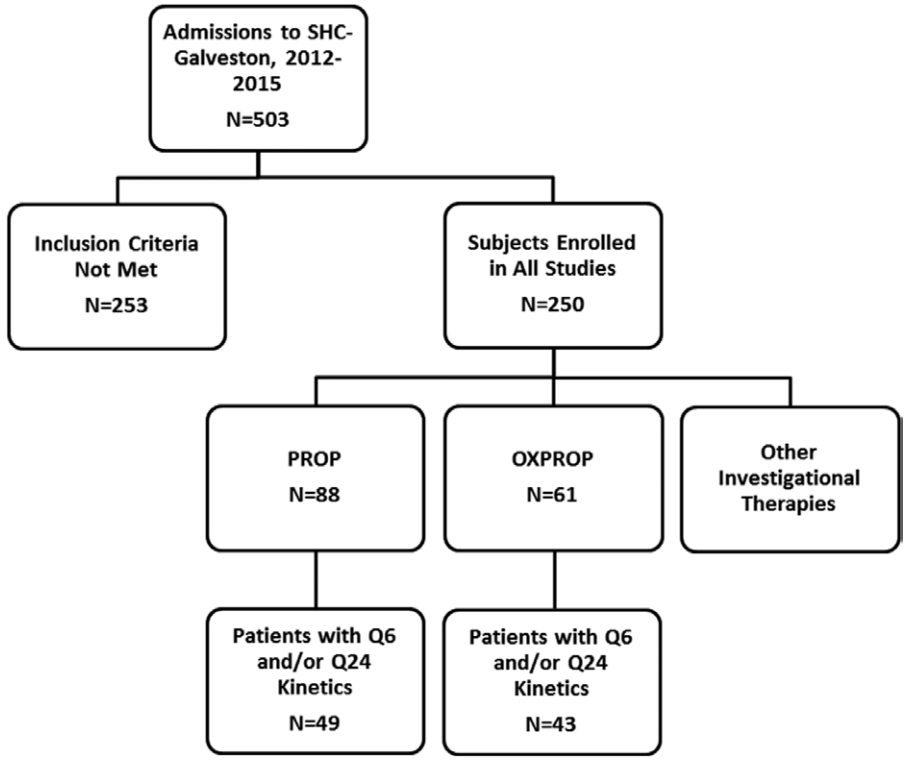

Figure 1. Consort diagram. Of 530 patients admitted to our institution between January 2012 and June 2015, 108 patients were included in our study. *OXPROP,* oxandrolone plus propranolol; *PROP,* propranolol; *SHC,* Shriners Hospitals for Children.

subjects were included in this study. Subjects were randomized to receive either PROP (n = 49) or oxandrolone plus PROP (OXPROP, n = 43) during their acute hospital stay in the intensive care unit (Figure 1), as described in a report of the effects of PROP, oxandrolone, and OXPROP on growth.[10]

Plasma PROP concentrations were determined in patients administered PROP (Roxane Laboratories, Columbus, OH) with or without oxandrolone (BTG Pharmaceuticals, West Conshohocken, PA; 0.1 mg/kg twice daily) according to one of two dosing strategies. Oxandrolone was administered at a dose of 0.1 mg/kg twice daily. PROP was given either every 6 hours (Q6) as a liquid formulation or as a once daily extended-release capsule (Q24) with a maximum dose of 16 mg/kg/d. Both PROP formulations were administered to reduce heart rate by 15%. Both PROP and OXPROP patients 6 years or older were switched from the liquid formulation to the extended-release capsule shortly before discharge from the intensive care unit as recommended by the attending physician and following successful completion of a swallow test. Thus, the kinetic studies testing the extended-release capsule were performed later during the patient's time in the hospital compared with the liquid formulation. Study drugs were started 2 ± 3 days after admission to our institution once consent (or assent) was obtained.

Plasma Propranolol Quantification

Kinetic studies were performed, once patients had received their study drug(s) for >3 consecutive days. Plasma was collected immediately before dosing and at regular intervals after dosing for two consecutive dosing intervals to determine PROP concentrations (Table 1). Measurements of PROP were performed after the drug was given for 15 ± 10 days. PROP was given as a racemic mixture consisting of two enantiomers with differing β-adrenergic receptor blockade abilities; thus, both were quantified. Extraction of PROP was performed as previously described.[3] High performance liquid chromatography was used to measure PROP concentrations according to a method adapted from Sigma Aldrich using a chiral Chirobiotic T column (25 cm × 4.6 mm, 5 μm) with a 15-mM ammonium formate mobile phase (in methanol), 5-μl injection volume, and a flow rate of 1 ml/min.[14] The signal was detected via fluorescence with excitation at 285 nm and emission at 350 nm. Both inter- and intraday coefficient of variation for this method was >10%. The lowest concentration that was reliably quantified was 0.05 ng/ml.

