Propranolol decreases cardiac work in a dose-dependent manner in severely burned children

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Background. Severe burn is followed by profound cardiac stress. Propranolol, a nonselective β1, β2-receptor antagonist, decreases cardiac stress, but little is known about the dose necessary to cause optimal effect. Thus, the aim of this study was to determine in a large, prospective, randomized, controlled trial the dose of propranolol that would decrease heart rate ≥ 15% of admission heart rate and improve cardiac function. Four-hundred six patients with burns >30% total body surface area were enrolled and randomized to receive standard care (controls; n = 235) or standard care plus propranolol (n = 171).

Methods. Dose–response and drug kinetics of propranolol were performed. Heart rate and mean arterial pressure (MAP) were measured continuously. Cardiac output (CO), cardiac index, stroke volume, rate–pressure product, and cardiac work (CW) were determined at regular intervals. Statistical analysis was performed using analysis of variance with Tukey and Bonferroni corrections and the Student t test when applicable. Significance was accepted at P < .05.

Results. Propranolol given initially at 1 mg/kg per day decreased heart rate by 15% compared with control patients, but was increased to 4 mg/kg per day within the first 10 days to sustain treatment benefits (P < .05). Propranolol decreased CO, rate–pressure product, and CW without deleterious effects on MAP. The effective plasma drug concentrations were achieved in 30 minutes, and the half-life was 4 hours.

Conclusion. The data suggest that propranolol is an efficacious modulator of the postburn cardiac response when given at a dose of 4 mg/kg per day, and decreases and sustains heart rate 15% below admission heart rate. (Surgery 2011;149:231-9.)

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Severe thermal injury is characterized by a profound hypermetabolic response directly proportional to the original injury that persists up to 2 years postburn.1 Pediatric burn patients show dramatic increases in resting energy expenditure, resting heart rate, cardiac output (CO) and cardiac work (CW) that may lead to physiologic exhaustion if left untreated.2,3 Furthermore, there are profound decreases in lean body mass, bone mineral content, bone mineral density, and nutritional deficiencies that can lead to impaired growth over time.1,4,6 These derangements are manifestations of the increased levels of plasma catecholamines postburn.7,8 Plasma catecholamine levels increase 10- to 20-fold post burn, and increases persist up to 12 months postinjury.7,8 This pattern leads to an hyperadrenergic response to the burn injury, propagating the cardiac and metabolic derangements in severely burned patients.9,10 Our group hypothesized that this effect is a detrimental, catecholamine-driven response and blocking this response at the receptor level would attenuate burn-induced changes.11 Propranolol, a nonselective β1, β2-receptor antagonist, attenuates the effects of endogenous catecholamines, thus decreasing CW when given during the acute hospitalization of pediatric burn patients.11 Propranolol mitigates the degree and extent of hypermetabolism, hypercatabolism, and immune dysfunction experienced by these patients.12,13 Clinically, propranolol decreases tachycardia and decreases
myocardial oxygen consumption in pediatric burn patients. When given to decrease resting heart rate 15–20% of admission heart rate, propranolol increases lean body mass and decreases resting energy expenditure over time compared with children receiving standard care.

Despite the efficacy of propranolol, little is known about the dose of propranolol necessary to cause this decrease in resting heart rates of pediatric burn patients. In addition, the pharmacokinetics of propranolol in this severely injured population is essentially unknown. Thus, the aim of this study was to determine in a large, prospective, randomized, controlled trial the dose of propranolol per kilogram of body weight that would elucidate the appropriate attenuation of CW during the acute hospitalization and the associated dose kinetics of the drug.

