The Anticatabolic and Wound Healing Effects of the Testosterone Analog Oxandrolone After Severe Burn Injury

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Purpose: **Severe burn injury leads to marked catabolism and decreased lean mass, which can impair healing. Anabolic agents can attenuate net catabolism. Our purpose was to determine whether the testosterone analog, oxandrolone, given during the acute post burn period decreased the degree of nitrogen loss and loss of body weight while also increasing the healing rate of a skin donor site.**

Materials and Methods: **Patients with burns between 40% and 70% of body surface were studied. A randomized double-blinded placebo-controlled study design was used. Patients were given oxandrolone 20 mg/day (n = 11) or a placebo 20 mg/day (n = 9) beginning between days 2 and 3 post burn. Net nitrogen balance and the healing time of a standardized donor site were measured. Patients were monitored until transferred to a burn rehabilitation facility, an average time period of 33 ± 9 days.**

Results: **Mean burn size was 49 ± 8% for placebo and 53 ± 9% of total body surface for the oxandrolone group. Smoke inhalation was present in approximately 50% of patients in both groups. All patients survived the burn injury. Net weight loss was 8 ± 3.1 kg in the placebo group compared with 3 ± 1.9 kg in the oxandrolone group, a statistically significant decrease. Net daily nitrogen loss over a 3-week period (days 7 to 28) was 13 ± 4 g in placebo treated compared with 4 ± 1.9 g for the oxandrolone group, a statistically significant decrease. The healing time of a standardized donor site, decreased from the placebo group value of 13 ± 3 days to 9 ± 2 days for oxandrolone treated patients, a significant improvement. No major liver dysfunction, or other complication attributable to an anabolic steroid was seen in either group.**

Conclusion: **We found the anabolic agent, oxandrolone, significantly decreased weight loss and net nitrogen loss and increased donor site wound healing compared with placebo controls. We noted no complications with the use of oxandrolone.**

SEVERE BURN injury leads to marked catabolism with loss of lean mass and a decrease in protein stores. Lost lean mass results in well-documented impairments in wound healing and musculoskeletal function.[1-7] The anabolic agent human growth hormone (HGH), when given in large doses, has been shown to decrease post-burn catabolism, maintain body cell mass, as well as increase the rate of wound healing.[8-13] Improved wound healing is likely due to the direct anabolic effect of HGH as well as that caused by the release of insulinlike growth factor.[8-13] Testosterone analogs have also been reported to decrease protein loss in catabolic patient populations.[14-18] Oxandrolone is a testosterone analog that has been used in a number of patient populations, including burn patients, to restore lean body mass and weight loss caused by the catabolic response to injury or infection.[17-20] The rate of lean mass gain in the post-burn recovery period, using oxandrolone and nutrition has been reported to be fourfold that of nutrition alone, with no significant complications.[18] However, the anticatabolic and wound healing effects of this agent have not been studied during the acute post-burn phase. Wound healing would be improved if protein stores were preserved. In addition oxandrolone may directly increase healing rate.

Our purpose was to compare the anticatabolic and also wound healing effects of oxandrolone, using a randomized double-blinded placebo-control protocol, beginning in the early post-burn period. The burn patients studied were those who would be expected to have a significant catabolic response and benefit from an anabolic agent. These criteria include patients with deep burns, between 40% and 70% of body surface, including patients with smoke inhalation injury, or other comorbid factors. Criteria were comparable to our previous studies on the effect of HGH on the post-burn response. The anabolic agent was begun between 2 and 4 days post burn depending on when nutritional intake reached at least 75% of requirements and continued until patients were discharged to an acute rehabilitation facility. Adequate nutrition, especially protein intake, is clearly necessary for any anabolic agent to be effective.[18] Wound healing was assessed by comparing the time to reepithelealization of the first

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donor site, usually obtained between days 2 and 4 post injury.

MATERIALS AND METHODS

Patient Population

Consecutive burn patients admitted in 1998 were studied. The entry criteria were that the patient have deep burns of 40% to 70% of total body surface (TBS) with at least 20% TBS requiring grafting. The study protocol was approved by the institutional review board for human studies. The randomization into the placebo or oxandrolone group was done by the research pharmacist, on the patients entry into the study. The study was blinded to all care providers.