Heart Rate and Blood Pressure

Heart rate and blood pressure were measured throughout the study period and recorded with each blood draw. Blood pressure was measured via arterial line or blood pressure cuff. Heart rate was compared with published data in age-matched nonburned children and graphed as the percentage of predicted heart rate.

Statistical Analysis

Separately for each dosing frequency (Q6 and Q24), the decay rate of plasma PROP was determined by regressing the log of the concentration over the linear portion of the decay curve (the elimination phase) and by taking the decay rate (lambda) as the negated coefficient of the slope of log (concentration) over time. Because patients received two consecutive doses of PROP, time was measured from the administration of the dose, and the beginning of the linear portion of the curve was taken as 2 hours after the Q6 dose and 7 hours after the Q24 dose. A mixed multiple regression modeled the log of concentration as a function of dose order (first vs second), enantiomer (S vs R), and time from dose, while blocking on subject to account for repeated measures. Bayesian information criteria and likelihood ratio tests were used to rule out more complex models incorporating age, time between burn and kinetics study, TBSA burned, sex, and treatment group (PROP vs OXPROP), either alone or in interaction with time, as well as interaction between enantiomer and time, as all failed to improve on the model.

The relationship between the percentage of predicted heart rate and PROP concentration was modeled by mixed linear regression separately for each drug dosing frequency (Q6 and Q24), adjusting for the effects due to dose order (first vs second), enantiomer (S vs R), and concentration, while blocking on subject to account for repeated measures. Concentration was log (base 2) transformed for better centering and interpretation. Data for all measured time points were included. The model for Q24 also adjusted for time from dose and age; these were excluded from Q6 as they did not improve the model. Bayesian information criteria and likelihood

Table 1. Propranolol kinetic study sampling schedule

Q6	Q24
Predose	Predose
15 min	2.5 hr
30 min	5 hr
1 hr	6 hr
2 hr	7 hr
4 hr	12 hr
6 hr (predose 2)	18 hr
	24 hr (predose 2)

ratio tests were used to rule out more complex models incorporating age, time from dose, time between burn and kinetics study, time on drug before kinetics study, TBSA burned, and treatment group (PROP vs OXPROP), either alone or in interaction with concentration, as well as interaction between enantiomer and concentration, as all failed to improve on the model, with the exception of age and time from dose in Q24.

Column analysis was performed by one- or two-way analysis of variances followed by the appropriate post hoc test. Statistical analyses were performed using R statistical software (R Core Team, 2015, version 3.2.1) or GraphPad Prism (GraphPad Software, 2007, version 5.01). In all statistical tests, $\alpha = 0.05$. Significance was accepted $P < .05$.

RESULTS

The percentage of TBSA burned, percentage of TBSA with third degree-burns, length of stay, and the time between burn and admit were similar between the groups (Table 2). Patients receiving the extended-release capsule (Q24) were significantly older in both treatment groups due to the study design (PROP, $P = .002$ and OXPROP, $P = .009$). As the kinetics for the Q24 formulation were performed toward the end of the acute hospitalization when patients were switched from the Q6 formulation, the Q24 kinetics were performed much later (PROP, $P = .022$ and OXPROP, $P = .013$). The time between the burn injury and the kinetics study ranged from 4 to 28 days post burn in the Q6 groups and 11 to 79 days post burn in the Q24 groups. Patients in the Q24 groups also received a significantly lower average PROP dose than those in the Q6 groups (PROP, $P = .0001$ and OXPROP, $P < .0001$).