PATIENTS AND METHODS

Four hundred and six patients with burns over 30% total body surface area (TBSA) who consented to an institutional review board–approved experimental protocol between 1998 and 2007 and were admitted to our burn unit and required ≥1 operative intervention were included in this study. All patients who were enrolled into the study were randomized to receive standard care (controls; n = 235) or standard care plus propranolol (n = 171). Both groups were similar in age, TBSA, and time from burn to hospitalization. After the patient or the patient’s legal guardian consented to the study, patients were randomized to receive standard care with propranolol to decrease heart rate by 15–20% or just standard of care. Propranolol was administered enterally, via a feeding tube every 6 hours throughout the entire acute hospital stay. Propranolol dose was initiated at 1 mg/kg per day and titrated to decrease heart rate by 15–20% of admission heart rate. Propranolol was given once patients were fluid stabilized, which was by 24–72 hours from admission.

Within 48 hours of admission, all patients underwent total burn wound excision, and the wounds were covered with available autograft. Any remaining open areas were covered with homograft. After the first operative procedure, it took 5–10 days until the donor site healed, and patients were then taken back to the operating room. This procedure was repeated until all open wound areas were covered with autologous skin. All patients underwent the same nutritional treatment. The caloric daily intake requirement was calculated as 1,500 kcal/m² body surface plus 1,500 kcal/m² area burned, as published previously. The enteral route was preferred in our patient population. Therefore, almost all patients received nutrition via a duodenal or nasogastric tube.

Patient demographics (age, date of burn and admission, gender, burn size, and depth of burn), morbidity, and mortality were recorded. Wound healing was evaluated from time of donor site healing and thus time between operative interventions.

Cardiac function. Heart rate (HR), and mean arterial pressure (MAP) were measured continuously throughout acute hospitalization by continuous cardiac monitoring in the intensive care unit using arterial lines. Daily averages were calculated and the means compared with accepted, published nomograms for normal, nonburned children. The heart rate was graphed as percent of normal to compare heart rate.

M-Mode echocardiograms were used to determine resting CO, cardiac index (CI), and stroke volume (SV). CO was adjusted for body surface area and expressed as an index. CO, SV, and CI were measured weekly during the acute hospitalization. In patients with chest burns or prohibitive burn wound dressings, measurements were collected once wounds were covered appropriately without risk of shearing. CO and SV were normalized for age by comparison with accepted, published nomograms for nonburned, age-matched children. All cardiac ultrasonographic measurements were made with the Sonosite Titan echocardiogram, with a 3.5-MHz transducer by an experienced echocardiographer. M-Mode tracings were obtained at the level of the tips of the mitral leaflets in the parasternal long axis position, and measurements were performed according to the recommendations of the American Society of Echocardiography. Left ventricular volumes were determined at end diastole and end systole and used to calculate SV, CO, and CI. Three measurements were performed and averaged for data analysis; recordings were performed with the subjects in a supine position and breathing freely. The echocardiography operator was blinded to treatment group.

Calculations. The rate pressure product (RPP) is used to estimate myocardial oxygen consumption. It is a correlate of myocardial oxygen consumption. The RPP is calculated by:

$$\text{RPP} = \text{MAP} \times \text{HR} \ (\text{mmHg} \times \text{beats per minute [bpm]})$$

$$\text{CW} = (1,500 \text{ kcal/m² body surface} + 1,500 \text{ kcal/m² area burned}) \times \text{bpm}$$
SV × MAP × HR (mL per beat × mmHg × bpm)

The RPP was measured daily and the CW was measured at regular weekly intervals during the acute hospitalization.

Drug kinetics. On day 3 of propranolol treatment, a baseline blood concentration for propranolol was obtained. With the next dose of propranolol, subsequent blood drug levels were obtained at 15 minutes, 30 minutes, and at 1, 2, 4, and 6 hours. The 6-hour level served as the baseline for the second dose of drug for that day. Blood drug levels were again obtained. The propranolol levels were analyzed by an original high-performance liquid chromatography method developed at this institution: Extraction on Oasis hydrophilic lipophilic balance cartridge (condition with 1 mL methanol and 1 mL water; load 200 µL of serum in 800 µL of acidic solution; wash with 50% methanol in water [pH, 2.9], elute with methanol [pH, 10.9]; evaporate to dry and reconstitute in 50% methanol/water); Haisil C18 column, 5 µm, 250 × 4.5; mobile phase 22% acetonitrile in water, first to a pH of 11.2 with triethylamine, then to a pH of 3 with phosphoric acid; ultraviolet detection at 220 nm; flow rate of 0.7 mL/min.

