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Pharmacologic Metabolic Modulation in Severe Burn Injury: A Review of the Literature for Oxandrolone and Propranolol

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Abstract

Severe burn injury is associated with a significant hypermetabolic and hypercatabolic response that results in an increase in resting energy expenditure up to twice normal. Consequences of hypermetabolism include lean muscle mass loss and delayed wound healing. Many interventions have been shown to attenuate this metabolic response including early excision and grafting, temperature regulation of the environment, nutrition support, and physical therapy. Pharmacologic agents with proven benefits for metabolic modulation in severe burn injury include oxandrolone, a synthetic testosterone analog, and propranolol, a non-selective beta-adrenergic antagonist. The published literature for these agents will be presented and evaluated in this review, and recommendations for use in patients with severe burn injury will be provided.

Keywords: Burn injury; Hypermetabolism; Oxandrolone; Propranolol

Abbreviations

AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; HGH: Human Growth Hormone; ILGF-1: Insulin-like Growth Factor 1; TBSA: Total Body Surface Area

Introduction

Severe burn injury is marked by a hyperdynamic cardiovascular and metabolic response that is directly proportional to the size and severity of the burn injury [1]. The body's physiologic response is divided into two stages - the ebb phase and flow phase. The ebb phase may last for up to 48 hours post-injury and is marked by decreased cardiac output, oxygen consumption, and metabolism. In contrast, the flow phase begins after 48 hours and is characterized by hyperdynamic circulation, hyperglycemia, and increased metabolic rate [2]. The flow phase has a much longer duration and may persist for up to three years in some patients [3].

While a hypermetabolic response may occur in all trauma patients, the hyperdynamic flow phase seen after severe burn injury is more profound and persistent than in any other population [4]. The resting metabolic rate may increase up to two-fold which may be attributed to increased levels of circulating catecholamines, glucagon, and cortisol [5,6]. Circulating catecholamine levels may increase ten-fold in the acute period surrounding thermal injury [7]. Complications of the metabolic alterations in burn injury include severe muscle wasting, decreased bone mineral density, hepatic fat deposition, and impaired wound healing [8].

Management of the hypermetabolic response associated with burn injury includes early excision and grafting, temperature regulation of the environment, nutrition support, and specialized rehabilitation programs [9]. There is also a growing body of literature examining several pharmacologic options to attenuate hypermetabolism in the post-burn period [10]. While early studies investigated the potential role of human growth hormone (HGH), insulin, and insulin-like growth factor 1 (ILGF-1), each of these agents have limitations that preclude their routine use. The anti-hypermetabolic agents most commonly used in practice today are oxandrolone and propranolol; the rationale and evidence behind their use is presented here.

Oxandrolone

Oxandrolone is a synthetic analog of testosterone used as adjunctive therapy to attenuate weight loss and offset protein catabolism after severe burn injury [11]. The Food and Drug Administration-approved indications include patients experiencing weight loss following extensive surgery, chronic infections, or severe trauma [12]. Oxandrolone has several advantages that make it a more attractive option than other anabolic agents. Unlike HGH, ILGF-1, or insulin, oxandrolone can be administered orally in patients with functioning gastrointestinal tracts. It is a less expensive alternative to injectable anabolic agents and is associated with a lower incidence of virility and androgenic adverse effects than its parent hormone testosterone [13,14].

The proposed mechanism of action of oxandrolone is similar to other anabolic androgenic steroids. Like testosterone, oxandrolone is lipophilic enough to diffuse through the cell membrane and bind to cytoplasmic androgen receptors [11]. The steroid-receptor complex translocates into the cell nucleus where it binds DNA and modulates expression of genes related to protein metabolism. To evaluate the actual mechanism in which oxandrolone impacts muscle protein kinetics, Hart et al. performed a prospective cohort study including 14 severely burned children with total body surface area (TBSA) burns exceeding 20% [15]. Oxandrolone 0.1 mg/kg administered orally twice daily for 5 days significantly improved net muscle protein balance from baseline as measured by the phenylalanine stable isotope infusion method compared to children who did not

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receive oxandrolone. There was no significant difference in protein breakdown between the oxandrolone and placebo groups, confirming that the benefits were related to enhanced protein synthesis and protein synthesis efficiency. Oxandrolone may potentially promote re-using amino acids that become available after protein breakdown [15]. These actions on the cellular level have translated clinically into increased nitrogen balance, protein synthesis, and overall skeletal muscle growth [11].