Plasma Propranolol Concentration

Average plasma PROP concentrations as a function of time are depicted in Figure 2. Conventional PROP formulations contain two enantiomers, S(−) and R(+), which differ in their β-adrenergic receptor-blocking potencies, as well as their clearance rates.[15] In our patient population, no difference was seen in the kinetic profiles between enantiomers. Concentrations of each PROP enantiomer peaked at 30 minutes and 5 hours after dosing in the Q6 and Q24 groups, respectively. Patients receiving PROP four times daily had plasma PROP concentrations within the therapeutic window (30–80 ng/ml) throughout the study period irrespective of treatment (Figure 2A, B).[16,17] Similarly, patients later treated with the extended-release capsule (without oxandrolone coadministration) maintained plasma concentrations within the therapeutic window despite receiving significantly lower PROP doses than the Q6 group (Figure 2C, D). However, patients in the Q24 OXPROP group had lower, albeit not statistically different, PROP concentrations than the Q24 PROP group, with the concentrations reaching subtherapeutic concentrations before the subsequent dose (Figure 2C, D). Maximum (Cmax) and minimum (Cmin) PROP concentrations did not significantly differ between PROP and OXPROP groups with Q6 administration or Q24 administration. There were also no significant differences in Cmax or Cmin between Q6 and Q24 (Figure 3A, B).

For the Q6 dosing strategy, PROP had a decay of $\lambda = 0.21$, corresponding to a half-life of 3.3 hours ($P < .0001$) with a 19% decrease in concentration per hour. The R enantiomer was associated with a 9% decrease compared with the S enantiomer ($P < .0001$). The Q24 dosing frequency had a decay rate of $\lambda = 0.06$, corresponding to a half-life of 11.2 hours ($P < .0001$) with a 6% decrease in concentration

Table 2. Patient characteristics

	PROP			OXPROP		
Characteristic	**Q6 (N = 41)**	**Q24 (N = 11)**	***P***	**Q6 (N = 45)**	**Q24 (N = 11)**	***P***
Age (yr)	8 ± 5	12 ± 4*	.002	7 ± 5	13 ± 4*	.009
TBSA burned (%)	48 ± 14	51 ± 15	.63	47 ± 11	44 ± 10	.42
TBSA burned third (%)	28 ± 22	39 ± 21	.16	23 ± 21	23 ± 21	.97
Length of stay (d)	32 ± 24	31 ± 21	.86	30 ± 19	33 ± 24	.68
Burn to admit (d)	4 ± 4	9 ± 20	.31	4 ± 6	7 ± 7	.22
Propranolol dose (mg/kg/d)	8 ± 4	4 ± 2*	.0001	7 ± 3	5 ± 2*	<.0001
Burn to kinetics (d)	16 ± 12	45 ± 34*	.022	15 ± 8	36 ± 23*	.013

OXPROP, oxandrolone plus propranolol; *PROP*, propranolol.
Data are represented as mean ± SD.
*Significant vs Q6.