Ethics and statistics. The study was reviewed and approved by the Institutional Review Board of the University of Texas Medical Branch, Galveston, Texas. Before the study, each subject, or parent or child’s legal guardian signed a written, informed consent form. Data are expressed as percentage, mean values ± standard deviation (SD) or standard error of the mean, as appropriate. Statistical analysis was performed by 1- and 2-way analysis of variance followed by the Tukey and Bonferroni corrections and the Student t test as appropriate. Significance was accepted at P < .05. This study’s clinical trial was registered at www.clinicaltrials.gov under the identifier number NCT00239668.

RESULTS

Demographics. Four-hundred six patients with burns encompassing >30% of their TBSA were included in the present study. Twenty patients were excluded from the control group, leaving 215 patients randomized to standard of care. Forty-six patients were excluded from the propranolol group leaving 125 patients. Patient demographics are included in the Table. Propranolol-treated patients were randomized to receive standard of care plus propranolol at an initial dose of 1 mg/kg body weight per day. Patients randomized to control were on average 8 years of age. Patients randomized to receive propranolol were on average 7 years of age. Both groups suffered from a severe burn injury with 55% TBSA (± 15% SD for the propranolol patients and ± 17% for control), and third-degree burns of >40% TBSA (± 22% SD for the propranolol patients and ± 25% for control). There were no significant differences in duration of stay in the intensive care unit or gender distribution.

Heart rate. Heart rate presented as percent of normal for both groups increased profoundly postburn (Fig 1, A). There were no differences in heart rate between groups before propranolol treatment was initiated (Fig 1, A). The average percent predicted heart rate on admission for control patients was 173 ± 4 (standard error of the mean) bpm, whereas the average heart rate for propranolol patients was 166 ± 1 bpm (Fig 1, A). There was a decrease in heart rate for the propranolol patients by day 2 of treatment compared with heart rates before treatment, which was sustained throughout treatment course (P < .001; Fig 1, A and B). For controls, the heart rate did not decrease throughout the study period compared with admission heart rate (P > .05). Propranolol-treated patients had a 15% decrease in percent of normal heart rate owing to treatment during the study period (P < .001). Compared with control patients, propranolol-treated patients had a decrease in percent of normal heart rate by 18% (P < .001; Fig 1, A and B).

Propranolol administered within the first week after hospital admission was initiated at a starting dose of 1 mg/kg body weight per day (mg/kg per day). This dose was sufficient to decrease heart rates by 10–15% of admission heart rates and between groups (P < .001). The dose of propranolol had to be increased to 4 mg/kg per day to achieve and maintain a decrease in heart rate of 15% compared with controls and compared with heart rate before treatment (Fig 1, B).

Rate–pressure product. There were no significant differences in RPP, which is associated with

<table>
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Data are presented as average values ± standard deviation, percentage, or ratio.
and a correlate of myocardial oxygen consumption, between the groups before propranolol treatment. With treatment, there was a decrease in RPP, suggesting that myocardial oxygen consumption was decreased ($P < .001$; Fig 1, C).

**Gender.** To further validate these findings, we stratified the data for gender, age, and TBSA burns. During the study period, female control patients had an average heart rate of 172 ± 1 bpm, whereas propranolol-treated females averaged 146 ± 1 bpm after propranolol was initiated ($P < .001$; Fig 2, A). Male control patients averaged 171 ± 1 bpm, whereas propranolol-treated male patients average 152 ± 1 bpm ($P < .001$; Fig 2, B). Before treatment, there were no differences between male and female patients. After treatment with propranolol, both males and females showed a significant decrease in heart rate (Fig 2, A and B). Both males and females required an average of 4 mg/kg per day to maintain significant decreases in heart rate during the acute hospitalization. There were no differences between dose requirements.