Oxandrolone is well-absorbed after oral administration and achieves peak serum concentrations within one hour. With 95% protein binding, the free fraction is impacted by changes in circulating albumin and α_1-acid glycoprotein after burn injury [12,16,17]. Oxandrolone is metabolized by the liver to a lesser extent than related anabolic androgenic steroids. It is partially metabolized by sulfation to 17-epioxandrolone, and 28% is excreted un-conjugated and unchanged in the urine [14]. These pharmacokinetic characteristics may provide advantages including higher plasma levels and less hepatotoxicity compared to methyltestosterone [13]. It has a biphasic half-life in adults with a distribution half-life of 30 minutes and an elimination half-life of 10.4 hours. This allows for twice daily administration following severe burn injury.

The role of oxandrolone to combat the hypermetabolic response in the post-burn period has been studied for nearly two decades. Demling et al. first demonstrated in 1997 that oxandrolone 10 mg orally twice daily in combination with a high protein diet (2 g/kg/day) resulted in more rapid recovery of weight loss compared to high protein diet alone in patients in the recovery phase after 30-50% TBSA burns [18]. Results from several placebo-controlled studies have since corroborated these findings [19-21].

The aforementioned studies suggesting utility of oxandrolone in the post-burn period never evaluated its performance relative to an active control group. A prospective randomized controlled trial compared the effects of oxandrolone or HGH, another anabolic option previously proven to maintain body mass in this setting, against no anabolic agent [22]. Thirty-six patients were randomized to either oxandrolone 10 mg enterally twice daily or HGH 0.1 mg/kg/day intramuscularly daily and compared those groups to 24 patients who received no agent at all. Both oxandrolone and HGH resulted in statistically significant reductions in net weight loss compared to the control group (3±1.2 kg for oxandrolone, 4±1.8 kg for HGH, and 8±2.1 kg for control) and reductions in net daily nitrogen loss. These benefits were demonstrated despite significantly greater TBSA burns and a higher percentage of full thickness burns in both intervention groups compared to the control group. This study was also the first to show that oxandrolone improved wound healing by reducing time to re-epithelialization of donor graft sites from 14.2±2 days in the control group to 10±2 days in the oxandrolone group ($p<0.05$). While oxandrolone and HGH had similar anti-catabolic effects, HGH was associated with more hyperglycemia and increases in metabolic rate. The lower incidence of adverse events combined with the option for oral administration with oxandrolone makes it a more favorable choice than HGH in this setting.

Despite evidence supporting its anti-hypermetabolic effects, none of the early studies addressed clinical outcomes associated with oxandrolone use. In 2008, the largest prospective randomized controlled trial of oxandrolone for thermal injury was performed to determine its impact on hospital length of stay [23]. Eighty-one patients with acute burn injury covering 20% to 60% TBSA who were eligible to begin enteral nutrition within 5 days were enrolled from 14 burn centers across the United States. Patients were randomized to oxandrolone 10 mg enterally every 12 hours or placebo starting 5 days after injury. The study was terminated at the first interim analysis when oxandrolone resulted in significantly shorter hospital length of stay compared to placebo (31.6±3.1 days vs. 43.3±5.3 days, $p=0.042$). The mean percent TBSA burns were similar between both groups (35% TBSA burned oxandrolone vs. 36% TBSA burned placebo, $p=0.612$). After adjusting hospital length of stay for TBSA burned, there was still a significant difference favoring oxandrolone (0.88±0.07 days/% TBSA burned vs. 1.23±0.15 days/% TBSA burned, $p=0.032$). Hospital length of stay and hospital length of stay indexed to percent TBSA burned favored oxandrolone even more after excluding patients who died in both groups. The reason for reduction in length of stay was unclear, but may be related to fewer surgical procedures required in the oxandrolone group.

A multicenter retrospective observational study utilizing data from the National Institutes of Health "Inflammation and Host Response to Injury" study aimed to further assess the impact of oxandrolone on mortality and inpatient clinical outcomes [24]. One-hundred and seventeen patients with at least 20% TBSA burns admitted to five different burn centers within 96 hours of injury were included. Patients were considered to be in the treatment group if they received oxandrolone within 7 days of admission for duration of at least 7 days of therapy. The actual dose and duration were left at the discretion of the treating teams. After multivariate logistic regression, oxandrolone therapy was independently associated with lower mortality (OR 0.1, 95% CI 0.02-0.70, $p=0.02$). However, there were no significant differences with respect to nosocomial infections, number of surgical procedures, ventilator days, intensive care unit or hospital length of stay. Therefore, the means by which oxandrolone reduced mortality could not be determined.