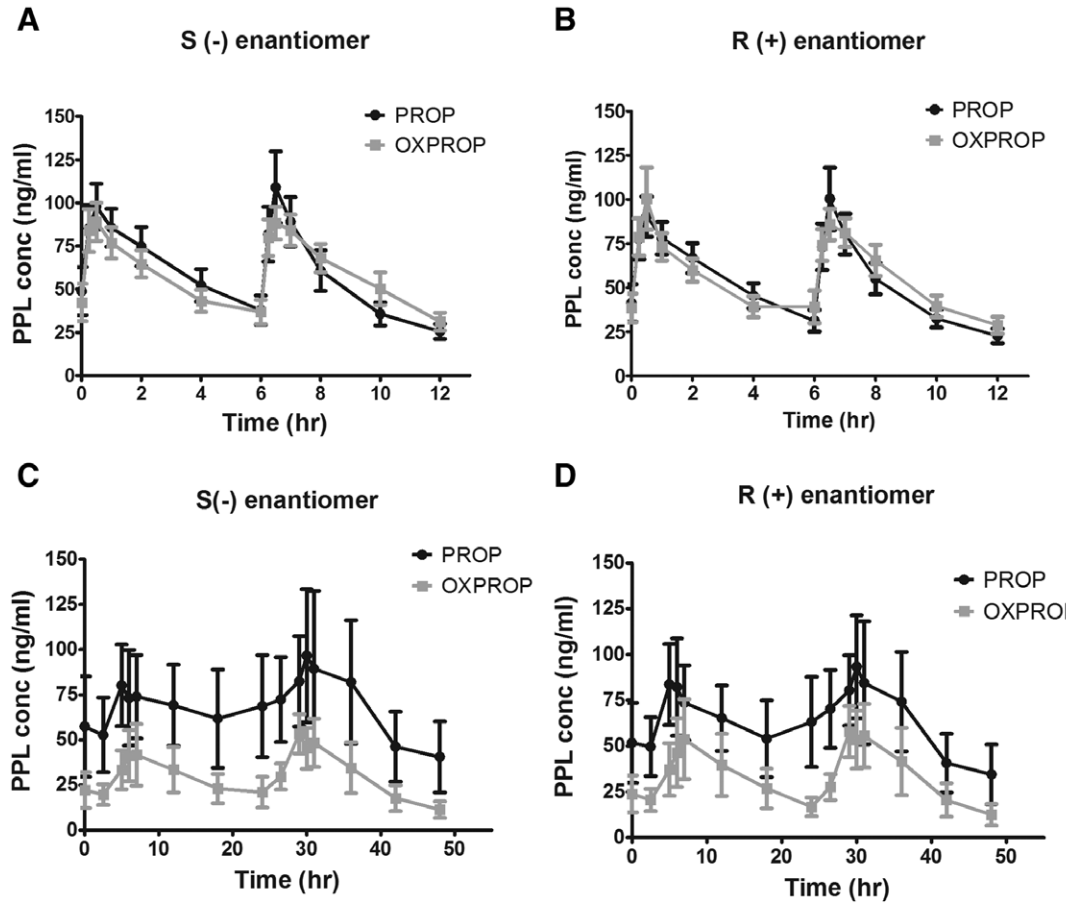

Figure 2. Oxandrolone coadministration does not change plasma propranolol kinetic profiles. Plasma PPL concentrations for both S- and R-enantiomers with and without oxandrolone coadministration are shown for both Q6 (A, B) and Q24 (C, D) dosing strategies. *OXPROP,* oxandrolone plus propranolol; *PPL,* propranolol; *PROP,* propranolol.

per hour. We detected no difference in concentration between the positive and negative enantiomers. Oxandrolone coadministration did not alter the half-life of PROP in either the Q6 or Q24 group.

Heart Rate and Blood Pressure

The percentage of predicted heart rate declined by 2.8% for each doubling of PROP concentration in the Q6 group ($P < .0001$; Figure 4A). There was no evidence of an effect due to the enantiomer or the addition of oxandrolone. In the Q24 groups, the percentage of predicted heart rate declined by 2.5% for each doubling of PROP concentration ($P < .0001$, Figure 4B). There was no evidence of an effect due to the enantiomer. Each additional year of age was associated with a 2.5% increase in heart rate ($P = .007$). Each additional hour after the dose was administered was associated with a 0.4% decrease in heart rate ($P < .0001$). Again, there was no evidence that oxandrolone coadministration affected these parameters. Finally, systolic and diastolic blood pressures were similar irrespective of treatment and/or PROP dosing strategy (Figure 5).

DISCUSSION

We have previously shown that PROP and oxandrolone alone can effectively improve outcomes and reduce morbidity in severely burned pediatric patients.[3,4,7,8] The antihypermetabolic, antihypercatabolic effects of these therapeutics arise from different mechanisms of action. PROP blocks the activation of β-adrenergic receptors by circulating catecholamines, thereby reducing stress-induced increases in heart rate, cardiac work, and proinflammatory signaling.[3,4,18,19] Oxandrolone improves burn-induced loss of lean body mass, muscle strength, and bone mineral content by activating proanabolic androgen receptors.[7,20,21] Thus, whether coadministration of oxandrolone and PROP synergistically affects patient outcomes merits investigation and is a focus of ongoing clinical trials. Recently we showed that the