**Age.** Patients were separated into 3 age groups: 0–3 years (propranolol [$n = 48$] versus control [$n = 65$]); 4–10 years (propranolol [$n = 49$] versus control [$n = 83$]); and 11–18 years (propranolol [$n = 28$] versus control [$n = 67$]). All 3 groups showed a decrease in heart rate with propranolol treatment ($P < .05$; Fig 3, A–C). All groups required an increase in propranolol dosing to 4 mg/kg by day 20 to maintain decreases in heart rate during the acute hospitalization.

**TBSA.** Patients were separated into 3 groups based on burn size suffered: 30–60% TBSA (propranolol [$n = 80$] versus control [$n = 139$]); 60–80% TBSA (propranolol [$n = 33$] versus control [$n = 58$]); and >80% TBSA (propranolol [$n = 12$] versus control [$n = 18$]). All 3 groups showed decreases in heart rate with propranolol treatment ($P < .001$; Fig 4, A–C). The smaller burns required 4 mg/kg per day (Fig 4, A). Burns encompassing 60–80% TBSA required doses of 4–6 mg/kg per day to maintain a decreased heart rate (Fig 4, B). The largest burns required 4 mg/kg per day (Fig 4, C).

**CO, CI, and SV.** During this study period, there were no differences between groups in CO, CI, or SV before treatment with propranolol was initiated. By week 2, there was a decrease in percent of normal CO in the propranolol patients compared with control patients and was sustained through the study period (135% ± 5% vs 158% ± 8%), respectively ($P < .05$). There was no decrease in CI. With treatment, the measured SV for propranolol patients was greater than control patients (112% ± 8%
compared with age-matched non-burned children for propranolol versus 94% ± 5% for control patients; *P < .02.

**CW.** There were no significant differences in CW between groups before propranolol treatment. With treatment, there was a decrease in CW for the propranolol-treated patients compared with control patients (337,186 ± 22,837 mL/beat × mmHg × bpm versus 476,372 ± 42,379 mL/beat × mmHg × bpm; P < .004).

**Drug kinetics.** The effective plasma drug concentration for therapeutic propranolol is 50 nanograms per milliliter (ng/mL). Peak levels are reached at 1–3 hours after administration. Pediatric burn patients receiving propranolol reached acceptable peak concentration levels by 30 minutes to 1 hour and trough levels by hour 2 (a representative patient presented in Fig 5). Actual heart rate decreased 10% (139 at baseline to 125 at 1 hour) at 1 hour after dosing (Fig 5). The half-life for this drug is between 4 and 6 hours.

**DISCUSSION**

The postburn hypermetabolic response is propagated by the uncontrolled surge of catecholamines. Clinically, patients have hyperdynamic physiology. Initially, there is an “ebb” phase demonstrated by a decrease in CO with an increase in myocardial oxygen consumption and demand. This ebb is followed by a “flow” phase, in which CO can increase up to 200% of normal CO accompanied by an increase in myocardial oxygen consumption. The heart rate also increased by up to 200% of normal despite resuscitative efforts. Increased heart rate results in a shortened ventricular filling time and thus results in a decrease in SV. To further complicate this clinical profile is the third and final stage of the hypermetabolic response postburn—physiologic exhaustion. If clinicians are not able to fully resuscitate the patient to attenuate the “flow” phase, these patients become even more physiologically deranged—increasing morbidity and mortality. We have shown that the clinical course for pediatric patients with large burns is often confounded by cardiac complications. Therefore, cardiac function is 1 of the main determinants of outcome from severe burn injury.