The study drug, which is approved by the Food and Drug Administration (FDA) for involuntary weight loss after injury, was given orally at a dose of 20 mg/day in two divided doses of four 2.5-mg tablets, either through a feeding tube or by mouth. The 20-mg daily dose for oxandrolone is the dose used in most studies for restoring post-injury or infection-induced weight loss.[17-20] The placebo drug was given in the same fashion. The composition of the oxandrolone pill is 2.5 mg of oxandrolone combined with 150 mg of lactulose monohydrate, corn starch, and methyl cellulose. The placebo was an identical-appearing pill that contained all the ingredients except the oxandrolone. Patients with deep burns exceeding 70% TBS were excluded to obtain a more homogeneous study population. Burns over 70% TBS make up less than 10% of our burn center admissions making group matching more difficult. Patients were maintained on the anabolic agent (or placebo) until the degree of wound closure and recovery was sufficient so as to be able to be transferred to an acute rehabilitation unit, identified as resolution of the stress response, no active infection and remaining open wound no greater than 10% TBS. Residual wounds were routinely covered with a skin substitute. The study was discontinued if a complication, which could be attributed to oxandrolone, developed. Progressive liver dysfunction is the only potential major complication, although rare in occurrence.

Measurements

On admission, age, pre-burn body weight (if known), burn size, depth, and comorbid factors were documented. Body weight was obtained weekly with wound dressings removed. Blood chemistries including liver function tests were obtained as a routine, twice a week, and more frequently if necessary. Also measured were metabolic rate, nutrient intake, net nitrogen balance, and healing time of a standardized donor site of a specific thickness.

Metabolic Support

Patients were managed in a temperature-controlled environment in individual isolation rooms with radiant heaters, to maintain air temperature at patient comfort or at least 85°F. Closed dressing technique was used to avoid excess heat loss. After initial fluid resuscitation, sufficient free water was provided to maintain an isosmolar state and urine specific gravity of less than 1.025.

Nutritional support, which began on day two, was provided primarily by the enteral route, with supplementation if needed by the parenteral route. Caloric requirement intake was initially estimated using the basal metabolic rate, BMR times a burn stress factor, according to the method of DeBiasse and Wilmore.[21] After the first week, caloric requirements were adjusted according to the indirect calorimetry.

Metabolic Assessment

Measurements were obtained in the morning between 8 AM and 10 AM before wound care. Metabolic rate was measured every 3 days with a portable bedside monitor (The Metabolic Gas Monitor - Utah Medical Products, Lehi Utah), which measures differences in the concentration of oxygen and carbon dioxide in inspired and expired air over a 20 to 30-minute period. Measurements are repeated until stable readings were obtained. Metabolic expenditure or resting energy expenditure (REE) was converted to Kcals/hr by the formula (REE = VO_2 L/min $\times$ 5 kcals/L $\times$ 60). Respiratory quotient was measured and maintained between .75 and .85. Measured metabolic rate was compared with a predicted pre-burn metabolic rate, based on standard tables, for age, size, and sex. Protein requirement was considered to be 2 g/kg/day for all patients.[21] Nitrogen balance was determined weekly by subtracting nitrogen intake from urinary nitrogen loss for a 24-hour period. Urine nitrogen was measured using an automated chemiluminescence analyzer.[22] Weight loss in our study was determined as the weight on transfer to a rehabilitation unit subtracted from pre-burn weight, determined by patient history or on admission if fluid resuscitation had just begun.

Wound Care

All deep burns were managed by early sequential excision and grafting, beginning by day 3, and continuing every 3 to 4 days until closure with autograft or skin substitutes was completed.

Healing Time of Skin Donor Site

The donor site was monitored for its healing rate and was obtained from an unburned area. The site was either on an arm or leg at a thickness of 12/1,000th of an inch. Donor sites were initially covered with xeroform gauze, which was then allowed to air dry. On the fifth postoperative day, a trained nurse evaluator examined the site and, using sterile technique, gently lifted each of the four corners of the xeroform, with minimal tension, to determine if the dressing was adherent. Healed areas had the xeroform trimmed. This procedure was performed every other day until complete removal of the dressing and reepithelialization. Donor site healing time was defined as at least a 95% of the wound had re-epithelealized.