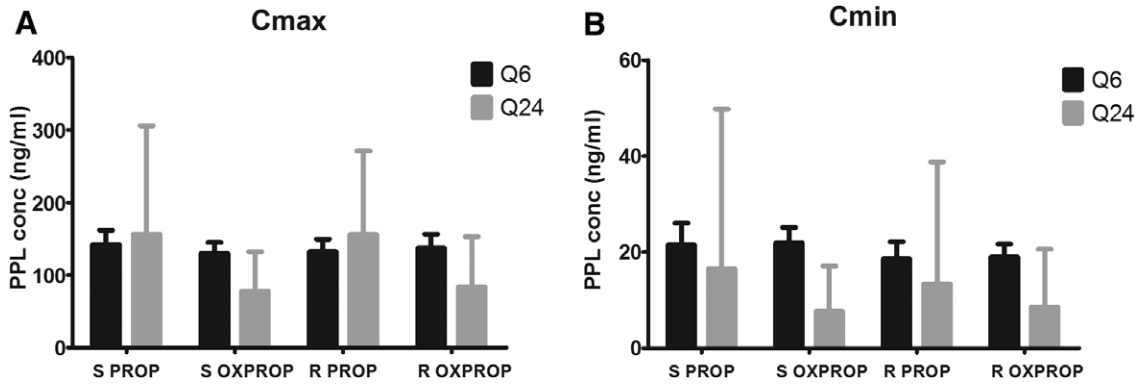

Figure 3. Oxandrolone coadministration does not change maximum or minimum plasma propranolol concentrations. Maximum (A) and minimum (B) concentrations for both propranolol enantiomers with or without oxandrolone coadministration are shown for both Q6 and Q24 dosing strategies. *Cmax,* maximum concentration; *Cmin*, minimum concentration; *OXPROP,* oxandrolone plus propranolol; *PPL,* propranolol.

combined administration of oxandrolone and PROP improves growth.[10] Given the preclinical and clinical data regarding interactions between androgen and β-adrenergic receptor activity, understanding how oxandrolone may affect PROP plasma concentrations is important for patient safety. The data reported in this study indicate that oxandrolone does not affect plasma PROP concentration or half-life.

As previously described in severely burned pediatric patients, peak PROP concentrations were achieved earlier than described in the literature.[3] Peak PROP concentrations occurred at 2.6 hours post dose in neonates treated with 0.5 mg/kg/6 hr PROP, whereas we observed peak concentrations at 0.5 hours post dose (Q6 administration).[22] Despite the earlier peak time, we observed a half-life of 3.3 hours when PROP was given four times daily, a value within the range of the published half-life of 3 to 6 hours.[23] The half-life of the extended-release capsule was also similar to what we expected based on previously published results in adults.[17] We measured both enantiomers of PROP, as there have been several reports indicating that the clearance of the enantiomers differ and can be affected by various disease states.[24] Based on our kinetic profiles (Figure 2), both enantiomers appear to be cleared at the same rate irrespective of treatment or dosing regimen. These data suggest that both dosing regimens are appropriate in this patient population.

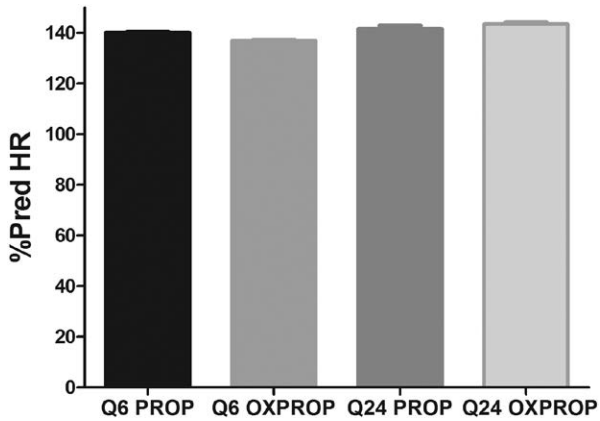

Figure 4. Oxandrolone coadministration does not alter percent of predicted heart rate. Percent predicted heart rate with or without oxandrolone coadministration during the study period for the Q6 and Q24 dosing strategies. *%Pred HR,* percent of predicted heart rate; *OXPROP,* oxandrolone plus propranolol; *PPL,* propranolol.

Mean PROP concentrations observed in severely burned patients were much higher than those previously reported in pediatric patients. Although the majority of patients received lower doses than were administered in our study, there was one patient who received a similar dose and whose mean PROP concentration was still much lower than that observed in our study.[25] Patients treated with conventional PROP maintained concentrations within the therapeutic window regardless of oxandrolone coadministration. However, those receiving PROP as an extended-release capsule with oxandrolone exhibited subtherapeutic PROP concentrations before receiving the next dose, although this change was not statistically significant. It is not clear whether this tendency for the oxandrolone-treated patients to have lower PROP concentrations is clinically significant, as dosing was similar between the two groups. Going forward we will monitor patients on the dual administration regimen to determine whether PROP dose and/or dosing frequency needs to be increased with oxandrolone coadministration. Additional studies are needed to verify this phenomenon and determine the mechanism. Patients in the Q24 groups also received a significantly lower average