Propranolol, a nonselective, β-adrenergic receptor antagonist may decrease mortality (unpublished data) in our patient population. A nonselective β-antagonist permits an unbalanced action of catecholamines on the peripheral vascular bed with no vasodilating action to counterbalance the effects of the catecholamines on peripheral α-adrenergic receptors. Propranolol decreases the effects of plasma catecholamines that propagate the hypermetabolic response. By decreasing the deleterious effects, propranolol mitigates the degree and extent of the hypermetabolic response. We have shown that by decreasing heart rates by 15–20% of admission heart rates, we decrease CW and RPP, which may indicate a decrease in myocardial oxygen consumption. Over time, by decreasing these physiologic demands, patients avoid further proteolysis, lipolysis, and muscle breakdown for energy requirements. The patients have increased lean body mass over time and increased bone mineral content and density. Specifically, propranolol has been shown...
to improve net muscle/protein balance by improving the efficiency of protein synthesis. In fact, in our study in 2001, the net balance of protein synthesis and protein breakdown achieved anabolic levels in patients that received propranolol treatment. Whereas the normal physiologic state post severe burn is one of profound proteolysis, and increases in resting energy expenditure, propranolol treatment accelerated protein synthesis and decreased resting energy expenditure. This physiologic change is attributed to an increase in the intracellular recycling of free amino acids. Although metabolic rates are not shown in this study, patients who underwent propranolol treatment had no significant increases in metabolic rate compared with control patients, who had a significant increase in metabolic rate during the study period.

Patients with burns encompassing 80--100% TBSA demonstrated a lot of variability in dosing during the acute hospitalization than the other size burns. This finding may be multifactorial in nature. These patients are the most critical patients. Both their status and response to treatment were tenuous during the acute hospitalization. Larger burns, in general, required more trips to the operating room and had greater resuscitation times on average. This likely attributed to the delay in increasing dose of propranolol.

Drug kinetic studies were performed on 50 patients in our hospital. Tests were performed to determine appropriate time and dosing. Data suggest that patients often fail to meet appropriate drug levels and thus need increasing doses. In addition, the data suggest that patients are so hypermetabolic that they reach peak levels much sooner than expected, and further tests need to be done to determine whether these patients require shorter dosing frequencies. Propranolol is absorbed completely after oral administration and distributed widely throughout tissues, with peak plasma levels achieved 1--3 hours after administration. It has variable bioavailability with extensive first-pass metabolism. Any hepatic dysfunction or impairment alters bioavailability. It is well-established that pediatric burn patients may have hepatic dysfunction during the acute phase postburn. Plasma concentrations can vary

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**Fig 3.** (A) Average percent predicted daily heart rates of control patients aged 0--3 years versus propranolol-treated patients aged 0--3 years during the first 20 days postburn or days of treatment with propranolol with daily dose of propranolol in milligrams per kilogram per day. Patients required 4 mg/kg per day to maintain a 10--15% decrease in heart rates. *$P < .05$. (B) Average percent predicted daily heart rates of control patients aged 4--10 years versus propranolol-treated patients aged 4--10 years during the first 20 days postburn or days of treatment with propranolol with daily dose of propranolol in milligrams per kilogram per day. Patients required 4 mg/kg per day to maintain a 10--15% decrease in heart rates. *$P < .05$. (C) Average percent predicted daily heart rates of control patients aged 11--18 years versus propranolol-treated patients aged 11--18 years during the first 20 days postburn or days of treatment with propranolol with daily dose of propranolol in milligrams per kilogram per day. Patients required 4 mg/kg per day to maintain a 10--15% decrease in heart rates. *$P < .05$. 

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quite widely owing to genetic differences or constitutional factors, such as age and environmental factors. The main metabolite after oral administration of the drug, 4-hydroxypropranolol, is also pharmacologically active and may be more potent than the parent compound. This factor may explain the decrease in heart rate even when the plasma concentration seems to be low.

One limitation of this study was M-mode echocardiography to determine CO and SV. Patients who had severe chest burns or prohibitive dressings had to have measurements taken at later time points, although within the study period. In addition, more invasive methods often show that M-mode echocardiograms may underestimate cardiac measurements, especially with confounding factors of pulmonary edema and fluid overload. Another limitation of our study is that there is a discrepancy in the number of patients in each arm of the study. At our institution, there are many prospective, randomized, controlled trials that require a control group. We use the same controls for the studies; thus, there is a larger control group compared with the many different drug doses.