Complications

Abnormal liver function tests for this study were defined as an increase in alanine amino transferase (ALT), aspartate amino transferase (AST), bibrubin, or alkaline phosphatase of 1.5 times normal. Nearly all major burns have a modest increase in at least alkaline phosphatase, especially with parenteral nutrition. An abnormal value, requiring discontinuation of oxandrolone, would be a sustained increase lasting over 5 days in one or more enzymes of at least double the normal value. Because of the short time course of the anabolic agent, hirisuitism, was not considered a complication requiring discontinuation, but was documented if present.

Length of Stay

The time to discharge to an acute rehabilitation setting was considered to be the length of stay for purposes of the study for weight loss and nitrogen loss assessment.[23] Criteria for discharge to a rehabilitation unit included a stable cardiopulmonary status and clean wounds (no eschar), usually covered with skin substitutes, of no greater than 10% of body surface.

Statistics

Within each group, paired data were compared with baseline at multiple post-burn time periods by means of ANOVA and the Newman-Keuls mared group data were compared at a given time period using the unpaired test. A *P* value of less than .05 was considered statistically significant.

RESULTS

Patient Population

A total of 26 patients met criteria for the study and of these 20 agreed to enroll in the study. Of these, 11 patients were assigned to the oxandrolone group and 9 patients to the placebo group. The remaining burns were also studied and monitored as per our normal protocol. All patients survived.

All group data are presented as group mean ± standard deviation. The degree of injury for the oxandrolone and placebo groups is presented in Table 1. Burn size, age, and presence of smoke inhalation injury were comparable between oxandrolone and placebo groups.

Metabolic and Wound Healing Effects

Metabolic rate was predictably increased in both groups to a comparable degree (Fig 1). The addition of oxandrolone did not alter post-burn metabolic rate. The mean group data is shown in Table 2 and in the figure. Net weight loss and net daily nitrogen loss were significantly less, in the oxandrolone group compared with the placebo group. Mean net nitrogen loss reached 13 ± 4 g/day between days 7 and 28 in the placebo group (Fig 1). Mean net nitrogen loss were only 4 ± 1.9 g/day in the oxandrolone treated group (Table 2).

There was also a significant increase in the rate of donor site healing with oxandrolone, compared with the placebo control group. Time to reepithelialization was 30% faster, that is, 9 days versus 13 days in the oxandrolone versus placebo group, respectively.

Nutrition

Mean calorie intake for patients in both groups reached 95 ± 6% of calorimetry determined goal

Table 1. Placebo-Treated and Oxandrolone-Treated Burn Groups

Patient	Age	%TBS Burn	%TBS Grafted	Inhalation Injury
Placebo-treated burn group				
LA	38	40	41	No
DG	43	58	40	Yes
AS	55	45	31	No
RG	35	42	28	Yes
KR	39	48	37	Yes
DK	37	65	51	Yes
TK	72	44	32	No
RH	35	51	35	No
Mean ± SD	44 ± 6	49 ± 7	39 ± 4	50%
Oxandrolone-treated burn group				
WD	46	55	40	No
WL	43	41	25	No
AS	46	54	39	No
RC	44	51	40	Yes
DM	44	64	28	No
AZ	75	42	36	Yes
WG	45	51	38	Yes
PM	38	48	32	No
AB	39	45	26	Yes
RS	49	59	40	Yes
AS	52	65	45	Yes
Mean ± SD	49 ± 13	54 ± 9	36 ± 8	52%