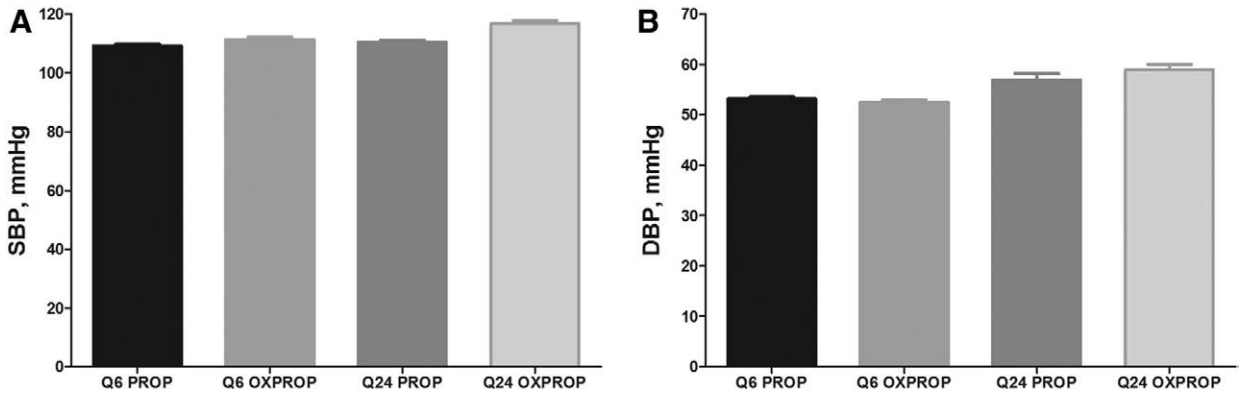

Figure 5. Oxandrolone coadministration does not alter blood pressure. Systolic (A) and diastolic (B) blood pressure with or without oxandrolone coadministration during the study period for the Q6 and Q24 dosing strategies. *DBP,* diastolic blood pressure; *OXPROP,* oxandrolone plus propranolol; *PROP,* propranolol; *SBP,* systolic blood pressure.

PROP dose than those in the Q6 groups. This may be due to limitations in the flexibility of dosing as the extended-release capsule is available only in discrete dosages. In addition, it has been postulated that, with chronic PROP administration, lower doses can achieve the same effect that required a higher dose during the acute administration.[23,26]

Similar to what has been published with PROP administration for hypertension and tachycardia in adults, we were unable to correlate the PROP dose given with the plasma concentration required to achieve the desired effect (data not shown).[16,23] This directly contrasts what was previously shown in newborns, where there was a significant correlation between PROP dose and plasma concentration.[22] Wilson et al[25] showed that, in a small subset of pediatric patients aged 2 to 14 years, there were significant individual variations in plasma concentrations despite receipt of similar doses. While our data show that oxandrolone coadministration does not significantly alter PROP kinetics, these data cannot be used to predict the optimal PROP dose or to estimate the effect of a given dose.

We have previously reported on propranolol kinetics in severely burned pediatric patients and determined that a dose of 4 mg/kg/d is needed to reduce cardiac work and heart rate by 15%.[3] The current study has used a more sensitive and accurate method of measuring PROP concentrations (ultraviolet detection vs fluorescence detection). In addition, the previous publication only investigated the kinetics of the conventional liquid formulation of PROP administered Q6, whereas we have reported and compared the conventional liquid formulation administered Q6 with the extended-release formulation administered Q24.[3] We further extended our previous report by statistically determining the decay rate, half-life, and relationship between PROP concentration and the percentage of predicted heart rate. Furthermore, our data demonstrate that the extended-release formulation is equally effective as the conventional formulation in severely burned children despite lower doses, which is a novel finding. Finally, our data show that oxandrolone coadministration does not significantly alter plasma PROP concentrations.

Limitations of this study include our inability to measure plasma 4-hydroxy PROP concentrations. 4-hydroxypropranol is an active metabolite that is formed after oral propranolol administration. In addition, because the majority of patients admitted to our institution are below the age of 5, our sample size for the Q24 administration was very small. While PROP concentrations tended to be lower with oxandrolone coadministration, this was insignificant, and a larger study is needed to definitively determine whether oxandrolone coadministration does indeed have an effect on plasma PROP concentration with Q24 administration.

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