**Fig 4.** (A) Average percent predicted daily heart rates of control patients with 30–60% TBSA versus propranolol-treated patients with 30–60% TBSA during the first 20 days postburn or days of treatment with propranolol with daily dose of propranolol in milligrams per kilogram per day. Patients required 4 mg/kg per day to maintain a 10–15% decrease in heart rates. *P < .05. (B) Average percent predicted daily heart rates of control patients with 60–80% TBSA versus propranolol-treated patients with 60–80% TBSA during the first 20 days postburn or days of treatment with propranolol with daily dose of propranolol in milligrams per kilogram per day. Patients required 4–6 mg/kg per day to maintain a 10–15% decrease in heart rates. *P < .05. (C) Average percent predicted daily heart rates of control patients with >80% TBSA versus propranolol-treated patients with >80% TBSA during the first 20 days postburn or days of treatment with propranolol with daily dose of propranolol in milligrams per kilogram per day. Patients required >4 mg/kg per day to maintain a 10–15% decrease in heart rates. *P < .05.

**Fig 5.** Plasma drug concentration of propranolol in nanograms per milliliter of 1 representative pediatric burn patient and time blood obtained with heart rate at time of blood draw. There was a decrease of 10% in actual measured heart rate at 1 hour.

Another limitation of this study was M-mode echocardiography to determine CO and SV. Patients who had severe chest burns or prohibitive dressings had to have measurements taken at later time points, although within the study period. In addition, more invasive methods often show that M-mode echocardiograms may underestimate cardiac measurements, especially with confounding factors of pulmonary edema and fluid overload. Another limitation of our study is that there is a discrepancy in the number of patients in each arm of the study. At our institution, there are many prospective, randomized, controlled trials that require a control group. We use the same controls for the studies; thus, there is a larger control group compared with the many different drug doses.
arms of the studies. In addition, there were a number of patients that were excluded from the study that some may feel represent a bias. Those patients were excluded for the following reasons: burns <30% TBSA, receiving other anabolic agents, futility on admission, withdrew after consent obtained by family, or never received propranolol, although they were randomized to receive propranolol. Those patients who need further explanation are patients who received other agents. Six patients who received propranolol and oxandrolone or intensive insulin and were excluded. Another group were the 4 patients whose care was deemed futile owing to the severity of injury or significant anoxic brain injury. One family withdrew after consent was signed, so that patient’s data were removed. The last group was the group that never received propranolol treatment because of physician error (failure to write the order), nursing error (failure to administer drug), or the patient received the drug only during the rehabilitative period and not during the acute hospitalization. We do not feel that these patients represent a significant bias.

In conclusion, when propranolol is given at 1 mg/kg per day, we saw a beneficial decrease in heart rates to 10% lower than admission heart rates. Over the first 10 days, patients need that dose increased to 4 mg/kg per day owing to either tachyphylaxis or the sustained “flow” phase of the hypermetabolic response. We did not see any clinically important hypotension in our pediatric patients randomized to propranolol treatment as indicated by a decrease in MAP to <60 mmHg. This lack of drug-induced hypotension may be related to the fact that these patients are so hyperdynamic that they can tolerate treatment. In addition, patients are resuscitated fully before beginning treatment, which may have prevented any untoward cardiac events. If a patient had any clinically important decreases in respiratory rate, bronschospasm, or hypotension, 1 propranolol dose was held and reinitiated with the next scheduled dose. Although we did not have any patients who had a history of asthma included in this study, they would have been excluded owing to the risk of bronchospasm with β-blockade. We need further evidence to see the safety of starting the dose at 4 mg/kg per day and to determine whether decreasing heart rates further would lead to detrimental effects on CO, CW, and myocardial oxygen consumption. For severely burned adult patients, oral propranolol at a standard dose of 20 mg every 6 hours is given and increased as needed. Our current findings, however, have led us to embark on a multicenter trial using propranolol at a dose of 4 mg/kg in the acute hospitalization to decrease cardiac stress postburn.

REFERENCES