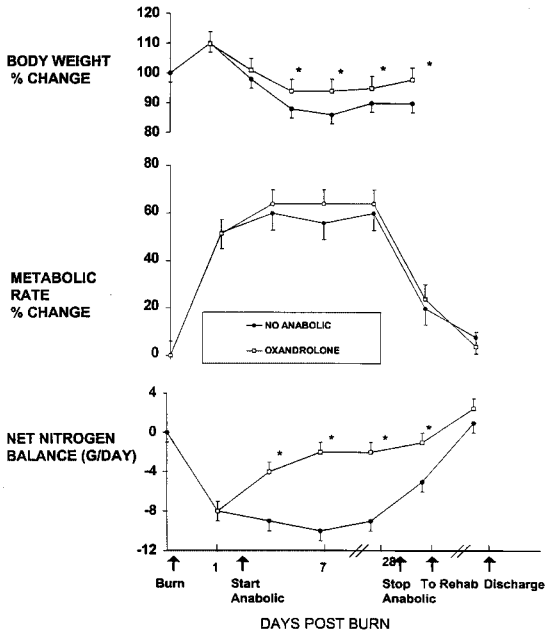

Fig 1. The effect of the anabolic agent oxandrolone versus placebo on post burn metabolic changes is shown. Mean group data ± standard deviation is shown for oxandrolone (open squares) versus placebo (closed circles). The daily net nitrogen and body weight loss was markedly attenuated by oxandrolone versus placebo, especially during the study period of days 7 to 28. Metabolic rate was significant post burn, increased to the same degree in both groups. An asterisk reflects a significant group difference, $P < .05$.

by day 10 and remained between 95% and 105% of goal for the study period. Mean calorie intake between the 7- and 28-day period was 32 ± 3 kcals/kg/day and 34 ± 3 kcals/kg/day in the oxandrolone and placebo group, respectively. Mean protein intake reach the recommended goal of 1.5 g/kg/day in both groups by day 10. Mean values between the 7 and 28 day period was 1.6 ± .3 g/kg and 1.7 ± .3 g/kg body weight per day in the oxandrolone and placebo group, respectively.

Complications

Mild liver dysfunction was seen in half of all the patients in both groups. No severe progressive liver dysfunction was noted and no complication developed that required discontinuation of the study. No hirsuitism was noted.

Length of Stay

Average burn center length of stay (LOS) before transfer to an acute burn rehabilitation setting was 35 ± 9 days for the placebo group and 29 ± 8 days for the oxandrolone group. A valid comparison could not be made between the placebo and the anabolic steroid group as to LOS because of the small size of the groups.

Table 2. Anabolic and Wound Healing Effects of Oxandrolone Versus Placebo After Burn Injury

Mean ± SD	Placebo (N = 8)	Oxandrolone (N = 11)
Donor site healing/days	13 ± 3	9 ± 2*
Net weight loss (kg)	8 ± 3	3 ± 2*
Net nitrogen loss g/day†	13 ± 4	4 ± 2*
Metabolic rate‡ (% increase)	65 ± 13	63 ± 14
Mild liver changes (% total)	57	50
Progressive liver dysfunction	0	0

*Significantly different from placebo $P < .05$.

†Mean loss between days 7 and 28.

‡Normal metabolic rate as predicted by age, size, sex, and a mild activity level.

DISCUSSION

The complications of acute burn induced loss of lean body mass are well described.[1-6] Both muscle and visceral protein losses begin immediately after injury and net protein losses can exceed 150 g/day.[1-5] Impaired immune function, increased infection, decreased wound healing, and generalized weakness occur with progressive losses of body protein.[1,6,7]

The progressive catabolism is the result of a generalized burn induced inflammation and the ensuing abnormal hormonal response.[2,4,5] Increased circulating levels of the catabolic hormones cortisol and catecholamines are seen along with decreased levels of the anabolic hormone, growth hormones, and testosterone.[9,23] Net losses of body protein can be measured directly as a loss of body cell mass and indirectly by a net negative nitrogen balance. Optimizing nutrient intake, especially protein, can decrease net protein losses, but by only about 50%.[24] In addition, fat mass can replace lost lean mass with restoration of lost weight.[25] Therefore, it is important to minimize the initial catabolic losses.