While oxandrolone has shown benefit in both the acute and recovery phases after burn injury, long-term effects after discontinuation have not been well characterized. One study prospectively randomized 45 patients with severe burns who were transferred to an inpatient burn rehabilitation center to receive oxandrolone 20 mg/day plus optimized nutrition and exercise or optimized nutrition and exercise alone [19]. All patients were provided specific physical and occupational therapy regimens. Oxandrolone was discontinued once patients regained at least 90% of the body weight lost from the time of hospital admission to the time of admission to the rehabilitation facility. This milestone occurred within one week of discharge in all patients in the intervention group. Patients in the oxandrolone group had significantly greater increases in lean body mass measured by bio-electric impedance analysis and overall body weight at weeks 1, 2, 3, and 4. At 6 months after discharge, body weight and lean body mass did not significantly change compared to discharge values in either group. Therefore, oxandrolone resulted in a faster recovery of lost body weight and lean body mass, and these benefits were maintained 6 months after discharge. It should be noted that all patients in this study had frequent follow-up in an outpatient burn clinic and followed strict nutrition and rehabilitation programs. Any

benefits observed from oxandrolone should be considered to be in combination with these other treatment modalities.

The major safety concerns with oxandrolone are related to androgenic side effects and hepatotoxicity [12]. Possible androgenic side effects include hirsutism, deepening of voice, baldness, clitoral enlargement, and menstrual irregularities in women. Of note, oxandrolone has a much higher anabolic to androgenic ratio (10:1) making these androgenic side effects significantly less common compared to testosterone or methyltestosterone [19]. Due to the high severity of illness associated with severe burns, the potential benefit of oxandrolone may outweigh the risks in this population. Clinicians should monitor patients closely for androgenic changes after initiation of therapy.

Oxandrolone carries a black box warning associated with peliosis, hepatitis and other potentially life-threatening liver failure. Hepatic adenoma and carcinoma have been reported after oxandrolone use. The most common liver-related adverse effects include transient elevations in liver enzymes including aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase [12]. Of the studies discussed in this review however, only one found oxandrolone to be associated with significant elevations in serum transaminases. Wolf et al. reported that patients who received oxandrolone were more likely to have ALT values greater than 100 mg/dL compared to placebo (21 values vs. 6 values, p=0.002). It should be noted that liver enzyme monitoring in this study was done at the discretion of the center without adherence to a specific protocol [24]. Another randomized controlled trial included 10 children who received oxandrolone 0.1 mg/kg enterally twice daily for one year after severe burn injury. ALT, gamma glutamyltransferase, and total bilirubin remained largely within normal limits at all time points. Alkaline phosphatase was slightly elevated in the oxandrolone group compared to placebo at 9 months (214±20 IU/L vs. 125±16 IU/L), but returned to lower levels than placebo at 12 months (125±25 IU/L vs. 137±21 IU/L) [16]. Patients receiving oxandrolone therapy after severe burn injury should be monitored frequently for elevations in liver function tests and hepatotoxicity. Clinical judgment should be used to discontinue oxandrolone if these side effects develop.

Literature involving the use of oxandrolone for pharmacologic metabolic modulation in the post-burn period has significant limitations. Most studies are single center studies of small sample size, retrospective, or utilize a historical control group. Therefore, it is difficult to establish clear recommendations for when to initiate or discontinue oxandrolone. Based on current evidence, a reasonable approach would be to consider oxandrolone in patients with severe burn injury characterized by greater than 20% TBSA burns and requiring treatment in a designated burn center. Once the decision is made to start oxandrolone, liver function tests should be monitored at baseline and at least weekly thereafter. Significant gaps remain in the literature regarding when to discontinue oxandrolone, but it is reasonable to consider stopping therapy after wound closure or sufficient recovery allowing the patient to be transferred to a rehabilitation facility or discharged home.

Propranolol

The hypermetabolic response seen in severely burned patients is thought to be mediated primarily by increased levels of circulating catecholamines. Since catecholamine signaling is primarily propagated through beta-adrenergic receptors, the use of catecholamine-blocking drugs, such as beta-blockers, has been explored in severely burned patients. Studies examining the use of propranolol in thermal injury date back to the 1970s. The precise mechanism by which propranolol induces a decrease in the metabolic response is unknown, but it is thought that inhibition of excessive catecholamine signaling attenuates both the hyperdynamic cardiovascular and catabolic response seen in patients with severe burn injury.

The use of propranolol in burn injury was first reported in 1974 by Wilmore et al; they described a decrease in the resting metabolic rate in severely burned patients treated with the combination of intravenous propranolol and phentolamine [7]. The early literature following this report consists primarily of small, non-randomized trials and case series. These studies yielded conflicting results but paved the way for larger, randomized, controlled trials in this area [8,25,26].

The majority of the literature examining the use of propranolol in burn injury has been conducted in the pediatric population. The first randomized, controlled trial included 25 children less than 18 years of age with greater than 40% TBSA burns [27]. Starting five days after the first surgical procedure, all included patients underwent metabolic studies including calculation of resting energy expenditure, net protein balance, and lean body mass. After the next surgical procedure, subjects were randomized to receive propranolol 0.33 mg/kg by nasogastric tube every four hours, titrated to achieve a 20% reduction in resting heart rate or placebo. At 14 days, a decrease in resting energy expenditure was seen in the propranolol group (1321 kcal/day vs. 1670 kcal/day, p=0.001). Propranolol also improved net muscle protein balance and preserved lean muscle mass during the study period, leading to an overall anabolic effect.