Increasing anabolic activity, post burn, by providing high doses of human growth hormone HGH has been shown to decrease lean body mass and body cell mass loss and improve wound healing, measured as more rapid donor site healing.[8-13] The

wound healing effects of HGH are believed to be due to both its overall anabolic effects as well as the release of insulinlike growth factors known to be direct wound healing stimulants.[8-12] However, HGH has limited use, due, in part, to cost and also to complications especially hyperglycemia. Also exogenous growth hormone, when given after severe injury, is known to further increase metabolic rate and body temperature likely due to a further stimulation of gluconeogenesis, a heat producing, energy requiring reaction.[8]

Testosterone analogs have also been used for controlling post-injury catabolism. Hepatotoxicity has been reported as a complication because most testosterone analogs are cleared by the liver. Also androgenic or musculinizing effects have been reported.[26,27] Oxandrolone is an oral 17α methyl derivative of testosterone, which is cleared completely by the kidney with negligible effects on liver or kidney.[19,20] In addition, anabolic activity is 10-fold that of testosterone.[20] Oxandrolone has been FDA approved for restoration of weight lost after any injury or infection. Use of this agent in patients with alcoholic hepatitis, along with good nutrition, resulted in a halving of mortality rate when compared with optimum nutrition alone.[14] This benefit was believed to be due to a more effective maintenance and restoration of lean body mass, thereby decreasing catabolism-induced mortality.[15-20]

Clinical trials, using oxandrolone in a variety of catabolic populations, including hepatitis, AIDS, and severe burns, have shown a greater restoration of lean mass in conjunction with optimum nutrition compared with nutrition alone.[15-18] Demling and DeSanti[18] reported a fourfold increase in the rate of weight gain in the recovery phase after severe burns when compared with optimum nutrition alone. Most of the weight restored was lean mass.[18]

Most of the studies, using testosterone analogs, have focused on restoring lost protein mass during the recovery period after injury rather than the prevention of catabolic losses during the acute catabolic phase. Also there are no studies addressing wound healing. We elected in this study to define the effects of oxandrolone on the degree of protein loss and weight loss in the acute post-burn period. We studied a burn patient population most likely to have catabolism induced complications and therefore benefit from an anabolic agent. This population included patients with deep burns exceeding 40% of body surface. We did not study burns exceeding 70% of TBS in this study as we believed that we would not have sufficient numbers for comparison to placebo for the between group comparison. Also, the mortality rate of burns of 40% to 70% TBS is quite low except for the elderly, decreasing the potential of loss of group participants. An increase in catabolism is evident within 24 hours post burn although the peak metabolic response is usually seen by days 5 to 10.[1-5] It is essential that sufficient nutrient intake be provided when an anabolic agent is being tested, as adequate energy and protein substrate is required for increased anabolism. The time period of 7 to 28 days has been shown by a number of investigators to have a relatively constant rate of net daily nitrogen loss after a large burn.[4]

We also looked at the effect of oxandrolone on wound healing using a standardized partial thickness wound. Any improvement in healing from an anabolic agent would be very clinically relevant. A 20% to 30% increase in the rate of donor site healing has been well described with the use of HGH.[8-11] We would surmise that an increase in healing would be present throughout the burn area, not just at the donor site, possibly resulting in other benefits, such as decreased length of stay.

We found that oxandrolone had a significant anticatabolic effect during the acute post-burn period. Weight loss and net nitrogen loss were decreased by over 50%, compared with the standard care placebo-treated group. Post-burn metabolic rate did not increase further with oxandrolone, despite the increased protein synthesis.[8] This finding could be explained by a more efficient partitioning of amino acids into the lean mass compartment while decreasing the rate of amino acid oxidation for fuel.[26] We also noted no insulin resistance, hyperglycemia, or hypercalcemia, known complications seen with the use of HGH.[8] The LOS as a group was not significantly decreased. Because the burn sizes and patient ages within groups varied considerably, we would expect that LOS assessment would require a much larger study population.

The healing rate of skin donor sites was also significantly increased with the use of oxandrolone compared with the placebo group. The same degree of improved healing was reported with the use of HGH.[8,11] However, the mechanism is likely different. Oxandrolone, being an androgen activates androgenic receptors that are present on mesenchymal cells, especially skin fibroblasts.[17] The increased

rate of re-epithelealization with this anabolic steroid may be explained by release of local growth factors through the stimulation of wound mesenchymal cells.[17] Further work is needed in this area.

We can conclude that the testosterone analog produced a significant decrease in the degree of negative nitrogen balance and an increase in wound healing rate in the acute post-burn period, compared with a well-matched burn patient population treated with a placebo. Oxandrolone was also found to have minimal side effects. However, we cannot state in this study that this agent improves survival from burn injury as all patients survived in this study.

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