While the previous study demonstrated the ability of propranolol to decrease resting energy expenditure, the optimal dose of propranolol remained unknown. A study by Williams et al. enrolled 406 pediatric patients with greater than 30% TBSA burns and randomized them to receive standard care or standard care plus propranolol [28]. Propranolol was initiated between 24-72 hours after admission. Dosing started at 1 mg/kg/day orally and was titrated to achieve a 15-20% decrease in resting heart rate. The mean age of enrolled patients was 8 years of age in the standard care group and 7 years of age in the propranolol group. The propranolol-treated patients had a significant reduction in heart rate compared to standard care by day two of treatment. Throughout the study period, propranolol was titrated up to 4 mg/kg/day in most patients in order to maintain the 15% reduction in heart rate. By week 2, propranolol significantly decreased the percent of normal cardiac output (135% vs. 158%, p<0.05) without inducing hypotension.

The previously mentioned studies explore the use of propranolol in the acute period after thermal injury. These studies are limited by a relatively short study period and duration of follow-up. Further studies were needed to elucidate the long-term benefits of propranolol therapy. A follow-up study randomized 179 pediatric patients with greater than 30% TBSA burns, who required at least one surgical intervention to receive standard-of-care plus placebo or standard-of-care plus propranolol for 12 months [29]. Based on

prior studies, propranolol was dosed at 4 mg/kg/day with a goal of decreasing patients' heart rate by approximately 15%. The mean age of patients in both groups was 7 years old. In order to assess the efficacy of propranolol on heart rate, an age-based predicted heart rate was calculated for each patient. Propranolol was associated with a significantly lower percentage of predicted heart rate at one year (110% vs. 119%, $p<0.01$) with a low incidence of adverse effects. At six months, propranolol was also found to have beneficial effects on percent predicted resting energy expenditure (106% vs. 119%, $p=0.01$) and actual lean body mass (11,187 grams vs. 10, 231 grams, $p=0.02$), but these benefits were not sustained throughout the remainder of the study period. In contrast, total bone mineral loss in the propranolol group was significantly decreased throughout the study period (OR 0.44, 95% CI 0.2-0.94). This was the first study to demonstrate the sustained benefits of treatment with propranolol for up to 12 months post-injury.

To date, only one randomized, controlled trial evaluated the use of propranolol in adult patients. This study included 79 patients with severe burn injury covering 20%-50% TBSA and set out to determine the effects of propranolol on wound healing [30]. Patients were randomized to receive either propranolol 1 mg/kg/day given orally in six divided doses titrated to achieve a 20% decrease in resting heart rate or placebo. Propranolol-treated patients had a shorter healing time for both superficial (16.13 days vs. 21.52 days, $p=0.04$) and deep (28.23 days vs. 33.46 days, $p=0.007$) burn wounds. A significant decrease was observed in the surface area of burn wound that required skin grafting in the propranolol group (13.75% vs. 18.72%, $p=0.006$). While there was no difference in rates of sepsis or mortality between groups, patients in the propranolol group had a shorter hospital length of stay (24.41 days vs. 30.95 days, $p=0.05$).

Current literature suggests propranolol is beneficial in patients with >20% TBSA burns. Propranolol should be initiated after the acute resuscitation period once the patient is hemodynamically stable, often 48-72 hours after the initial injury. As with oxandrolone, there are significant limitations to the available evidence for the use of propranolol in severe burn injury. The body of literature exploring the role of propranolol in thermal injury continues to grow. Ongoing trials are attempting to identify the specific molecular mechanisms responsible for the protective effects of propranolol, the subpopulations most likely to benefit from propranolol, and the optimal dosing regimens. Once completed, these trials will provide valuable information regarding the use of propranolol for metabolic modulation in thermal injury.

Conclusion

Pharmacologic metabolic modulation is one component of a multifaceted approach to managing hypermetabolism after burn injury. Based on current evidence, oxandrolone and propranolol have become the most commonly utilized agents for this patient population. However, significant gaps in the literature leave many unanswered questions about attenuating the hypermetabolic response. High quality research is needed to close those gaps and serve as the foundation for clear treatment recommendations. At the current time, the University of Texas is enrolling patients for a prospective randomized controlled trial to assess a variety of options for metabolic modulation including the possibility of using propranolol and oxandrolone for an extended duration of up to two years post-burn (NCT00675714). This study and other future studies are critical to identifying the optimum approach to managing metabolic derangements after severe burn injury.

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